NZBLOOD

Transfusion Medicine Handbook Third Edition, 2016

A Guide to the Clinical Use of Blood Components, Blood Products and Blood Transfusion Procedures in New Zealand

NEW ZEALAND BLOOD SERVICE

New Zealand Blood Service (NZBS) was formed in 1998 integrating all hospital-based transfusion services into a single national organisation. Since 2001, NZBS has managed the recruitment of blood donors, and the collection, processing and accreditation of all donated blood. This ensures that the demand for blood components used in the treatment of patients in all public and private hospitals is met.

As well as the collection of blood from donors at many fixed and mobile sites throughout the country, a wide range of activities are carried out at the main centres. These include recruitment of donors for high titre immune plasma (anti-D, tetanus, hepatitis B and zoster immunoglobulin), recruitment of apheresis donors predominantly for plasma and platelets but also granulocytes, and collection of haemopoietic progenitor cells. NZBS also carries out therapeutic plasma exchange, therapeutic venesection and collection of autologous blood.

Other functions of NZBS include specialist immunohaematology, tissue typing for transplantation, skin and bone banking, production of serum eye drops and cryogenic storage of blood components. The national stock of rare blood, national immunohaematology Reference Laboratory, national Tissue Typing Laboratory and the New Zealand Bone Marrow Donor Registry are all located at the NZBS Auckland centre.

NZBS is responsible for the collection and coordination of plasma supply to CSL Behring in Melbourne where New Zealand plasma is fractionated into plasma products, which NZBS then distributes to hospitals and health professionals.

NZBS maintains close liaison with public and private hospitals, general practitioners and midwives. Hospital transfusion committees operate in most major hospitals and NZBS is involved with these in an advisory capacity.

NZBS manages the blood banks in six of the country's major hospitals, with the remainder being managed by the District Health Boards (DHBs) or local community laboratory providers. The blood banks carry out various activities including the final compatibility checking and issuing of blood components and plasma products for transfusion.

A national computer system, eProgesa, links NZBS and all the main hospital blood banks. eProgesa manages the whole transfusion process with full traceability of each individual blood component from donation to its final fate. Information from eProgesa allows NZBS to monitor blood component usage and, together with the DHBs, actively manage demand.

There are many elements to the transfusion process that need to be managed effectively to ensure blood components are used appropriately, and the relationship between NZBS and the DHBs is a key part of this. NZBS undertakes audits of clinical transfusion practice and blood use, monitors transfusion-related adverse events through a national Haemovigilance programme and provides a wide range of clinical, nursing and technical oversight and support.

CONTENTS

ABBREVIATIONS AND GLOSSARY

ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADAMTS-13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADP	Adenosine diphosphate
Adverse event	Untoward occurrence associated with the collection, testing, processing, storage and distribution of blood components and fractionated products. Serious adverse events are those which may lead to death or to life-threatening, disabling or incapacitating conditions for donors/patients, or which result in, or prolong, hospitalisation or morbidity.
Adverse reaction	Untoward response in a donor or patient associated with the collection or transfusion of blood components and fractionated products. Serious adverse reactions are those which may lead to death or to life-threatening, disabling or incapacitating conditions or which result in, or prolong, hospitalisation or morbidity.
AHF	Antihemophilic factor
AHTR	Acute haemolytic transfusion reaction
AIDS	Acquired immunodeficiency syndrome
AIHA	Autoimmune haemolytic anaemia
ALI	Acute lung injury
Allogeneic blood	Collected from one individual and intended for use by another individual (as in allogeneic blood donation).
ANH	Acute normovolaemic haemodilution
Anti-HBs	Antibody to hepatitis B surface antigen (HBsAg). The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus (HBV) infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
ANZSBT	Australian and New Zealand Society of Blood Transfusion
APTT	Activated partial thromboplastin time
ARCBS	Australian Red Cross Blood Service
ARDS	Adult respiratory distress syndrome
ASH	American Society of Hematology
ASTH	Australasian Society of Thrombosis and Haemostasis
ATG	Anti-thymocyte globulin
Autologous blood	Collected from an individual and intended for their own use (as in autologous blood donation).

ATIII	Antithrombin III
BCSH	The British Committee for Standards in Haematology
Blood component	A therapeutic constituent separated from human blood (red cells, platelets, fresh frozen plasma, cryoprecipitate and white cells).
Blood (fractionated) product	A therapeutic protein fraction prepared from large pools of human plasma under pharmaceutical conditions, e.g., coagulation factors, albumin, immunoglobulins.
BMI	Body mass index
BMS	Blood management system
BNP	B-type natriuretic peptide
BU	Bethesda unit
CHAD	Cold haemagglutinin disease
CMO	Chief Medical Officer
CMV	Cytomegalovirus is a member of the herpesvirus family, transmissible by transfusion, and which may cause disease in immunosuppressed patients.
CNS	Central nervous system
CoE	Council of Europe
CPAP	Continuous positive airways pressure
CPD / CPDA	Citrate phosphate dextrose and citrate phosphate dextrose adenine anticoagulant solutions used when collecting blood donations.
CSL	Compound sodium lactate
CSL Behring	A manufacturer of plasma therapies whose name derives from the merger of several parent companies including CSL (Commonwealth Serum Laboratories) Limited and ZLB Behring.
CVP	Central venous pressure
DAT	Direct antigobulin (Coombs) test
DDAVP	1-desamino-8-d-arginine vasopressin (Desmopressin)
DHB	District Health Board
DHTR	Delayed haemolytic transfusion reaction
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
DSTR	Delayed serologic transfusion reaction
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin

FBC	Full blood count
FEIBA	Factor VIII inhibitor bypassing activity
FFP	Fresh frozen plasma
FIX	Factor IX
FMH	Fetomaternal haemorrhage
FNAIT	Fetal and neonatal alloimmune thrombocytopenia
FNHTR	Febrile non-haemolytic transfusion reaction
Fractionated product	A therapeutic protein fraction prepared from large pools of human plasma under pharmaceutical conditions, e.g., coagulation factors, albumin, immunoglobulins.
FVIII	Factor VIII
FXIII	Factor XIII
G-CSF	Granulocyte-colony stimulating factor
GP	Glycoprotein
GVHD	Graft-versus-host disease
HAE	Hereditary angioedema
HBsAg	Hepatitis B surface antigen; a serologic marker on the surface of hepatitis B virus (HBV). It can be detected in high levels in serum during acute or chronic hepatitis. The presence of HBsAg indicates that a person is infectious.
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDFN	Haemolytic disease of the fetus and newborn
HES	Hydroxyethyl starch
HFE	High Iron Fe gene; mutations of HFE are responsible for genetic haemachromatosis.
HLA	Human leucocyte antigen
HPA	Human platelet antigen
HPC	Haematopoietic progenitor cell
HIT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplant
HTC	Hospital transfusion committee
HTLV	Human T-cell lymphotrophic virus
HUS	Haemolytic uraemic syndrome
ICH	Intracranial haemorrhage
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalised ratio

ITP	Immune thrombocytopenic purpura
IVIg	Intravenous immunoglobulin
IU	International units
IUT	Intrauterine transfusion
JVP	Jugular venous pressure
LDH	Lactate dehydrogenase
MBOS	Maximum blood order schedule
MTP	Massive transfusion protocol
MO	Medical Officer
NBA	Australian National Blood Authority
NHI	National Health Index
NHMRC	National Health and Medical Research Council of Australia
NOAC	Non-vitamin K-dependent oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
NZBS	New Zealand Blood Service
NZRC	New Zealand Resuscitation Council
PAS	Platelet additive solution; nutrient media used in place of plasma for platelet storage.
PBSC	Peripheral blood stem cell
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PHARMAC	Pharmaceutical Management Agency of the New Zealand Government
PID	Primary immunodeficiency diseases
PLT	Single therapeutic dose of platelets
PT	Prothrombin time
PTP	Post-transfusion purpura
RAADP	Routine antenatal anti-D prophylaxis
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCNA	Royal College of Nursing of Australia
RCo	Ristocetin cofactor
Resuspended red cells	Red cells from which the majority of plasma has been removed and replaced with a nutrient or preservative solution, e.g., saline, adenine, glucose, mannitol (SAG-M)
RhD	RhD red cell antigen
RNA	Ribonucleic acid
SCIg	Subcutaneous immunoglobulin
SED	Serum eye drops

SHOT	Serious Hazards of Transfusion; UK haemovigilance programme.
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TA-GVHD	Transfusion-associated graft-versus-host disease
TMS	Transfusion Medicine Specialist
TNS	Transfusion Nurse Specialist
TPE	Therapeutic plasma exchange
TPO	Thrombopoietin
TPR	Temperature/Pulse/Respiratory rate
TRAE	Transfusion-related adverse event
TRALI	Transfusion-related acute lung injury
TRIM	Transfusion-related immunomodulation
TTI	Transfusion-transmitted infection
TTP	Thrombotic thrombocytopenic purpura
vCJD	Variant Creutzfeldt-Jakob disease
vWF	von Willebrand factor
vWD	von Willebrand disease
VZV	Varicella zoster virus
Whole blood	Blood collected from a donor prior to separation into constituent red cells, platelets and plasma.
WBCT	Whole blood clotting time
WBIT	Wrong blood in tube
WHO	World Health Organisation

FOREWORD

This handbook is designed to assist hospital staff and other health professionals in modern transfusion medicine practice, particularly those who are prescribing and administering blood products. In addition to information about the blood products and services offered by the NZBS, it provides a framework for the clinical indications for their use, the procedures for administration, and the management of adverse reactions in patients.

The NZBS Clinical Compendium, NZBS Manufacturing Standards, hospital clinical policies and other departmental manuals cover aspects of these guidelines in more detail. The contents of the NZBS Clinical Compendium are also available on the NZBS website (www.nzblood.co.nz). If information in these should not accord with the principles outlined in this document, the differences should be referred in writing to the New Zealand Blood Service, attention National Medical Director:

The National Medical Director
New Zealand Blood Service
Private Bag 92071
Auckland 1142

Telephone (09) 523 5733
Facsimile (09) 523 5754

The assistance of Transfusion Medicine Specialists and Transfusion Nurse Specialists in the review of these guidelines is gratefully acknowledged. Comments and suggestions for improvements in future editions are invited and should be addressed to the National Medical Director.

If assistance is required for the management of transfusion support for patients in particular clinical circumstances further information and advice can always be obtained from NZBS Transfusion Medicine Specialists.

INTRODUCTION

1.1 Audience

Many people play an essential part in ensuring that the right blood components and products are given to the right patient at the right time. This handbook is therefore intended for all staff responsible for prescribing, supplying and administering blood components and fractionated products. They include:■

- Registered medical practitioners, nurses and midwives who assess patients and who prescribe and order blood components and fractionated products to be transfused.
- Phlebotomists and others who collect and send pretransfusion samples.
- Laboratory staff who ensure that blood components are compatible for transfusion.
- Orderlies and other personnel who deliver blood components and fractionated products to hospital wards and clinics where patients are transfused.
- Nurses and other clinical staff who check that, before being administered, the supplied blood components and fractionated products are intended for the identified patient, and who then observe the patient during and after the transfusion.
- Medical and nursing students involved in any of the above activities.
- Telephone operators who may have to make vital contacts in an emergency.

1.2 Evidence

Correctly used, transfusion can save lives and provide numerous clinical benefits. However, the effectiveness of many current transfusion practices has not been rigorously proven by clinical trials. It is not possible to offer complete evidence-based guidelines for practice. Where good evidence is not available, the contents of this handbook reflect best efforts to give a balanced view of current opinion about the clinical practice of transfusion for patients in New Zealand.

1.3 Clinical Practice Guidelines

Australasian guidelines are available for the administration and appropriate use of blood components and fractionated products. These have been developed by the Australian & New Zealand Society of Blood Transfusion (ANZSBT) and the Australian National Blood Authority (NBA) and supported by specialist colleges and medical specialists of both Australia and New Zealand.

The NBA Patient Blood Management Guidelines, approved by the Australian National Health and Medical Research Council (NHMRC), cover the use of blood components (red blood cells, platelets, fresh frozen plasma, cryoprecipitate) and are available from the NBA website at www.blood.gov.au/pbm-guidelines.

A summary of transfusion guidelines can be found on the reverse of the NZBS Request for Blood Components or Products form and are presented in more detail in Chapter 4: Blood Components. Other sources of information that may prove useful are listed in Table 1.1.

However, the most important factors driving the success of moves toward improved clinical quality reside within New Zealand hospitals (both DHB and private). Evidence from the New Zealand National Haemovigilance Programme and similar programmes overseas, such as the UK's Serious Hazards of Transfusion scheme (SHOT), shows that most serious errors relating to transfusion practice arise from administrative and clerical errors, most of which are avoidable.

Table 1.1 Sources of Information

Organisation	Website
New Zealand Blood Service	www.nzblood.co.nz
NZBS Blood Resource	www.clinicaldata.nzblood.co.nz/resourcefolder
Australian Red Cross Blood Service	www.transfusion.com.au
Australian National Blood Authority	www.blood.gov.au
Australian and New Zealand Society of Blood Transfusion (ANZSBT)	www.anzsbt.org.au
Joint UK Blood Transfusion and Tissue Services Professional Advisory Committee	www.transfusionguidelines.org.uk
British Committee for Standards in Haematology (BCSH)	www.bcshguidelines.com
UK Serious Hazards of Transfusion scheme (SHOT)	www.shotuk.org
NZ Ministry of Health	www.moh.govt.nz
New Zealand legislation	www.legislation.govt.nz

1.4 Haemovigilance

Blood components and fractionated products are biological in nature and carry inherent risks in respect of infection or reactions in the recipient. Common and, for the most part, minor reactions include febrile non-haemolytic and allergic transfusion reactions. A small number of problems account for the majority of difficulties and dangers associated with transfusion, for example delay in obtaining blood components needed urgently, transfusing blood components and fractionated products intended for another patient, over-transfusion leading to circulatory overload and pulmonary oedema, and transfusion-transmitted bacterial infections. Fortunately, the risk of transfusion-transmitted viral infections such as HIV, hepatitis B and hepatitis C is relatively low when compared with other risks.

Clinical staff have the responsibility for recognising and reporting transfusion-related complications to the blood bank, NZBS Transfusion Medicine Specialist/Medical Officer or a Transfusion Nurse Specialist.

It is the task of NZBS and manufacturers of fractionated products to ensure that blood supply and transfusion practice is as safe as possible. Similarly, local hospital blood bank staff and the hospital transfusion committee should ensure that adverse events are effectively investigated and reported.

Some Common Causes of Problems

Most of the problems associated with transfusion that cause delays and may put the patient at risk are caused by poor communication, failure to follow documented procedures and inadequately trained staff. The most frequently occurring problems are:

- Prescribing blood components and fractionated products that are not required by the patient or are not the most suitable treatment for the patient's clinical condition.
- Incomplete or inaccurate completion of request forms or sample tube labels.
- Improper collection of samples possibly leading to 'wrong blood in tube' (WBIT) incidents.
- Delays caused by a failure to communicate accurately when and where blood components and fractionated products are needed.
- Transfusion of blood components and fractionated products that are intended for another patient.
- Failure to recognise and appropriately manage an adverse reaction occurring during transfusion.

Notification and Investigation of an Adverse Transfusion Reaction

NZBS has produced a form for notifying the blood bank of the occurrence of a transfusion reaction. Copies of the Notification and Investigation of Adverse Transfusion Reaction form are normally available in each ward or from the blood bank.

On the reverse side of this form are guidelines for the management of adverse transfusion reactions to assist clinical staff in the immediate care of the patient.

Haemovigilance Activities

NZBS is obliged to monitor the occurrence of adverse events during the transfusion process from vein-to-vein (i.e., from donation collection through to transfusion), in line with principles contained in the Council of Europe Guide to the Preparation, Use and Quality Assurance of Blood Components. Donor incidents, specimen labelling errors, blood bank errors, bedside checking errors and transfusion reactions are all examples of activities which fall under the umbrella of 'haemovigilance' and for which NZBS has systems in place to capture information.

In turn, the National Haemovigilance Programme specifically receives notification of adverse events that occur during, or as a result of, transfusion. All New Zealand hospitals and blood banks participate in the programme, reporting any transfusion-related adverse events experienced by patients in the hospitals they serve. NZBS also works with hospitals to ensure that adverse events are appropriately managed and reported in a timely manner.

Transfusion is a complex process involving many different staff groups in the hospital. Any failure in the transfusion chain has the potential to cause significant harm to, or even death of, patients. Therefore all personnel involved in the transfusion process should be encouraged to be vigilant and report any untoward events that they may observe.

Further information about the nature of adverse effects of transfusion and how they should be reported to NZBS can be found in Chapter 7: *Adverse Events of Transfusion*.

COLLECTION, TESTING AND PROCESSING OF BLOOD DONATIONS

2.1 Blood Donors

Blood donors are essential to NZBS and the national blood supply. Up to 800 donors are needed each working day to meet the country's transfusion needs and the supply of plasma for the manufacture of fractionated products. A great debt is therefore owed to the many volunteer donors who so willingly help in this way.

There are five categories of blood donation:

- **Whole blood donation** where a single unit of blood is collected. Whole blood donors usually give about 470 mL of blood (with an additional 30 mL taken for routine testing) and can donate up to four times per year.
- **Apheresis donation** where plasma, platelets or white cells are specifically collected from the donor's whole blood using a machine known as a cell-separator. Once these components are harvested, the donor's red cells are usually returned to them. Apheresis donors can donate more frequently than whole blood donors and as often as every two weeks.
- **Pre-operative autologous donation** where blood components are collected from patients for transfusion to themselves during elective surgery. Refer to Section 8.1: *Autologous Blood Collection and Transfusion* for further information.
- **Directed donation** where one individual seeks to identify another individual who will donate to provide blood components for either themselves or a close family relative.
- **Selected donation** where NZBS identifies donors to provide blood components for recipients with rare blood types, or with red cell or platelet antibodies.

2.2 Donor Selection Criteria

The donor selection process contributes significantly to the safety of the donor pool and the blood supply:

- Whole blood donors are accepted from their 16th birthday up to their 66th birthday. Established donors (those who have donated in the previous two years) can donate up to their 71st birthday and thereafter up to their 76th birthday, subject to annual medical review by an NZBS Medical Officer.
- Donors must be in good health and weigh more than 50 kg. This ensures that the process of donation is not detrimental to the donor's health as well as protecting the recipient from blood-borne infectious disease (such as bacterial sepsis, HIV, hepatitis B and hepatitis C, malaria and variant Creutzfeldt-Jakob disease), donor medications or other contaminants that could be harmful to them.
- At each donation the donor completes a detailed health questionnaire and signs a declaration that the health information provided is correct.
- The donor's haemoglobin level is checked each time they donate.

- The donor's completed medical history is evaluated by a suitably qualified health professional and the donor accepted or deferred accordingly.

The NZBS website (www.nzblood.co.nz) provides detailed information on the current donor eligibility and deferral criteria.

2.3 Self-Sufficiency and the Volunteer Status of Donors

New Zealand has adopted recommendations of the World Health Organisation (WHO) in achieving self-sufficiency in safe blood supply, based on voluntary non-remunerated blood donation (VNRBD).

Defined by the WHO, self-sufficiency means that the national needs of patients are met in a timely manner, that patients have equitable access to transfusion services, blood components and fractionated products, and that these are obtained from VNRBD of national, and where needed, of regional origin, such as from neighbouring countries.

Donation is considered voluntary and non-remunerated if the person gives blood, plasma or cellular components of his/her own free will and receives no payment for it, either in the form of cash, or in kind which could be considered a substitute for money. This would include time off work other than that reasonably needed for the donation and travel. Small tokens, refreshments and reimbursements of direct travel costs are compatible with voluntary, non-remunerated donation.

2.4 Informed Consent for Donation

Informed consent is a requirement of the *Code of Health and Disability Services Consumer's Rights (1996)*. Donors are required to be fully informed about the donation process, the risks involved and their obligations as donors. The donor's consent is obtained when they complete the health questionnaire.

In consenting to donate, donors agree to the testing of their blood for blood group and evidence of infectious diseases, as well as the use of their blood for transfusion, teaching, diagnostic purposes or quality testing.

Information leaflets about the blood donation process and blood safety along with a copy of the health questionnaire are available from NZBS blood centres and also from the NZBS website.

2.5 Apheresis Donation

Apheresis is a procedure used to collect:

- Plasma (plasmapheresis)
- Cellular components (cytapheresis) including:
  - Platelets (plateletpheresis)
  - Granulocytes (granulocytapheresis)
  - Haematopoietic progenitor cells (HPCs) derived from peripheral blood

Red cells can also be collected by erythrocytapheresis (although NZBS does not offer this service).

2.6 Directed and Selected Donation

When a person seeks to identify another individual who will donate blood to provide blood components for either themselves or a close family relative, the practice is termed a **directed donation**. The request usually occurs within family relationships, in particular parents of children, where there may be significant emotional anxiety reflecting a concern regarding the perceived safety of a transfusion. There is no evidence that directed donations either lead to improved patient care or reduce the risk of acquiring transfusion-transmitted infections. As a result, NZBS does not support the practice of directed donations and will discourage such requests. However, if a directed donation is collected, the procedures for collecting, testing, storing, handling and transfusing the unit must follow the procedures recommended for non-directed allogeneic blood donations. For the purposes of directed blood donations only, the meaning of the terms donor and donation refer to a volunteer who provides blood that is to be used for a purpose specified by the person providing the blood, or to the derived blood components, respectively. If a directed donation is not used for the purpose specified, i.e., transfusion to the intended recipient, the donation and associated components will be discarded and not made available for other recipients.

In some circumstances it may be necessary for NZBS to seek a compatible donor from relatives. This practice is at the discretion of a Transfusion Medicine Specialist and involves a **selected donation**, not a directed donation. Donors are selected for matched platelets, peripheral blood stem cells and rare blood groups.

Apheresis donors should normally meet the requirements for whole blood donation. Exceptions to this must be authorised by a NZBS Transfusion Medicine Specialist/ Medical Officer. Such exceptions will normally only be made when the plasma or platelets are of unusual therapeutic value and only when the NZBS Transfusion Medicine Specialist/Medical Officer, who is aware of the health status of the donor, has documented that the donor's health permits apheresis donation.

2.7 Haemochromatosis

Genetic or hereditary haemochromatosis is mainly associated with a defect in the *HFE* (High Iron Fe) gene. *HFE* helps regulate the amount of iron absorbed from food.

There are two important mutations in *HFE*, namely C282Y and H63D, of which C282Y is the most important. When inherited from both parents, C282Y causes a variable increase in iron absorption which, if untreated, may lead to iron overload and organ dysfunction.

Management consists of lifelong monitoring, avoidance of an iron-rich diet and, depending on clinical phenotype, therapeutic venesection to deplete iron stores followed by maintenance venesection to prevent recurrence of iron overload.

Patients who are clinically well and meet all blood donor acceptance criteria may be enrolled as normal blood donors. NZBS checks the ferritin level periodically while iron depletion is in progress. Once stable iron-deplete levels are achieved, annual monitoring by the patient's general practitioner is recommended.

2.8 Cord Blood Donation

NZBS currently does not routinely provide this service and all requests for the collection of directed cord stem cells should be referred to a NZBS Transfusion Medicine Specialist.

2.9 Testing of Donor Blood

Every unit of blood collected is tested for the following:

- ABO and RhD blood groups
- Red cell antibodies
- Infectious diseases:
  - HIV (HIV Ag/Ab and HIV RNA)
  - Hepatitis B (HBsAg and HBV DNA)
  - Hepatitis C (anti-HCV and HCV RNA)
  - Syphilis (*Treponema pallidum* antibodies)

Other testing restricted to specific donor groups and, where indicated, individual donors or donations:

- HTLV-I /II antibody on all new donors
- CMV antibody on donations to be used as components for patients at high risk from CMV infection
- *Plasmodium* antibody on donations from malaria-risk donors
- *Trypanosoma cruzi* antibody on donations from Chagas-risk donors
- Ferritin on donors failing the haemoglobin screening test
- Direct antiglobulin test (DAT)
- Extended red cell antigen typing
- HLA antibody on previously pregnant (> 20 weeks gestation) female plateletpheresis donors
- HLA (human leucocyte antigen) or HPA (human platelet antigen) genotyping

2.10 Leucodepletion

All blood components for direct clinical transfusion are leucodepleted. Leucodepletion is a process for removing white cells (leucocytes) from blood components. This is achieved by means of a special filter or by differential centrifugation. Leucodepleted blood components should contain $< 5 \times 10^6$ white cells per unit.

NZBS introduced universal prestorage leucodepletion in July 2001, initially as one of a series of precautionary measures against the potential risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion.

There is good evidence to support the value of leucodepletion in preventing transfusion-associated transmission of some infectious agents and in reducing some of the adverse immunomodulatory effects of allogeneic transfusion:

- Reduction in frequency of febrile non-haemolytic transfusion reactions.
- Prevention or delay of alloimmunisation to human leucocyte antigens.

- Prevention or delay of platelet refractoriness due to alloimmunisation.
- Reduction in the risk of CMV transmission.

Leucodepletion also has other theoretical advantages:

- Reducing the risk of other leucocyte-associated blood borne infections, such as transmission of HTLV-I/II, and inadvertent bacterial contamination of blood components.
- May reduce the risk of perioperative infection or cancer recurrence by reducing the immunomodulatory effects of blood transfusion.
- May prevent some cases of transfusion related acute lung injury (TRALI).

2.11 Processing of Collected Blood to Components

Blood donations are processed into various components including red cells, platelet concentrates, fresh frozen plasma and cryoprecipitate. Blood components are prepared at NZBS processing centres under strictly controlled manufacturing conditions.

Blood Component Labelling
Blood components supplied for transfusion have a blood component label applied by the manufacturer specific to each individual component type. These labels provide important information for those who administer blood components and also allow the origins of the component to be traced.

Labels should state the details of the component and its composition, the conditions under which it can safely be stored and the date and time of expiry. Components from single donors must carry the unique donation number that identifies the donation.

Compatibility Labels
A 'compatibility label' will be applied by the blood bank issuing the component to the patient. This label uniquely identifies the patient for whom the component has been selected. An essential bedside check before transfusing any blood component is to make sure that the details on the compatibility label match exactly those of the patient.

2.12 Processing of Collected Blood to Fractionated Products

Fractionated products, also known as plasma derivatives, are partially purified therapeutic preparations of plasma proteins. They are manufactured in large-scale pharmaceutical processes from large volumes of source plasma. For example, each batch of Intragam®P typically uses 7.5 - 10 tonnes of plasma (from approximately 25,000 - 30,000 individual whole blood donations).

The plasma is processed by a variety of techniques classically involving Cohn fractionation but more recently chromatographic techniques such as gel filtration, ion exchange and affinity chromatography have been used.

Finally, the purified plasma undergoes specific virus removal or inactivation steps, for example heat-treatment, solvent/detergent treatment, incubation at low pH or filtration. The final products are supplied as freeze-dried powders or solutions.

All of the plasma obtained by NZBS through the collection of whole blood, together with approximately 80% of the apheresis plasma, is forwarded to CSL Behring in Melbourne for the manufacture of fractionated products.

Product labelling
Fractionated products are identified by both the carton packaging and labels of the product container. Included with every product is an insert provided by the manufacturer with detailed information concerning the product relating to its composition, indication for use and administration.

Blood bank labelling
All fractionated products issued to a patient have a computer-generated label attached that provides details of the patient and product batch number. This label is used at the bedside check of the patient's identity and then placed in the clinical notes as a record of transfusion.

2.13 Blood Components and Fractionated Products as Medicines

Blood components and fractionated products are classified as prescription medicines under New Zealand legislation. The *Medicines Act 1981, Medicines Regulations 1984, Medicines Amendment Regulations 2011* and *Medicines Amendment Act 2013* provide the legal framework under which blood components and fractionated products may be manufactured and supplied as well as stipulating who may prescribe them. Under the regulations, medical practitioners, registered midwives and nurse practitioners all have prescribing rights for blood components and fractionated products in accordance with their regulated scopes of practice.

Both blood components and fractionated products are biologic material and, in the case of components containing blood cells, are living human tissues. They are prescription medicines intended for use by medical practitioners and midwives in the treatment of patients.

Blood transfusion therapy has had a central role in the advances and practice of modern medicine. As in other areas of clinical medicine, prescribers need to consider both the benefits and risks of blood transfusion. Professional judgement based on clinical evaluation determines selection of blood components and fractionated products, dosage, rate of administration and sometimes other decisions in situations not covered in this general introduction to blood transfusion practice.

The presence of contaminants such as immunogenic cellular and protein elements, viable donor cells and infectious agents in blood cannot be totally avoided and indeed may cause undesirable side effects in some recipients. The information in this handbook cannot therefore be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described blood components or fractionated products when used for their intended purpose.

3.1 Clinical Governance

A quality management system is needed wherever transfusion therapy is practised. In this context 'quality' includes adequate documentation of both the transfusion process and its outcomes.

All institutions that transfuse blood components and fractionated products should develop and maintain local policies and procedures that reflect best national and international transfusion practice. Local policies and procedures should include guidance on:

- Informed consent.
- Requesting blood components and fractionated products.
- Collection of blood samples for pretransfusion compatibility testing.
- Collection of blood components and fractionated products from the hospital blood bank or other sites.
- Delivery of blood components and fractionated products to where the transfusion is to be given.
- Administration of blood components and fractionated products.
- Care and monitoring of patients receiving a transfusion.
- Documentation of transfusion.
- Management and reporting of adverse events.
- Staff responsibilities and the training required for these procedures.

3.2 Prescribing Blood Components and Fractionated Products

Prescribing blood components and fractionated products is normally the responsibility of a registered medical practitioner. Registered midwives and nurse practitioners have limited prescribing rights as defined by the *Medicines Regulations 1984* and *Medicines Amendment Regulations 2011*. For example, registered midwives are able to prescribe prescription medicines but only in the course of antenatal, intrapartum and postnatal care.

Decisions to transfuse should, taking individual patient needs into account, be based on international and regional guidelines such as the Australian National Blood Authority *Patient Blood Management Guidelines*.

It is the responsibility of the prescribing practitioner to ensure that transfusion therapy is given only when clearly indicated and that the patient is appropriately monitored during the transfusion procedure.

The following questions should be taken into consideration when deciding to transfuse:

- What improvement in the patient's condition am I aiming to achieve?
- Can I minimise blood loss to reduce the patient's need for transfusion?
- Are there any other treatments I should give before making the decision to transfuse?
- What are the specific indications for transfusing this patient?
- Do the benefits of transfusion outweigh the risks to this particular patient?
- Has the patient been given a clear explanation of the potential risks and benefits of blood transfusion therapy in his or her particular case?

Once the decision to transfuse has been made it is also important to consider the following:

- Have I recorded my decision to transfuse and the reasons for transfusion on the patient's chart and completed any documentation used in the ordering or administration of blood components or fractionated products?
- Will a trained person monitor this patient and respond immediately if any acute transfusion reactions occur?
- Has crossmatching and other relevant testing been carried out?

Prescribing Unapproved Pharmaceuticals

Practitioners should, where possible, prescribe pharmaceuticals that are approved under the Medicines Act 1981. If Practitioners are planning on prescribing an unapproved pharmaceutical or a pharmaceutical for an indication for which it is not approved, Practitioners should:

a) be aware of and comply with their obligations under Section 29 of the Medicines Act 1981 and otherwise under that Act and the Medicines Regulations 1984;

b) be aware of and comply with their obligations under the Health and Disability Commissioner's Code of Consumer Rights, including the requirement to obtain informed consent from the patient; and

c) exercise their own skill, judgement, expertise and discretion, and make their own prescribing decisions with respect to the use of an unapproved pharmaceutical or a pharmaceutical for an indication for which it is not approved.

Where medicines, supplied under Section 29 of the Medicines Act, are used for emergency situations, the required patient details may be retrospectively provided to the supplier.

3.3 Informed Consent to Receive a Blood Transfusion

Informed consent for transfusion is a requirement of the *Code of Health and Disability Services Consumers' Rights* (a regulation under the *Health and Disability Commissioner Act 1994*). This requires that patients be provided with information and an explanation of the purpose for which blood components and fractionated products are being prescribed and that they consent to transfusion.

Patients or their relatives may be worried about the risks of transfusion. Although most patients will be prepared to give consent for a transfusion after receiving appropriate information, some will seek and require quite detailed reasons for the transfusion, information on the risks involved and the alternatives available (such as autologous transfusion).

Some patients may refuse transfusion for personal or religious reasons, for example members of the Jehovah's Witnesses faith. Some of these patients may be prepared to accept fractionated products or other alternatives.

The seeking of informed consent, together with the reasons for the transfusion, should be recorded in the clinical record of the patient.

NZBS provides a range of leaflets to support the process of gaining informed consent. Copies of these should be available at all sites where blood may be transfused and can also be obtained from NZBS Transfusion Nurse Specialists or the hospital blood bank. This information is also available on the NZBS website (www.nzblood.co.nz).

3.4 Requesting Blood Components and Fractionated Products

The NZBS *Request for Blood Components and Products* form is used in most New Zealand hospitals and follows a prescription written in the patient clinical record. Blood components and fractionated products are normally obtained from the hospital blood bank and local hospital policies will determine which staff can place orders. It should be noted that the form used to request blood components and fractionated products is not a prescription.

The request form must:

- Correctly identify the patient.
- Provide details of any previous transfusion or obstetric history.
- Indicate the quantity of the blood component or fractionated product required, when it is required and where it should be sent to.

Full and accurate completion of the request form is essential for:

- Ensuring that the right quantity and type of blood component or fractionated product is made available to the right patient, at the right time, and in the right place.

- Minimising the risk of patient identification errors.
- Alerting the blood bank to the possibility of antibodies, based on a history of previous transfusions or pregnancy, in which case suitably matched blood may be required.

Patients who, at the time of admission, cannot be reliably identified must be given an identity band with a unique number. This number must be used to identify this patient until full and correct details are available and are properly communicated to the blood bank.

3.5 Blood Stock Management: The Maximum Blood Order Schedule

The maximum blood order schedule (MBOS) is one way a blood bank manages blood stock. A typical MBOS lists surgical and other interventional procedures along with the number of red cell units normally required in preparedness for transfusion in association with these procedures. The number of units is determined by analysis of historical blood usage figures. Many laboratories formulate a MBOS based on local surgical experience, while others adopt a generic schedule. An example of such a schedule is available in the 2016 Australian and New Zealand Society of Blood Transfusion (ANZSBT) *Guidelines for Transfusion, Pre and Postnatal Immunohaematology Testing (www.anzsbt.org.au)*.

The goal of the MBOS is to promote efficient use of red cells. It provides guidance to (junior) medical staff on the number of units of red cells likely to be required for various surgical procedures and is also a valuable guide for the blood bank, particularly those which routinely perform serological crossmatching (generally smaller facilities). For procedures where red cells are seldom required, the MBOS will simply recommend that no units should be crossmatched and a group and screen performed.

If more red cells are ordered for a patient than required or they are held crossmatched unnecessarily, then these units may be unavailable for other patients and there is a chance that the red cells will expire before being used. The clinician therefore needs to have a valid rationale to order more units than is mandated by the MBOS.

If the patient has a positive antibody screen or special transfusion requirements the blood bank may adjust the number of red cells crossmatched (from what is specified in the MBOS) to avoid potential problems should transfusion be required.

Together, the MBOS, regular monitoring of crossmatch-to-transfusion (C:T) ratios for individual surgical procedures and adoption of a 'group and screen' policy are all helpful in ensuring maximum use of the available stock of red cell components.

3.6 Collecting Blood Samples for Pretransfusion Testing

Correct identification of the patient before collecting the pretransfusion sample is vital in avoiding 'wrong blood in tube' (WBIT) episodes. Only when the patient's identity is positively confirmed can the request form be completed, blood sample taken and sample tube labelled.

Sample collection must be performed in accordance with hospital policy (or the laboratory manual) and observe the following principles:

- At the time of taking the sample ask the patient (if conscious or rational) to state their given name(s), family name and date of birth.

- Check this information against the patient's identification bracelet and details on the request form to make sure that the details are identical.
- Collect the blood sample into the correct sample tube.
- Hand label the sample* with the following information:
    - Patient's family name
    - Patient's given name(s)
    - Patient's NHI number
    - Patient's date of birth
    - Signature or initials of the collector
    - Date and time sample collected

**Please note: The information on the request form will be checked against that on the sample tube and both must be identical. NZBS Blood Bank does not accept pretransfusion samples labelled with pre-printed labels.*

- Sample tubes must be hand labelled in the presence of the patient, at the time the blood is collected, by the person who obtained the sample:
    - Sample labelling must never be delegated to a third party.
    - Sample tubes must not be prelabelled before the sample is obtained because of the risk of bleeding the patient's blood into the wrong tubes.
    - Sample tubes must never be labelled away from the patient's presence because of the risk of labelling the sample tube and/or request form with another patient's details.
- In the case of an unconscious (or irrational) patient, alternative identification procedures may be necessary, for example verification by the next of kin, as well as checking the identification wristband.
- The sample acceptance criteria used by NZBS are based on ANZSBT *Guidelines for Transfusion, Pre and Postnatal Immunohaematology Testing*. Blood Bank staff are not authorised to accept samples which do not meet labelling requirements. Where necessary these will be rejected and new samples requested. Where a dispute arises in relation to a sample, the final decision on suitability for testing will lie with an NZBS Transfusion Medicine Specialist/Medical Officer.

3.7 Pretransfusion Testing

Using the pretransfusion blood sample taken from the patient, the blood bank will perform a 'group and screen' (sometimes also referred to as 'group and hold', 'group and save' or 'type and screen'). A 'group and screen' consists of the following procedures:

- ABO and RhD group.
- Antibody screen.
- Checking for previous or duplicate records for the patient and, when these are available, comparing current results with historical findings.

If red cells are subsequently required the blood bank will select appropriate donor units and perform a final compatibility check.

Various approaches exist for compatibility testing. This may involve either a serological crossmatch of the patient's plasma versus donor red cells or, in some hospitals, an electronic crossmatch, where the blood bank computer performs the last compatibility check. Once pretransfusion testing is completed blood can be issued to the ward or operating theatre.

3.8 Patients with a Positive Antibody Screen

If the patient is found to have a clinically significant red cell antibody during antibody screening, blood that does not have the corresponding antigen will be needed for transfusion. The relevant antigen-negative donor blood is selected and crossmatched against the patient's plasma. This can be a time-consuming process but is necessary if the patient is to receive compatible blood.

If there is insufficient time for full identification of the antibody or to obtain antigen-negative units, transfusion of (potentially) incompatible blood may be recommended. In these circumstances a NZBS Transfusion Medicine Specialist/Medical Officer will contact the clinical staff to discuss the comparative risks of delaying transfusion versus transfusing potentially incompatible blood.

3.9 Sample Validity ('72-Hour Rule')

The sample validity period, during which time a pretransfusion sample may be held and used to provide crossmatched blood, depends on the patient's transfusion or obstetric history.

Red cell antibodies can rapidly appear in response to stimulation by transfused red cells or as a result of pregnancy. Consequently, if in the three months preceding collection of the pretransfusion sample the patient has been transfused with red cells (or platelets), is currently pregnant (or has been), the sample will have a validity of 72 hours. This is known as the '72-hour rule'.

Longer expiry times are applied if the patient is known not to have a history of transfusion or pregnancy.

Table 3.1: Sample Validity Criteria

Patient History	Sample Expiry
Patient transfused or pregnant in previous 3 months (or history not known) or has history of clinically significant red cell antibodies	72 hours
Patient neither transfused nor pregnant in last 3 months and no history of clinically significant red cell antibodies	7 days
Preadmission sample and patient neither transfused nor pregnant in last 3 months and no history of clinically significant red cell antibodies	21 days

For preadmission samples, the requirement for 21-day expiry must be clearly noted on the request form along with the proposed date of surgery or procedure. Details of

whether or not the patient has a transfusion and/or obstetric history must also be given. Failure to provide this information will result in the sample being given a 72-hour expiry.

Once a transfusion episode has commenced the pretransfusion sample, and any associated results, will cease to be valid either at the original expiry of the sample, or 72 hours from when transfusion of the first unit commenced, whichever eventuates first.

If further transfusions are necessary a new sample will be required. Each new sample will have an expiry of 72 hours until a gap of three months between transfusions (or since pregnancy) has occurred.

Extensions to sample expiry times may be possible at the discretion of a NZBS Transfusion Medicine Specialist/Medical Officer. If you have any queries regarding sample validity contact the local blood bank for advice.

3.10 Provision of Red Cells in an Emergency

The nature and availability of red cells in an emergency situation depends on the urgency with which blood is required and the extent of pretransfusion testing that can be completed within the appropriate response time.

Table 3.2: Availability of Red Cell Units

Tests Completed	Units Selected	Availability
None	Emergency O RhD negative blood (uncrossmatched)	Immediate
Limited testing (ABO/RhD type only)	ABO/RhD group specific blood (uncrossmatched)	15 minutes
All testing (Full 'Group and Screen')	ABO/RhD group specific and compatible blood	45 minutes[1]

[1]*Assuming a negative antibody screen.*

If red cells are required immediately and before pretransfusion testing can be completed, the use of emergency group O RhD negative units should be considered.

As stocks of group O RhD negative red cells are limited, a timely switch to red cells of the patient's group is recommended. It should be noted that whilst emergency red cells are group O RhD negative, complete serological compatibility cannot be guaranteed as the patient may have a red cell antibody.

Where time allows a confirmed ABO/RhD type to be obtained, uncrossmatched blood of the same group as the patient will be provided. On completion of a full group and screen, and as long as the patient does not have a red cell antibody, group-specific and crossmatch-compatible blood is available.

If the patient has a red cell antibody, finding compatible blood may be delayed while the antibody is identified and antigen-negative red cells selected and crossmatched. Under these circumstances, if blood is still urgently required, incompatible red cells may have to be used. However the decision to transfuse should be made in discussion with a NZBS Transfusion Medicine Specialist/Medical Officer.

3.11 Removal from Storage and Time Limits for Infusion

It is important that blood components are transfused as soon as possible following receipt from the blood bank so that the required efficacy is achieved and unwanted bacterial proliferation is avoided.

Red Cells

- Transfusion should begin as soon as possible following removal of the unit from a monitored blood refrigerator or validated transport container.
- Transfusion of red cells should be completed within four hours of removal from a monitored blood refrigerator or validated transport container.
- Where a short delay occurs (or is anticipated) before starting a transfusion, red cells may be held at ambient temperature provided the transfusion can be completed within four hours of the blood being issued from a monitored blood refrigerator.
- If transfusion cannot be started within 30 minutes, the unit should normally be returned without delay to a monitored blood refrigerator for controlled storage.
- Red cells must be stored in a refrigerator that is manufactured and validated for the purpose of storing red cell components and has permanent temperature monitoring. They must not be stored in a ward refrigerator, domestic refrigerator or refrigerator intended for vaccine storage.
- If a unit of red cells has been out of controlled storage for more than 30 minutes and there is no prospect of imminent transfusion it should be returned to the blood bank for disposal. The unit cannot be accepted back into blood bank stock.

Platelets

- Transfusion should begin as soon as the platelets are received from the blood bank.
- Transfusion of platelets should be completed within one hour of issue from the blood bank.
- If not used immediately, platelets must be returned to the blood bank and controlled storage within one hour of issue.
- Platelets are stored (usually in the blood bank) at room temperature 20 - 24ºC with constant agitation.
- Platelets must not be transported or stored in a refrigerator or chilled transport container.
- If platelets have been out of controlled storage for more than one hour, acceptance back into blood bank stock is conditional on evidence of suitable storage.

Fresh Frozen Plasma

- Transfusion should begin as soon as the thawed plasma is received from the blood bank.

- Transfusion of plasma should be completed within four hours of thawing.
- If the plasma is not going to be used or transfusion cannot be started within 30 minutes it must be returned to the blood bank immediately. If returned within 30 minutes of issue then it can be stored for up to 24 hours at 2 - 6°C during which time it may be reissued to the same or a different patient. If not used within 24 hours, the returned plasma expires.
- If the plasma has been out of controlled storage for more than 30 minutes it cannot be accepted back into blood bank stock.
- Once thawed, plasma must not be refrozen.

Cryoprecipitate

- Transfusion should be started as soon as the thawed cryoprecipitate is received from the blood bank.
- Transfusion of cryoprecipitate should be completed within four hours of thawing.
- If the cryoprecipitate is not going to be used or transfusion cannot be started within 30 minutes it must be returned to the blood bank immediately, where it can then be stored for up to 4 hours at ambient (room) temperature during which time it may be reissued to the same or a different patient. If not used within 4 hours, the returned cryoprecipitate expires.
- If the cryoprecipitate has been out of controlled storage for more than 30 minutes it cannot be accepted back into blood bank stock.
- Once thawed, cryoprecipitate must not be stored in the refrigerator nor should it be refrozen.

3.12 Administration and Observation of Transfusion

All transfusions should be performed and monitored in accordance with relevant hospital policies and guidelines. The 2011 ANZSBT & Royal College of Nursing of Australasia (RCNA) *Guidelines for the Administration of Blood Products* may provide supplementary guidance.

- Before transfusion always check the identity of the recipient, that the correct blood component or fractionated product has been obtained, and that it has not expired.
- Transfuse only if the patient can be observed and monitored by trained staff.

3.13 Rate of Infusion and Precautions

The appropriate rate of transfusion may vary significantly according to the clinical circumstances:

- Patients who are actively bleeding and/or are in hypovolaemic shock will require blood components to be transfused as rapidly as possible.
- Patients with cardiac failure are at risk of circulatory overload and it will be necessary to transfuse slowly and cautiously with frequent monitoring. Concomitant use of diuretics should also be considered.

- For fractionated products, the package insert provides guidance on specific protocols regarding the administration of the product.

Advice must be sought from the doctor responsible for the patient if there is any doubt about the way or how rapidly a blood component or fractionated product should be transfused.

3.14 Infusion Pumps

Approved infusion pump devices may be used to assist transfusion. Check the manufacturer's instructions before using a pump to transfuse red cells or platelet concentrates.

3.15 Blood Administration Sets and Filters

All blood components, including platelets and plasma components, must be transfused through a standard sterile blood administration set incorporating a suitable integral screen filter (normally 170 - 200 micron pore size). The filter is designed to trap cellular aggregates, cellular debris and clots potentially harmful to the patient. Microaggregate filters are not indicated.

In New Zealand, bedside leucocyte-depleting filters are not required as all blood components undergo prestorage leucodepletion during processing.

Blood administration sets must be used in accordance with the manufacturer's instructions and hospital policy. The following provides a general guide to the use of blood administration sets.

Administration sets may be primed with 0.9% sodium chloride ('normal saline') or the component being transfused. Compound sodium lactate (Hartmann's or Ringer-Lactate), Plasmalyte in 5% glucose and dextrose solutions must not be used.

- Because of the risk of bacterial proliferation, each administration set should only be used for up to 12 hours of transfusion or until the filter becomes clogged.
- One administration set may be used for transfusing up to 4 red cell units provided the flow rate remains adequate.
- In a massive transfusion setting, 8 - 10 units may be transfused before the set is changed, provided the flow rate remains adequate without evidence of filter clogging and the set is changed at least every 12 hours.
- Transfuse platelets through a fresh administration set. Transfusing platelets through an administration set previously used for red cells is not recommended.
- Administration sets should be flushed with normal saline before and after platelet transfusion if the same set is to be subsequently used for the transfusion of red cells or FFP.
- If there is doubt about the appropriateness of filters or their use, contact the blood bank, NZBS Transfusion Medicine Specialist/Medical Officer or NZBS Transfusion Nurse Specialist.

3.16 Warming of Blood Products

If warming is clinically indicated, use only an appropriate and approved system. The warming system must be equipped with a visible thermometer and an audible alarm

as malfunction can result in red cell haemolysis. Blood components must not be warmed above 41°C.

Clinical indications for the use of blood warmers:

- Large volumes transfused rapidly, for example > 50 mL/kg/hr in adults and > 15 mL/kg/hr in children.
- Neonatal exchange transfusions.
- Trauma situations in which core-rewarming measures are indicated.
- Patient rewarming phase during cardiopulmonary bypass surgical procedures.
- Transfusions for patients with clinically significant cold reactive antibodies ('cold agglutinins'), i.e., symptomatic cold haemagglutinin disease (CHAD).

Blood warmers are not indicated for routine transfusion of blood. Blood warming is seldom necessary or desirable for elective transfusion at conventional rates, even for patients with asymptomatic cold agglutinins.

3.17 Compatible Intravenous Solutions

- No drugs or additives, other than 0.9 % sodium chloride ('normal saline') intravenous infusion, are recommended to be mixed with red cells before or during transfusion.
- Do not use Plasmalyte 148 in 5% glucose or 5% dextrose solutions as these may induce haemolysis.
- Do not use Gelofusal® or compound sodium lactate solutions, e.g., Hartmann's or Ringer-Lactate, as these contain calcium and may induce clot formation in the blood component bag and/or administration set.

3.18 Adding Medication to Blood Components

Do not add medication to any blood component unless specifically approved by hospital policy. If there is doubt, contact a NZBS Transfusion Medicine Specialist/ Medical Officer or NZBS Transfusion Nurse Specialist for advice.

3.19 Documentation of Transfusion

Full and accurate documentation of every step of the transfusion process is vital. Not only is this important for effective investigation of serious transfusion-related adverse events such as transfusion-transmitted infections, it also facilitates auditing of all aspects of the transfusion process and is essential in ensuring vein-to-vein traceability of blood components and fractionated products. Table 3.1 summarises the requirements of documentation associated with transfusion.

The majority of transfusion errors are administrative or clerical. Common errors include:

- Failure to identify the patient properly when taking pretransfusion blood samples.
- Failure to correctly label the patient's pretransfusion blood sample at the bedside.
- Transcription errors in the laboratory.
- Failure to clearly identify the intended recipient prior to transfusion.

Table 3.1: Documentation of Transfusion

Requirement	Action
Prescription	Constitutes the legal instruction (from the medical practitioner, registered midwife or nurse practitioner) to administer blood components and fractionated products and must be placed in the patient's medical record. The prescription must be legibly written, be dated and include the prescriber's name and signature. The prescription must specify: ■ blood component / fractionated product to be administered ■ quantity ■ route of administration ■ rate of infusion ■ any special requirements
Justification for transfusion	Document the transfusion decision (based on recognised clinical practice guidelines) in the patient's medical record.
Informed consent	Must be obtained from the patient and documented (in the medical record) except in emergencies where appropriate communication is not possible.
Patient's medical record	■ Prescription of the blood component / fractionated product. ■ Evidence of informed consent. ■ The compatibility label (or other labelling with patient and blood component / fractionated product details), which should be removed after completing the transfusion and attached to the transfusion record. ■ Evidence of the bedside checking procedure. ■ Vital signs during the transfusion. ■ The indication for the use of the blood component / fractionated product. ■ The date of transfusion and the time transfusion started and finished. ■ The number and type of blood components / fractionated products (including the donation / batch numbers). ■ Whether or not the desired effect was achieved. ■ A record of the occurrence and management of any transfusion-related adverse event.
Retention of records	▪ In accordance with statutory requirements, namely the *Health (Retention of Health Information) Regulations 1996*, amended by section 111(2) of the *New Zealand Public Health and Disability Act 2000*, records of transfusion must be retained for a minimum of 10 years.

3.20 Local Systems and Procedures

It is important to be familiar with local hospital policies in regard to transfusion practices. Visiting the blood bank may also be useful in gaining an appreciation of the local system for obtaining blood components and fractionated products and meeting the clinical, nursing and scientific staff who provide transfusion services. There is no substitute for talking with people who are working to help you care for your patients.

3.21 Reporting of Adverse Events

If the patient experiences a reaction as a result of transfusion, has received an inappropriate transfusion, received a blood component or fractionated product intended for another patient or where special requirements (for example, irradiated components) are not met, these are regarded as transfusion-related adverse events.

Transfusion reactions can cause a patient's condition to rapidly deteriorate with respiratory distress, hypotension and collapse. Any signs or symptoms suggesting a reaction should not be ignored, but rather assessed immediately.

Any untoward reaction or event occurring during or after the transfusion must be reported immediately to the blood bank and serious events (life-threatening or with a risk of major morbidity) should also be reported to a NZBS Transfusion Medicine Specialist/Medical Officer or NZBS Transfusion Nurse Specialist.

Adverse effects of transfusion and the reporting of events is covered in detail in Chapter 7: *Adverse Effects of Transfusion*.

BLOOD COMPONENTS

Blood components are made from blood donations and may involve one or more simple physical processing steps to separate the constituents of blood.

The entries in this section are summaries of information presented in the NZBS *Clinical Compendium*, which is a source of reference for the clinical activities of NZBS. The compendium provides a framework for clinicians on the nature, composition and clinical use of the components and contains detailed individual component descriptions, quality specifications, storage requirements, dosage and administration guidelines, precautions and contraindications to use, along with information on potential adverse reactions.

The compendium is a controlled document. Regular updates of the individual documents it contains are produced and disseminated to holders. Documents within the compendium can also be found in the *Clinical Information* section of the NZBS website (www.nzblood.co.nz).

4.1 ABO Blood Groups and Antibodies

ABO is the most important of the human blood group systems. There are four different ABO blood groups, determined by whether or not an individual's red cells carry one, both or neither of the A and B antigens.

Normal healthy individuals, from early childhood, make red cell antibodies against the A or B antigens that are not expressed on their own cells. These naturally occurring antibodies are mainly IgM immunoglobulins and can rapidly bind to and destroy red cells carrying the corresponding antigen.

If ABO incompatible red cells are transfused, intravascular haemolysis of these red cells can occur. An ABO incompatible transfusion reaction may result in overwhelming disruption of haemostatic equilibrium and complement activation, resulting in shock and renal failure. This can be fatal, even after transfusion of a small volume of incompatible blood.

Table 4.1: ABO Blood Groups and Antibodies

Patient's ABO Blood Group	Red Cell ABO Antigens	Plasma ABO Antibodies
A	A	Anti-B
B	B	Anti-A
AB	A and B	None
O	None	Anti-A and Anti-B

4.2 Avoiding ABO Incompatible Transfusions

Safe transfusion depends on avoiding ABO incompatibility between the patient and transfused blood components, either between donor red cells and the patient's ABO antibodies or conversely donor plasma ABO antibodies and the patient's red cells.

Red cells of the same ABO group as the patient, i.e., ABO identical, should normally be selected. Only when these are unavailable should alternative ABO compatible red cells be selected (see Table 4.9: *ABO Compatibility for Red Cell Components*). In life-threatening situations, where a confirmed blood group for the patient is not available, group O red cells should be given. Group O donations identified as emergency units have low levels of anti-A and anti-B to avoid potential sensitisation and destruction of the patient's red cells (in non-group O recipients).

Platelet concentrates should ideally be ABO identical or alternatively ABO compatible with the patient's red cells (see Table 4.11: *ABO Compatibility for Platelet Components*). This is however not a strict requirement and, due to logistics or supply issues, platelets with a different ABO group may be supplied in clinically urgent situations following consultation with an NZBS Transfusion Medicine Specialist. Additional pretransfusion testing is not required for platelets.

Fresh frozen plasma and cryoprecipitate should be ABO compatible with the patient's red cells (see Table 4.14: *ABO Compatibility of Fresh Frozen Plasma and Cryoprecipitate*). Additional pretransfusion testing is not required for FFP and cryoprecipitate.

4.3 RhD Antigen

After ABO, the RhD antigen ranks next in importance for transfusion. Patients and blood donors are routinely typed for the RhD antigen and on the basis of its presence or absence are called either RhD positive or RhD negative.

Antibodies to the RhD antigen only occur as a result of transfusion or pregnancy in individuals who are RhD negative. The RhD antigen is highly immunogenic and a RhD negative person only needs to be exposed to a small volume of RhD positive red cells for immunisation to occur, stimulating production of anti-D.

Red cell and platelet transfusions are normally of the same RhD type as the patient. RhD negative components may be given to RhD positive recipients without any risk of immunisation.

In life-threatening situations or where RhD identical components are not readily available, it may be necessary to transfuse RhD negative recipients with red cells or platelets from a RhD positive donor. In these circumstances the blood bank will provide guidance. It is essential that the treating clinician is informed and the appropriateness of administration of prophylactic anti-D immunoglobulin considered. In the case of RhD negative females with child-bearing potential, transfusion of RhD positive red cells must only be considered following discussion with a NZBS Transfusion Medicine Specialist.

If supplies of RhD negative red cells are low, RhD positive red cells may be provided by the blood bank for RhD negative males and for females beyond reproductive years.

Residual red cells in RhD positive platelet components may sensitise RhD negative patients to form anti-D. When platelet components from a RhD positive donor are transfused into a RhD negative recipient, in particular females of childbearing age or female children, prophylactic anti-D immunoglobulin must be considered.

Section 5.4.7: *Rh(D) Immunoglobulin-VF* contains guidelines on dosing of prophylactic anti-D following transfusion of RhD positive blood components.

4.4 Other Blood Group Systems

Red cells possess many different antigens. Transfusion or pregnancy can stimulate antibody production where a person is exposed to a red cell antigen that they lack. Some of these antibodies can cause transfusion reactions or haemolytic disease of the fetus and newborn (HDFN). Before transfusion and during pregnancy it is important to detect clinically significant antibodies in a patient so that compatible red cells can be provided and appropriate advice given during pregnancy.

4.5 Cytomegalovirus (CMV)

Prior to the introduction of routine prestorage leucodepletion, CMV was readily transmitted by transfusion. CMV can cause severe and even fatal disease in certain immunocompromised patients not previously exposed to the virus. Such patients should receive CMV 'safer' blood components, i.e., components that have undergone prestorage leucodepletion or found to be CMV-antibody negative.

The use of either prestorage leucodepletion or selection of CMV-antibody negative blood components, obtained from a regular donor who has donated at least once in the preceding 6 months, significantly reduces the risk of CMV transmission and CMV disease in susceptible recipients. However, neither method alone or in combination can completely avoid transmission from the occasional donor with CMV viraemia in the "window" period prior to the development of antibodies following acute infection or when reactivation of latent infection occurs.

Since all blood components in New Zealand are leucodepleted, NZBS has adopted a policy that restricts the requirement for the use of blood components from CMV-antibody negative donors to:

- Intrauterine and neonatal transfusion.
- A selected individual patient following discussion and agreement between the treating clinician and a NZBS Transfusion Medicine Specialist.

4.6 Irradiation

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare but usually fatal complication of transfusion. The risk associated with an individual transfusion depends on the number and viability of contaminating lymphocytes, the susceptibility of the patient's immune system to donor lymphocyte engraftment (primarily related to the degree of T-cell immunosuppression) and the degree of immunological incompatibility between donor and patient.

Cellular components, with the exception of thawed cryopreserved haematopoietic progenitor cells (HPC) intended for transplantation, must be irradiated to prevent TA-GVHD in at-risk patients. Frozen plasma components and fractionated products do not require irradiation.

The following tables summarise the clinical indications for blood component irradiation recommended by the 2011 Australian & New Zealand Society of Blood Transfusion (ANZSBT) *Guidelines for Prevention of Transfusion-Associated Graft-Versus-Host Disease* and the 2010 BCSH *Guidelines on the Use of Irradiated Blood Components.*

Table 4.2: Definite Clinical Indications for Use of Irradiated Blood Components

Directed donations (from blood relatives)
HLA selected/matched platelet transfusions
Granulocyte transfusions
Intrauterine and all subsequent neonatal exchange transfusions
Congenital cellular immunodeficiency disorders
Allogeneic and autologous haematopoietic stem cell transplantation (HSCT)
Hodgkin lymphoma
Purine nucleoside analogues and the related agent bendamustine[1] for malignant or non-malignant disorders
Alemtuzumab for malignant or non-malignant disorders

[1]Bendamustine combines the alkylating properties of mechlorethamine and the purine antimetabolite properties of benzimidazole.

Table 4.3: Possible Clinical Indications for Use of Irradiated Blood Components

Premature infants and infants weighing less than 1300g
All newborn infants
Acute leukaemia
Non-Hodgkin lymphoma
Patients with B-cell malignancy who receive non-nucleoside analogue containing chemotherapy and/or radiotherapy leading to lymphopenia < 0.5 $x10^9$/L
T-cell malignancy
Patients receiving high doses of chemotherapy and/or irradiation sufficient to cause lymphopenia < 0.5 $x10^9$/L
Patients receiving long term or high dose steroids as therapy for malignant disorders
Aplastic anaemia receiving immunosuppressive therapy
Massive transfusion for trauma

Table 4.4: No Clinical Indication for Use of Irradiated Blood Components

HIV/AIDS (where none of the above listed indications apply)
Congenital humoral deficiency disorders
Solid organ transplantation

Table 4.5: Recommendations on Duration of Use of Irradiated Blood Components

Autologous HSCT
From 7 days prior to initiation of conditioning and until at least three months post-autograft, or six months if total body irradiation (TBI) is used.
Allogeneic HSCT
From initiation of conditioning and continued while post-transplant GVHD prophylaxis is given, for a minimum of 6-12 months or until lymphocytes > $1x10^9$/L. Patients with active chronic post-transplant GVHD should continue to receive irradiated components.
Aplastic anaemia treated with ATG immunosuppression
From initiation of therapy. No clear recommendations as to duration, but possibly until lymphocytes > $1x10^9$/L.
Hodgkin lymphoma
At all stages of disease and therapy. Continued indefinitely.
Purine nucleoside analogues[1] **and bendamustine**
From initiation of therapy. Continued indefinitely.
Alemtuzumab
From initiation of therapy. No clear recommendations as to duration, but at least 12 months from last dose.

[1]*Fludarabine, deoxycoformycin (pentostatin), chlorodeoxyadenosine (cladribine) and clofarabine.*

4.7 Blood Components Available from NZBS

Table 4.5: Red Cell Components Available from NZBS

Component	Description	Typical Mean Volume (mL)	Haematocrit (%)	Expiry	Indication for Use / Comments
Red Cells Resuspended	Red cells prepared from whole blood donation with plasma removed and replaced by additive solution	298	0.50 - 0.70	35 days (2 - 6°C)	Used to increase tissue oxygenation when critically reduced by blood loss or anaemia Virtually all red cells are issued in this form
Red Cells Resuspended Neonatal	As for Red Cells Resuspended Split into equal volume aliquots suitable for neonatal use CMV negative Does not contain high titres of anti-A or anti-B	70	0.50 - 0.70	35 days (2 - 6°C)	As for Red Cells Resuspended Not suitable for large volume transfusion or exchange transfusion Potassium content, when fresh is 2.0 mmol/L, and at expiry 15-35 mmol/L (may be raised if component is irradiated)
Red Cells For IUT	Fresh whole blood donation (< 5 days old) collected into CPD and prepared to specified haematocrit by removal of plasma CMV negative Does not contain high titres of anti-A or anti-B (also negative for other red cell antibodies)	206	0.75 - 0.90	5 days (2 – 6°C) 24 hrs once irradiated	Must be irradiated

Table 4.5: Red Cell Components Available from NZBS continued

Component	Description	Typical Mean Volume (mL)	Haematocrit (%)	Expiry	Indication for Use / Comments
Whole Blood Plasma Reduced	Whole blood donation prepared to specified haematocrit by removal of plasma CMV negative Does not contain high titres of anti-A or anti-B	360	0.45 - 0.55	5 days (2 - 6°C) for neonatal exchange transfusion 28 days (2 - 6°C) for other uses	Product of choice for neonatal exchange transfusion Exchange transfusion for clinically significant anaemia with or without hyperbilirubinaemia due to haemolytic disease of the fetus and newborn (HDFN) or other causes Should be irradiated if for neonatal exchange transfusion, although a strict requirement only where the infant has previously received IUT Can also be used for large volume transfusions in neonates and for adult transfusions
Red Cells Washed	Red cell donation washed leaving total residual plasma protein < 0.5 g per unit Resuspended in additive solution	328	0.40 - 0.70	24 hrs (2 - 6°C)	Used in response to persistent allergic reactions, for some IgA deficient patients with anti-IgA, and when anti-T depleted red cells are indicated
Whole Blood	Whole blood donation collected into CPD or CPD-A1 Autologous and directed donations are issued in this form	493	0.30 - 0.50	CPD-A1: 35 days (2 - 6°C) CPD: 28 days (2 - 6°C)	Restricted access to this product Used to increase tissue oxygenation when critically reduced by blood loss or anaemia Primary cardiac bypass circuit in paediatric bypass surgery

Table 4.5: Red Cell Components Available from NZBS continued

Component	Description	Typical Mean Volume (mL)	Haematocrit (%)	Expiry	Indication for Use / Comments
Whole Blood Autologous	Specifications and storage requirements the same as Whole Blood				Unit is labelled and stored for transfusion to the patient from whom it was collected. If not transfused to the identified patient, unit is discarded at the designated expiry of the component

Table: 4.6: Platelet Components Available from NZBS

Component	Description	Typical Mean Volume (mL)	Platelets (x 10^9)	Expiry	Indication for Use / Comments
Platelet Pool	Platelet pool derived from the buffy coats of four whole blood donations Resuspended in platelet additive solution (PAS)	307	■240	7 days (20 - 24°C with constant agitation) If irradiated original expiry applies	Replacement where deficiency of platelets or platelet dysfunction is causing or may cause a significant haemostatic problem One unit provides an adequate clinical response in most adult patients With increased platelet consumption or destruction the dose is determined by the clinical response
Platelets Apheresis	Platelets from a single apheresis donation Resuspended in platelet additive solution (PAS)	228	≥240	As for Platelet Pool	As for Platelet Pool Also to provide compatible platelets for patients with HPA or HLA antibodies and refractory to random donor platelets

Table: 4.6: Platelet Components Available from NZBS continued

Component	Description	Typical Mean Volume (mL)	Platelets (x 10^9)	Expiry	Indication for Use / Comments
Platelets Neonatal Apheresis	Single apheresis donation suspended in plasma Divided into equal volume aliquots suitable for neonates CMV negative	45	≥40	As for Platelet Pool	As for Platelet Pool
Platelets Apheresis Washed	Platelets from a single apheresis donation, washed with an approved platelet additive solution. Total residual plasma protein < 0.5 g per unit.	227	■≥240	Closed system: 24 hrs (20 - 24°C with constant agitation) Open system: 6 hrs (20 - 24°C with constant agitation)	May be indicated in patients who have recurrent severe allergic reactions to plasma-containing components and in some IgA deficient patients with anti-IgA antibodies

Table 4.7: Granulocyte Components Available from NZBS

Component	Description	Typical Mean Volume (mL)	Granulocytes (x 10^9)	Platelets (x 10^9)	Expiry	Indication for Use / Comments
Granulocyte Apheresis	Granulocytes (with some red cells and platelets) from a single apheresis donation CMV negative if indicated	Variable	≥10	≥ 200	24 hrs (20 - 24°C)	Supportive therapy for profound neutropenia <0.5 x 10^9/L, bone marrow hypoplasia and infection not responding to antibiotics within 48 hours, and where there is potential for recovery of marrow function Irradiate prior to use
Buffy Coat	Granulocytes (with some red cells and platelets) from single whole blood donation	50	≥ 1	≥ 50	As for Granulocyte Apheresis	Clinical indications as for apheresis granulocytes Multiple buffy coats ■ ≥10 will be required to achieve a standard adult therapeutic

Table 4.8: Frozen Plasma Components Available from NZBS

Component	Description	Typical Mean Volume (mL)	Factor VIIIc (IU/mL)	Mean Fibrinogen (g)	Expiry	Indication for Use/Comments
Plasma Fresh Frozen	Plasma collected using an apheresis procedure from a male donor (to reduce the risk of TRALI), rapidly frozen within 8 hours of collection to maintain labile coagulation factors	279	≥ 0.7		24 months (-25°C or below) 24 hrs post thawing (2 - 6°C) Do not refreeze	Replacement of coagulation factors and other plasma proteins when levels or activity are critically reduced
Plasma Fresh Frozen Neonatal	As for Plasma Fresh Frozen Split into equal volume aliquots suitable for neonates Does not contain high titres of anti-A or anti-B	60	≥ 0.7		As for Plasma Fresh Frozen	As for Plasma Fresh Frozen

Table 4.8: Frozen Plasma Components Available from NZBS continued

Component	Description	Typical Mean Volume (mL)	Factor VIIIc (IU/mL)	Mean Fibrinogen (g)	Expiry	Indication for Use/Comments
Plasma Cryodepleted Apheresis	Supernatant from apheresis cryoprecipitate frozen within 2 hours of collection Plasma Fresh Frozen depleted of fibrinogen, factor VIII, von Willebrand factor, factor XIII, and fibronectin	473			As for Plasma Fresh Frozen	Used for plasma exchanges particularly in the treatment of Thrombotic Thrombocytopenic Purpura (TTP)
Cryoprecipitate Apheresis - High Fibrinogen	Plasma collected using an apheresis procedure from a male donor (to reduce the risk of TRALI) Concentrated source of fibrinogen, factor VIII, von Willebrand factor, factor XIII, and fibronectin	98	≥ 1.5	1.2	24 months (-25°C or below) 4 hrs post thawing (stored at room temperature) Do not refreeze	Correct haemostatic defects associated with fibrinogen deficiency and dysfibrinogenaemia May be of clinical value for treating bleeding due to uraemia If specific concentrate therapy is inappropriate or unavailable can be used to treat von Willebrand disease, haemophilia A or factor XIII deficiency

4.8 Red Cell Components

ABO Compatibility

It is important that transfusion recipients receive red cell components compatible with their own ABO group. Incompatible transfusion can result in serious harm or death of the recipient.

It is best practice to transfuse donor red cells that are matched for the recipient. In some circumstances it may not be possible to transfuse the recipient with donor cells of the same group. The following table outlines alternative donor groups that may be given to a recipient if supplies of ABO identical red cells are not available or are in short supply.

Table 4.9: ABO Compatibility for Red Cell Components

Recipient Group	**Compatible Donor Groups** *(in order of preference)*
Unknown	Group O[§] cells Preferably RhD negative for premenopausal females The transfusion of group O cells is usually continued only until the patient's blood group is known
O	O
A	A or O
B	B or O
AB	AB or A or B or O[§]

[§]These group O components should test negative for 'high titre' anti-A and anti-B.

RhD Compatibility

Red cell and platelet transfusions are normally of the same RhD type as the patient. RhD negative components may be given to RhD positive recipients without any risk of immunisation.

In life-threatening situations it may be necessary to transfuse RhD negative recipients with RhD positive red cells. In these circumstances the blood bank will provide guidance. It is essential that the treating clinician is informed and the appropriateness of administration of prophylactic anti-D immunoglobulin considered.

If supplies of RhD negative red cells are low, RhD positive red cells may be provided by the blood bank for RhD negative males and for females beyond reproductive years.

In the case of RhD negative females with child-bearing potential, transfusion of RhD positive red cells must only be considered following discussion with a NZBS Transfusion Medicine Specialist.

Section 5.4.7: *Rh(D) Immunoglobulin-VF* contains guidelines on dosing of prophylactic anti-D following transfusion of RhD positive components.

Guidelines for Appropriate Use

In deciding whether or not to transfuse red blood cells, the haemoglobin level, although important, should not be the sole deciding factor. Patient factors, signs and symptoms

of hypoxia, ongoing blood loss, the degree of urgency required in correcting the anaemia and the risk of transfusion-related adverse effects should all be considered. The key issue is delivery of adequate amounts of oxygen to tissues. For a 70-80 kg patient, a transfusion of 4-5 mL/kg will increase the circulating haemoglobin by about 10 g/L.

Some specific factors to consider before deciding to transfuse:

- **Cardiopulmonary reserve**
  If cardiac or pulmonary function is not normal, it may be necessary to consider transfusing at a higher haemoglobin level.
- **Volume of blood loss**
  Clinical assessment should attempt to quantify the volume of blood loss before, during, and after surgery, to ensure maintenance of adequate blood volume.
- **Oxygen consumption**
  This may be affected by a number of factors including fever, anaesthesia, shivering and thyrotoxicosis. If oxygen consumption is increased it may be necessary to consider transfusing at a higher haemoglobin level.
- **Atherosclerotic disease**
  Critical arterial stenosis to major organs, particularly the heart, may modify indications for the use of red cells.

The Australian National Blood Authority *(NBA) Patient Blood Management Guidelines* and the 2012 British Committee for Standards in Haematology (BCSH) *Guidelines on the Management of Anaemia and Red Cell Transfusion in Adult Critically Ill Patients* provide the following recommendations for red cell component use in adults.

Table 4.10: Indications for Transfusion of Red Cells in Relation to Haemoglobin Level

Hb Level	Indication
< 70 g/L	Transfusion of red cells is usually indicated however a lower threshold may be acceptable in patients without symptoms and where specific therapy is available, e.g., cobalamin or iron deficiency anaemia.
< 80 g/L	Transfusion of red cells is likely to be appropriate in patients with acute coronary syndrome and the haemoglobin should be maintained > 80-90 g/L.
70 - 100 g/L	Transfusion of red cells is likely to be appropriate during surgery associated with major blood loss or with evidence of impaired tissue oxygen delivery.
> 90 g/L	Transfusion of red cells is not likely to be appropriate in the critically ill, in whom a restrictive transfusion policy is associated with reduced mortality. Exceptions may include patients with any of the following: sepsis together with evidence of impaired tissue oxygen delivery, subarachnoid haemorrhage, ischaemic stroke, and cerebral ischaemia complicating traumatic brain injury.
> 100 g/L	Transfusion of red cells is not likely to be appropriate unless there are specific indications.

Restrictive Red Cell Transfusion Policy

The decision to transfuse should take into account the risks, benefits and alternatives available, and should not be based on haemoglobin level alone. With this in mind, increasingly restrictive transfusion policies are being implemented in a variety of clinical settings.

Policies aim to safely provide the minimum amount of blood required for an individual patient through setting appropriate transfusion triggers and, where indicated, encouraging assessment of the patient's clinical status after transfusion of each single unit of red blood cells before determining that further transfusion is required. Restrictive policies are supported by evidence from a number of clinical areas of improved or equivalent clinical outcomes after minimising exposure to allogeneic blood.

One such policy, the 2014 Australian NBA Single Unit Transfusion Guide (available at http://www.blood.gov.au/single-unit-transfusion), has been designed for use in stable, normovolaemic adult patients, in an inpatient setting, who do not have clinically significant bleeding.

4.9 Platelet Components

ABO and RhD Compatibility

Transfused platelets should ideally be the same ABO and RhD type as the recipient although platelet stocks may not always permit this. Preferably platelet components that are ABO/RhD compatible but plasma incompatible should be selected for transfusion. This compromise is relatively free of adverse reactions although antibodies in the plasma may occasionally cause a haemolytic reaction or a transiently positive direct antiglobulin test (DAT).

Table 4.11: ABO Compatibility for Platelet Components#

Recipient Group	**Compatible Donor Groups** *(in order of preference)*
Unknown	Group O[§] or A platelets Preferably from RhD negative donor for premenopausal females
O	O or A
A	A or O[§]
B	B or O[§]
AB	AB or A or B or O[§]

[#]NZBS routinely makes platelet components from group A and O donors only.

[§]These group O components should test negative for 'high titre' anti-A and anti-B.

In the event of life-threatening bleeding, ABO and/or RhD incompatible platelet components may be transfused.

Rh antigens are not expressed on platelets and RhD incompatibility has no effect on the survival of transfused platelets. Residual red cells in RhD positive platelet components may however sensitise RhD negative patients to form anti-D. When platelet components from a RhD positive donor are transfused into a RhD negative

recipient, and in particular females of childbearing age or female children, administration of prophylactic anti-D immunoglobulin must be considered. Section 5.4.7: *Rh(D) Immunoglobulin-VF* contains guidelines on dosing of prophylactic anti-D following transfusion of RhD positive blood components.

Clinical Indications

The 2006 BCSH *Guidelines on the Management of Massive Blood Loss* and the Australian NBA *Patient Blood Management Guidelines* along with expert consensus opinion provide the following recommendations for platelet component use in adults.

Table 4.12: Clinical Indications for Use of Platelets

Indication	Management
Chemotherapy-induced Bone Marrow Failure	■ Prophylactic platelets are indicated in patients when the platelet count is <10 x 10^9/L in the absence of risk factors. ■ Prophylactic platelets are indicated in patients when the platelet count is <20 x 10^9/L in the presence of risk factors for systemic haemostatic failure such as fever or minor bleeding.
Surgery/Invasive Procedure	■ Patients with a platelet count ≥50 x 10^9/L can generally undergo invasive procedures without serious bleeding; lower counts may be tolerated in certain clinical situations. ■ For surgical procedures with high risk of bleeding (e.g., ocular or neurosurgery) it may be appropriate to maintain the platelet count ≥100 x 10^9/L.
Platelet Function Disorders	■ Rarely require platelet transfusion. May be appropriate in inherited or acquired disorders. ■ The platelet count is not a reliable indicator of platelet haemostatic function (e.g., following extended cardiac bypass surgery of more than 2 hours duration or administration of anti-platelet medications). ■ Alloimmunisation to missing glycoproteins may occur if platelets are given to patients with certain inherited functional defects.
Bleeding	■ May be appropriate in any patient in whom thrombocytopenia is considered to be a major contributing factor. ■ In critically ill patients, in the absence of bleeding, prophylactic platelet transfusion to prevent bleeding may be appropriate at a platelet count <20 x 10^9/L. ■ In non-critically ill medical patients, lower platelet counts may be tolerated. ■ In patients with chronic marrow failure syndromes, prophylactic platelet transfusions may lead to alloimmunisation and subsequent platelet refractoriness.

Table 4.12: Clinical Indications for Use of Platelets continued

Indication	Management
Massive Haemorrhage/ Massive Transfusion	■ To adequately maintain the platelet count >50 x 10^9/L while allowing for a margin of error, a transfusion trigger of 75 x 10^9/L is recommended. ■ The platelet count should be maintained >100 x 10^9/L in the presence of diffuse microvascular bleeding, multiple or CNS trauma, or platelet dysfunction. ■ Massive transfusion protocols, recognising that a platelet count <50 x 10^9/L can be expected after replacement of 2 x blood volume, empirically include platelet concentrates. Regular laboratory and/or point-of-care monitoring may identify patients likely to benefit from additional platelet transfusion.

Patients Refractory to Platelet Transfusion

A proportion of patients become refractory to random platelet transfusions. When a platelet transfusion fails to achieve the desired response it is important to find out whether the failure is due to rapid immunological or non-immunological platelet consumption. Clinical factors such as sepsis, disseminated intravascular coagulation (DIC), and splenomegaly are more common than alloimmunisation as the cause of platelet refractoriness.

Identifying patients with antibodies to human leucocyte antigens (HLA) or human platelet antigens (HPA) is important since the use of HLA- or HPA-matched platelet components may result in improved transfusion response.

In deciding how to treat a refractory patient there may be a number of appropriate strategies for improving the response to platelet transfusions such as matching for HLA or HPA, increasing the transfused dose or even discontinuing transfusion.

NZBS has produced *Guidelines for the Management of Patients Refractory* to *Platelets* from which the table below is taken. These guidelines can be found in the *Clinical Information* section of the NZBS website (www.nzblood.co.nz).

Table 4.13: Options for Managing Patients Refractory to Platelets

Indication	Management
Patient's HLA type not known and serum sample(s) not yet available	■ Consider transfusing ABO compatible, single donor platelets (preferably 'double-dose').
Patient serum samples available but HLA type not known	■ Platelets from the donation inventory can be prospectively crossmatched and compatible units selected for transfusion, although this is not the preferred option.
Patient's HLA type is known, and HLA-matched platelets are available	■ Consider transfusing HLA-matched platelets prior to the completion of antibody testing, as HLA immunisation is the most common cause of immune refractoriness.

Table 4.13: Options for Managing Patients Refractory to Platelets continued

The patient has HLA and/or HPA antibodies	■ Antigen negative (compatible) platelets should be selected for transfusion. ■ Further antibody testing is recommended every 3 months or if refractoriness returns.
The patient does not have HLA or HPA antibodies	■ Consideration should be given to non-immunological causes for which a haematologist or NZBS TMS/MO will advise management options.

Matched platelets are prepared for a specific recipient after consultation with a NZBS Transfusion Medicine Specialist. They normally require at least 48 hours notice, as, in addition to usual pre-release testing for bacterial contamination, suitable donors first need to be identified and then bled.

Contraindications

Transfusion of platelets is generally contraindicated in the following conditions:

- Thrombotic thrombocytopenic purpura (TTP)
- Haemolytic uraemic syndrome (HUS)
- Heparin-induced thrombocytopenia (HIT)
- Posttransfusion purpura (PTP)

Severe adverse reactions have been reported in patients with TTP and HIT following platelet transfusion. Platelet transfusion to these patients may also precipitate thrombotic events and can aggravate their clinical condition.

In this next group, platelet transfusion is unlikely to cause any sustained increase of platelet count:

- Immune thrombocytopenic purpura (ITP)
- Drug-induced thrombocytopenia of immune origin

Prophylactic use of platelet transfusion in these patients is of little benefit but platelet transfusion may be useful to stop active bleeding. These complex disorders of haemostasis should be managed in consultation with, or supervised by, a haematologist.

Adverse Reactions

Adverse reactions to platelets are predominantly allergic or febrile non-haemolytic transfusion reactions. The frequency of adverse reactions during transfusion of platelet concentrates has reduced following the introduction of platelet additive solution (PAS) as suspension medium.

4.10 Granulocyte Components

Granulocyte components may by collected by apheresis or harvested from buffy coats obtained from whole blood donations. Granulocytes must be ABO and RhD compatible with the recipient and must be irradiated before transfusion.

NZBS has produced a *Policy for Collection and Transfusion of Granulocytes* available in the *Clinical Information* section of the NZBS website (www.nzblood.co.nz).

A request for granulocyte components must be made in consultation with a NZBS Transfusion Medicine Specialist.

Clinical Indications

The literature has shown granulocyte transfusions may be beneficial and even life-saving in severely neutropenic patients with systemic bacterial or invasive fungal infections not responding to antimicrobial therapy after 24 to 48 hours, and in whom there is the potential for recovery of marrow function.

The literature on prophylactic granulocyte transfusions does offer some support for high-dose crossmatch compatible granulocyte transfusions. The Council of Europe does not currently include prophylaxis as an indication for granulocyte transfusions.

Adverse Reactions

As with other blood components, adverse reactions may occur, with febrile non-haemolytic transfusion reactions (FNHTR) being the most common and often dose related. The development of HLA antibodies and subsequent immune refractoriness to platelet components may further complicate blood transfusion support in recipients of granulocytes.

4.11 Plasma Components

ABO Compatibility

To avoid red cell haemolysis caused by transfusion of donor anti-A or anti-B, the ABO group of plasma components should be compatible with the ABO group of the recipient.

If high titre anti-A or anti-B are present in the plasma, the unit will be labelled accordingly and should only be transfused to a recipient with a compatible ABO group.

Table 4.14: ABO Compatibility of Fresh Frozen Plasma and Cryoprecipitate[#]

Patient's ABO Blood Group	ABO Group of Plasma Component
ABO Unknown	AB if urgent
O	O[§] or A or B or AB
A	A or AB
B	B or AB
AB	AB (A if AB is unavailable)

[#] Cryoprecipitate is free from high titre isoagglutinins anti-A and anti-B and can usually be given regardless of ABO group, however it is usual to follow the compatibility rules.

[§] Group O fresh frozen plasma is no longer routinely available.

RhD Compatibility

Although frozen plasma components may contain small amounts of red cell stroma, sensitisation following transfusion of RhD positive units is most unlikely, as stroma is less immunogenic than intact red cells. Therefore, FFP and cryoprecipitate of any RhD type may be given, regardless of the RhD type of the recipient. No prophylactic anti-D immunoglobulin need be given if RhD negative patients receive RhD positive FFP or cryoprecipitate.

Clinical Indications

Guidance on the indications for and dose of plasma components may be sought from a haematologist or NZBS Transfusion Medicine Specialist.

The following references provide recommendations for the appropriate use of plasma components:

- Australian NBA *Patient Blood Management Guidelines*
- 2013 ASTH *Consensus Guidelines for Warfarin Reversal*
- 2004 BCSH *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant*

Adverse Reactions

Acute transfusion reactions to plasma components may be seen and include febrile non-haemolytic transfusion reactions (FNHTR), allergic reactions to plasma protein antigens, circulatory overload (TACO) following transfusion of volumes excessive for the patient, haemolytic reactions due to ABO incompatible plasma, bacterial contamination and transfusion-related acute lung injury (TRALI), although the latter has reduced in frequency following the introduction of male-only plasma (see Chapter 7: *Adverse Effects of Transfusion*).

Contraindications

It is not appropriate to use plasma components as a plasma expander or for replacement of plasma proteins in chronic hypoproteinaemic states. Fresh frozen plasma is generally not used for plasma exchange procedures except where performed for thrombotic thrombocytopenic purpura or in the presence of severe coagulopathy. The use of fresh frozen plasma is generally not considered appropriate for treating immunodeficiency states or for urgent reversal of vitamin K deficiency due to warfarin anticoagulation when a prothrombin complex concentrate (PCC) is readily available.

4.12 Fresh Frozen Plasma

Fresh frozen plasma is collected using an apheresis procedure and rapidly frozen within 8 hours of collection to maintain labile coagulation factors.

Table 4.15: Clinical Indications for Use of FFP

Indication	Comments
Single Coagulation Factor/Protein Deficiencies	▪ When a specific factor concentrate is unavailable or is inappropriate, including isolated deficiency of factor II, V, VII, X, XI, XIII, antithrombin, C1-esterase inhibitor or pseudocholinesterase. ▪ The dose will depend on the clinical circumstances and the required level of activity in the patient. Consult a haematologist or NZBS TMS/MO.
Massive Blood Transfusion	▪ In patients with clinically abnormal haemostasis and reduced levels of coagulation factors following rapid transfusion of large volumes of blood. ▪ Massive transfusion protocols (MTP) empirically provide FFP units in a ratio to red cells of 1:1. ▪ Where a MTP is not available, an adult dose of 12-15 mL/kg (i.e., 1 L or 4 units FFP) is likely to be required after 1-1.5 x blood volume replacement in order to maintain the PT/APTT <1.5 x mean control. ▪ In patients with ongoing blood loss and consumption of coagulation factors, close monitoring of clinical status and levels of coagulation factors should be used to guide additional doses of FFP. Note however that the INR/APTT may not fully correct with the use of FFP.
Reversal of Warfarin Effect	▪ Use of FFP in this setting should be based on ASTH consensus guidelines (see Section 6.5.1: *Warfarin*). ▪ In summary, FFP should only be used to reverse warfarin anticoagulation in the presence of bleeding or prior to emergency surgery where a prothrombin complex concentrate (PCC) is unavailable or deemed inappropriate. In the case of life threatening bleeding, FFP may have a supplementary role in addition to PCC for warfarin reversal.
Thrombotic Thrombocytopenic Purpura (TTP)	▪ Accepted treatment is plasma exchange using FFP or cryosupernatant plasma as replacement fluid. ▪ If apheresis is not immediately available, infusion of FFP or cryosupernatant plasma may be given until plasma exchange can be initiated.

Table 4.15: Clinical Indications for Use of FFP continued

Indication	Comments
Liver Disease	▪ FFP may be appropriate in the presence of bleeding and abnormal coagulation, or as prophylaxis prior to invasive procedures. ▪ Due to reduced levels of natural anticoagulant proteins in liver disease, values of PT/APTT may overestimate the bleeding risk in liver disease. ▪ The usual adult dose is 10-15 mL/kg, however the response in liver disease is variable, partial and transient and close laboratory monitoring may be required.
Cardiac Surgery	▪ There is no evidence that prophylactic use of FFP (or cryoprecipitate and platelets) reduces bleeding. ▪ FFP (and other components) may be used to correct coagulopathy in bleeding patients, guided by clinical response and laboratory monitoring.
Disseminated Intravascular Coagulation (DIC)	▪ Indicated only when the consumptive coagulopathy is complicated by bleeding, in which case maintaining PT/APTT <1.5 x mean control and fibrinogen >1.5 g/L may be of benefit. ▪ The initial recommended dose is 15 mL/kg, however this will depend on the severity of the DIC. ▪ Subsequent doses should be guided by frequent laboratory testing. Cryoprecipitate may be required if fibrinogen is severely reduced.

4.13 Cryoprecipitate Apheresis - High Fibrinogen

Cryoprecipitate is a concentrated source of fibrinogen and also contains von Willebrand factor, factor VIII, factor XIII and fibronectin.

A dose of one unit per 30 kg body weight will produce an increment in plasma fibrinogen of approximately 1.0 g/L.

Table 4.16: Clinical Indications for Use of Cryoprecipitate

Indication	Comments
Disseminated Intravascular Coagulation (DIC) with Bleeding	▪ Consumptive fibrinogen deficiency is commonly encountered in DIC. ▪ At fibrinogen levels lower than 1.5 g/L and where there is clinical bleeding, use of cryoprecipitate to maintain the fibrinogen level above 1.5 g/L may be indicated.

Table 4.16: Clinical Indications for Use of Cryoprecipitate continued

Indication	Comments
Fibrinogen Deficiency and Dysfibrinogenaemia	■ Cryoprecipitate may be appropriate where there is clinical bleeding in the event of an invasive procedure, trauma or DIC. ■ The actual dose should be determined from the recipient's measured functional fibrinogen level, the nature and degree of bleeding and other relevant clinical factors.
Coagulation Factor Deficiencies	■ May be used as an alternative product for the treatment of bleeding associated with von Willebrand disease, haemophilia A and deficiency of factor XIII (fibrin stabilising factor) if specific concentrates are not available or are considered inappropriate. ■ The dose will depend on factor levels and the nature and extent of bleeding.
Bleeding Associated with Uraemia	■ The transfusion of one unit per 30 kg body weight usually is effective in controlling bleeding however repeated doses may be necessary.

4.14 Cryosupernatant Plasma

Cryosupernatant plasma is the supernatant from apheresis cryoprecipitate frozen within 2 hours of collection and is essentially FFP that has been depleted of factor VIII, von Willebrand factor (high molecular weight multimers being more thoroughly removed than smaller multimers), factor XIII, fibrinogen and fibronectin.

Cryosupernatant may be used as an alternative to FFP as a source of ADAMTS-13 protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) without replacing high molecular weight multimer vWF during plasma exchange in the treatment of thrombotic thrombocytopenic purpura.

FRACTIONATED PRODUCTS

Fractionated products, also known as plasma derivatives, are partially purified therapeutic preparations of human plasma proteins. They are manufactured under pharmaceutical conditions from large volumes of donor plasma with the final products supplied as freeze dried powders or solutions.

Careful screening of every donation contributing to a plasma pool is vital since any one donation could potentially introduce infectious agents into the pool. Even with rigorous screening of every donor and infectious diseases testing of every donation, some infectious agents might still find their way into the plasma pool. To counter this risk, manufacturing processes include two or more specific steps to inactivate any such agents that may escape detection.

Some points to note regarding transfusion of fractionated products:

- The manufacturer's instructions should be carefully read. Specific information about the administration of each product is given in the product information sheet, which comes packaged with each unit.
- Products should be transfused promptly following issue from the blood bank. If there is any delay they must be stored in a refrigerator at 2-8°C (unless otherwise indicated by the manufacturer).
- Freeze-dried preparations must be infused immediately after reconstitution. Do not refrigerate after reconstitution.
- Products not containing an antimicrobial preservative must be transfused within 3-4 hours of breaking the product seal.
- Multiple vials or bottles of the same product may be pooled together immediately prior to infusion to the patient.
- Products should not be used if turbidity or particulate matter is present in the vial or bottle. If observed this should be reported to NZBS.
- ABO compatibility does not normally need to be considered. Residual anti-A and anti-B in the final product are usually at clinically insignificant levels. However in some situations, such as where high doses of Intragam® P are being given to non-group O patients, these patients should be monitored for signs of intravascular haemolysis.
- Patients may experience adverse reactions due to transfusion of fractionated products. These should be reported to NZBS using *a Notification of Adverse Reaction to Fractionated Blood Product* form.

The information contained within this chapter relates to the fractionated products distributed by NZBS and has been adapted from the most recently available datasheet and/or the manufacturer's product information sheet for each product. These sources should be consulted prior to administration. Current versions of the datasheets can be accessed through the *Clinical Information* section of the NZBS website (www.nzblood.co.nz) and also the Medsafe website (www.medsafe.govt.nz). NZBS Transfusion Medicine Specialists/Medical Officers and Transfusion Nurse Specialists can also provide valuable information regarding the use of fractionated products.

5.1 Coagulation Factors

The National Haemophilia Management Group has produced guidelines for the management of haemophilia, including vWD, and these are available from the Haemophilia Centres. Most patients diagnosed with haemophilia A and B have their treatment supervised by a specialist haematologist. For any individual patient, the various fractionated and recombinant products used in the management of haemophilia are not interchangeable without prior discussion with the treating haematologist.

The following guidelines are to assist in the immediate management of a patient until consultation with a specialist haematologist or NZBS Transfusion Medicine Specialist. The exact loading and maintenance dose and dosing interval should be based on the patient's clinical condition and response to therapy. Where possible, pre- and post-infusion factor assays should be carried out, at least for the first course of treatment. Coagulation factor therapy as a continuous infusion to cover surgical procedures should be administered under the supervision of a specialist haematologist and with laboratory tests performed to ensure that the desired plasma factor concentrations are achieved.

5.1.1 Biostate® (Factor VIII)

Biostate® is a high purity, sterile, freeze-dried powder containing purified human coagulation factor VIII (FVIII) and human von Willebrand factor (vWF) complex. Biostate® is available as vials of 500 IU and 1,000 IU factor VIII. The reconstituted product has a vWF to FVIII ratio of 2:1 as detailed in Table 5.1. Biostate® contains 10 mg/mL human albumin as a stabiliser.

The FVIII/vWF complex in Biostate® is purified from cryoprecipitate using selective precipitation and chromatography steps. The manufacturing process of Biostate® includes solvent detergent and dry heat treatment steps to reduce the potential for viral transmission. The combination of solvent detergent, dry heat treatment, and partitioning steps are effective for inactivation/removal of HIV, hepatitis A, hepatitis B, and hepatitis C and also have some effect on parvovirus B19.

Table 5.1: Biostate® Composition

Active ingredients IU/vial (nominal)	**Biostate®**	
	500 IU (50 IU/mL)	**1000 IU (100 IU/mL)**
Factor VIII	500	1000
vWF:RCo[1]	1000	2000
Reconstitution volume (mL)	10	10

[1]*vWF:Ristocetin Cofactor – an in vitro indicator of vWF activity.*

Indications for Use

Biostate® is indicated for:

- Treatment and prophylaxis of bleeding associated with FVIII deficiency due to haemophilia A

- Treatment and prophylaxis of bleeding associated with von Willebrand disease (vWD) when desmopressin (DDAVP) treatment alone is ineffective or contraindicated

The number of vials of Biostate® to be reconstituted for administration is determined by dividing the total number of International Units (IU) required by 500 or 1,000 (according to vial size being used), rounded up to the nearest whole number of vials.

Table 5.2: Biostate® Dosage Guidelines for Haemophilia A

Indication	Dose (IU/kg)	Dose Frequency (per day)	Treatment Duration (days)	Target FVIII (%) (IU/dL)
Minor haemorrhage	10-15	1-2	1-2	peak 20-30
Moderate to severe haemorrhage				
■ Haemarthroses	15-40	1-3	1-4	peak 30-80
Life threatening haemorrhage				
■ Intracranial haemorrhage	50-60	2-3	7-10	peak ≥100 trough 80-100
Minor surgery				
■ Loading dose	20-30	stat	preoperatively	peak 40-60
■ Maintenance[1]	15-30	1-2	≥4	trough 20-50
Major surgery				
■ Loading dose	40-50	stat	preoperatively	peak 80-100
■ Maintenance[1]	10-25	1-3	≥7	trough 40-80
Dentistry[2]				
■ Loading dose	35-40	stat	preoperatively	peak 70-80
■ Maintenance[1]	25-30	2	1-3	trough 50-60
Prophylaxis	25-40	3x/week	ongoing	trough 1

[1]An alternative is to use continuous infusion.
[2]For single tooth extraction, extensive dental clearance or surgery, higher levels may be necessary for longer periods of at least 6 - 10 days. The use of an antifibrinolytic agent such as tranexamic acid is strongly recommended.

Table 5.3: Biostate® Dosage Guidelines for Von Willebrand Disease[1]

Indication	Dose (IU/kg)		Dose Frequency (per day)	Treatment Duration (days)	Target FVIII/ vWF (%) (IU/dL)
	FVIII:C	vWF:RCo			
Spontaneous haemorrhage	12.5-25	25-50	initial	-	peak vWF >50, FVIII >30
	12.5	25	1-2	2-4	trough vWF >30
Minor surgery[2]	30	60	1	2-4	trough vWF/FVIII >30
Major surgery[2]	30-40	60-80	preoperatively	-	peak vWF >100, FVIII >60
	15-30	30-60	1-2	5-10	trough vWF/FVIII >50
Prophylaxis	12.5-25	25-40	3x/week	ongoing	trough 1

[1]Dosage guidelines above are for patients with severely reduced vWF levels, e.g. <10% of normal. Doses may need to be adjusted down in patients with less severe vWF deficiencies (>20% of normal) to ensure that the desired plasma concentrations of vWF and FVIII are achieved. It is recommended that plasma vWF and FVIII concentrations are determined at suitable time intervals.
[2]An alternative is to use continuous infusion.

Precautions

- **Allergic reactions**
  Allergic reactions or fever are rarely observed. Depending on the nature of an adverse reaction, the rate of injection should be slowed or stopped to alleviate symptoms.

- **Antibodies to factor VIII**
  Patients with congenital factor VIII deficiency may develop neutralising alloantibodies (inhibitors) to factor VIII after treatment. If this occurs specialist advice must be sought.

- **Antibodies to von Willebrand factor**
  Patients with von Willebrand disease, especially type 3 patients, may very rarely develop neutralising alloantibodies (inhibitors) to von Willebrand factor. Such antibodies may occur in close association with anaphylactic reactions. Therefore patients experiencing anaphylactic reactions should be evaluated for the presence of an inhibitor.

- **Thrombosis**
  Thromboembolic events have rarely been reported in vWD patients receiving coagulation factor replacement therapy, especially in the setting of known risk factors for thrombosis, and may be related to the generation of supranormal FVIII levels.

5.1.2 MonoFIX®-VF (Factor IX)

MonoFIX®-VF is a sterile, freeze-dried powder containing purified human coagulation factor IX. MonoFIX®-VF is available as vials of 500 IU and 1,000 IU factor IX. Each vial also contains small amounts of heparin, antithrombin III and plasma proteins.

The factor IX in MonoFIX®-VF is purified using ion-exchange and heparin affinity chromatography to remove other vitamin K-dependent factors II, VII and X. The manufacturing process of MonoFIX®-VF includes solvent detergent treatment and nanofiltration steps to reduce the potential for viral transmission. The current procedures are effective for inactivation/removal of HIV, hepatitis A, hepatitis B, and hepatitis C and also have some effect on parvovirus B19.

Indications for Use

MonoFIX®-VF is indicated for:

- Treatment and prophylaxis of bleeding associated with factor IX deficiency due to haemophilia B (Christmas disease)

MonoFIX®-VF is not indicated for the treatment of factor II, VII or X deficiency because it does not contain therapeutic levels of these coagulation factors. MonoFIX®-VF is not indicated for the treatment of haemophilia A patients with factor VIII inhibitors.

The number of vials of MonoFIX®-VF to be reconstituted for administration is determined by dividing the total number of International Units (IU) required by 500 or 1,000 (according to vial size being used), rounded up to the nearest whole number of vials.

Table 5.4: MonoFIX®-VF Dosing Guideline for Haemophilia B

Indication	Dose (IU/kg)	Dose Frequency (per day)	Treatment Duration (days)	Target FVIII (%) (IU/dL)
Prophylaxis[1]	25-40	2x/week	ongoing	trough 1
Minor haemorrhage	20-30	1	1-2	peak 20-30
Moderate to severe haemorrhage				
■ Haemarthroses	30-50	1-2	1-5	peak 30-50
Life threatening haemorrhage				
■ Intracranial haemorrhage	80-100	2	10-12	peak ≥100 trough 80-100
Minor surgery[2]				
■ Loading dose	40-60	stat	preoperatively	peak 40-60
■ Maintenance[3, 4]	15-40	1-2	7-10	trough 20-50
Major surgery				
■ Loading dose	70-100	stat	preoperatively	peak 70-100
■ Maintenance[3, 4]	20-90	1-2	10-12	trough 20-90

[1]*Prophylaxis in children.*
[2]*Includes single tooth extraction. The use of an antifibrinolytic agent such as tranexamic acid is strongly recommended.*
[3]*Initially (days 1-3) aim for levels at the higher end of this range. Gradually reduce to lower level during subsequent days.*
[4]*An alternative is to use continuous infusion.*

Precautions

- **Allergic reactions**
  Allergic reactions or fever are rarely observed. Depending on the nature of an adverse reaction, the rate of injection should be slowed or stopped to alleviate symptoms.

- **Antibodies to factor IX**
  Patients with congenital factor IX deficiency may develop neutralising alloantibodies (inhibitors) to factor IX after treatment. If this occurs specialist advice must be sought. The reported prevalence for the formation of inhibitors in patients receiving plasma-derived factor IX is approximately 4%. There has been no clinical experience with MonoFIX®-VF with respect to inhibitor development in previously untreated patients.

- **Heparin**
  MonoFIX®-VF contains 50 - 140 IU heparin in each 500 IU vial and 100 - 280 IU heparin in each 1000 IU vial. Heparin is known to cause thrombocytopenia and the possibility of heparin-induced thrombocytopenia (HIT) syndrome should be considered if thrombocytopenia, with or without thrombosis, develops during treatment. Consideration should be given to the clinical effect of heparin if high doses of MonoFIX®-VF are required.

- **Laboratory tests**
  MonoFIX®-VF is formulated with heparin and antithrombin. Therefore the results of anticoagulation tests should be interpreted with care.

- **Thrombosis and DIC**
  High doses of prothrombin complex concentrates (PCC) have been associated with disseminated intravascular coagulation (DIC). Although MonoFIX®-VF contains purified factor IX, the potential risk of thrombosis and DIC should be recognised. The use of products containing factor IX could be hazardous in patients with a history of fibrinolysis, myocardial infarction, DIC or liver disease.

5.1.3 Prothrombinex®-VF (Factors II, IX and X)

Prothrombinex®-VF is a sterile, freeze-dried powder containing purified human coagulation factors II, IX, and X. When reconstituted each vial contains 500 IU of factors IX, approximately 500 IU of factors II and X, and 25 IU antithrombin III, 200 IU heparin. The product also contains small amounts of factors V and VII.

Prothrombinex®-VF is prepared by adsorption of coagulation factors from plasma onto an ion-exchange medium followed by selective elution. The manufacturing process of Prothrombinex®-VF contains dedicated steps including dry heat treatment and nanofiltration to reduce the potential for viral transmission. The current procedures are effective for inactivation/removal of HIV, hepatitis A, hepatitis B, and hepatitis C and may also have some effect on parvovirus B19.

The coagulation factors II, VII, IX and X, synthesised in the liver with the help of vitamin K, are together commonly called the prothrombin complex.

Isolated congenital deficiency of factor IX is known as haemophilia B. Isolated deficiency of factor II or factor X is very rare but in severe form can cause a bleeding tendency similar to that seen in classical haemophilia. Isolated severe deficiency of factor VII

leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis.

Acquired deficiency of the vitamin K-dependent coagulation factors occurs during treatment with coumarin vitamin K antagonists such as warfarin. It may also result from vitamin K deficiency due to malabsorption syndromes, antibiotic therapy, cholestasis or prolonged parenteral alimentation. If the deficiency progresses, a severe bleeding tendency results, characterised typically by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage.

Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K-dependent coagulation factors and may lead to a clinical bleeding tendency. The haemostatic situation is however often complex due to simultaneous ongoing low-grade intravascular coagulation, low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

Indications for Use

Prothrombinex®-VF is indicated for:

- Treatment and perioperative prophylaxis of bleeding associated with acquired deficiency of prothrombin complex factors such as that caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required
- Treatment and prophylaxis of bleeding associated with single (or multiple) congenital deficiency of factors IX, II or X when purified specific coagulation factor product is not available

Section 6.4: *Oral Anticoagulant – Warfarin Induced Bleeding or Overdose* of this Handbook summarises the updated Australasian Society of Thrombosis and Haemostasis (ASTH) *Consensus Guidelines for Warfarin Reversal* published in the Medical Journal of Australia, 198 (4): 198-199, 2013. The recommendations for the use of prothrombin complex concentrate (PCC) in the setting of warfarin-related bleeding or warfarin overdose have been incorporated in the NZBS app *Reversing Warfarin*, available for iPhone and Android. Consultation with a specialist haematologist or NZBS Transfusion Medicine Specialist/Medical Officer is recommended.

Table 5.5: Prothrombinex®-VF Dosing Guideline for Haemophilia B

Indication	Dose (IU/kg)	Dose Frequency (per day)	Treatment Duration (days)	Target FIX (%) (IU/dL)
Minor haemorrhage	20-30	1	1-2	peak 20-30
Moderate to severe haemorrhage				
▪ Haemarthroses	30-50	1-2	1-5	peak 30-50
Minor surgery				
▪ Loading dose	40-60	stat	preoperatively	peak 40-60
▪ Maintenance	15-40	1-2	7-10	trough 20-50

For congenital deficiencies of factors II and X, calculation of the required dose of Prothrombinex®-VF is based on recovery data obtained for other PCC products showing that 1 U of factor II or X per kg body weight raises the respective plasma factor activity by 2% of normal.

Required units (IU) = body weight (kg) x desired rise in factor II or X (as %) x 0.5

Prothrombinex®-VF should not be infused at a rate greater than 3 mL/minute.

Precautions

- **Allergic reactions**
  Allergic reactions are rarely observed although severe anaphylaxis has been reported, particularly in patients with factor IX inhibitors. Depending on the nature of an adverse reaction, the rate of injection should be slowed or stopped to alleviate symptoms.

- **Antibodies to factor IX**
  Patients with congenital factor IX deficiency may develop neutralising alloantibodies (inhibitors) to factor IX after treatment. The reported prevalence for the formation of inhibitors in patients receiving plasma-derived factor IX is approximately 4%.

- **Antifibrinolytic agents**
  Use of Prothrombinex®-VF with epsilonaminocaproic acid or tranexamic acid is not recommended since only limited data are available on the concomitant administration of prothrombin complex concentrates and antifibrinolytic agents.

- **Heparin**
  Prothrombinex®-VF contains 200 IU heparin in each vial. Heparin is known to cause thrombocytopenia and the possibility of heparin-induced thrombocytopenia (HIT) syndrome should be considered if thrombocytopenia, with or without thrombosis, develops during treatment. Consideration should be given to the clinical effect of heparin if high doses of Prothrombinex®-VF are required.

- **Thrombosis and DIC**
  Patients receiving Prothrombinex®-VF, especially at doses greater than 50 IU/kg of factor IX or following repeated doses, may be predisposed to venous and arterial thromboembolism, DIC or myocardial infarction. It should be used with caution in neonates, in who immature hepatic function may lead to delayed clearance of activated coagulation factors and an increased risk of thrombotic complications.

5.1.4 FEIBA NF® (Factor VIII inhibitor bypassing fraction)

FEIBA NF® is a sterile, freeze-dried powder of human plasma fraction with factor VIII inhibitor bypassing activity. FEIBA NF® is available as 20 mL vials containing 500 U and 1000 U factor VIII inhibitor bypassing activity for reconstitution and intravenous administration. The potency of FEIBA NF® is expressed in arbitrary units. One Unit of activity is defined as that amount of FEIBA NF® that shortens the activated partial thromboplastin time (APTT) of a high titre factor VIII inhibitor reference plasma to 50% of the blank value.

FEIBA NF® is prepared by adsorption of coagulation factors from plasma onto an ion-exchange medium followed by selective elution. The manufacturing process of FEIBA NF® contains dedicated steps including nanofiltration and vapour heat treatment to reduce the potential for viral transmission. The current procedures are effective for inactivation/removal of HIV, hepatitis B, and hepatitis C and may also have some effect on hepatitis A and parvovirus B19.

FEIBA NF® is a concentrate of vitamin K-dependent factors in both zymogen and active form (factors II, IX, and X, mainly non-activated, and factor VII, mainly activated). The product contains approximately equal unitages of factor VIII inhibitor bypassing activity and prothrombin complex factors. In addition, 1 - 6 units of factor VIII coagulant antigen (FVIII C:Ag) per mL are present. The preparation contains only traces of factors of the kinin generating system. It contains no heparin.

The process of coagulation involves activation of factor X to form Xa, which with cofactor Va catalyses the formation of thrombin from prothrombin. The production of sufficient quantities of Xa usually requires a complex of factors VIIIa and IXa. Patients (often those with haemophilia A or B) can acquire inhibitors to factor VIII or IX during the treatment with factor VIII or IX replacement therapy, which then prevents the formation of the complex that catalyses Xa production. FEIBA NF® results in the generation of Xa and thrombin without the help of the factor VIIIa-IXa complex, thereby bypassing the inhibitory action of factor VIII (or factor IX) inhibitors.

Indications for Use

FEIBA NF® is indicated for:

- Routine prophylaxis of bleeding episodes in haemophilia A and B patients with inhibitors, experiencing ≥ 12 bleeding episodes per year and refractory to increased dosing with, respectively, factor VIII and IX concentrates
- Treatment of bleeding episodes and to cover surgical interventions in haemophilia A and B patients with, respectively, factor VIII and IX inhibitors
- Longterm use, in combination with factor VIII concentrates, for immune tolerance induction to eliminate factor VIII inhibitors in patients with haemophilia A, so as to allow for regular treatment with factor VIII concentrates as in patients without inhibitors
- Treatment of severe or life-threatening bleeding episodes in non-haemophiliacs with acquired inhibitors to factors VIII, XI and XII

Clinical experience suggests that patients with a factor VIII inhibitor titre < 5 Bethesda units (BU) may be successfully treated with antihemophilic factor (AHF). Patients with titres ranging between 5 BU and 10 BU may either be treated with AHF or FEIBA NF®. Patients with factor VIII inhibitor titres > 10 BU have generally been refractory to treatment with AHF. However, since a single dose of FEIBA NF® contains considerably less factor VIII than factor VIII concentrate, FEIBA NF® is considered the treatment of choice in high responder patients, even if the current inhibitor titre is low.

Table 5.6: Guideline for Treatment of Patients with Haemophilia A and Factor VIII Inhibitors

Inhibitor Titre (BU[1]/mL)	Response to FVIII	Minor / Moderate Bleeding	Severe / Life-threatening Bleeding or Surgery
< 5	low responder	FVIII or FEIBA NF®	FVIII or FEIBA NF®
> 5	high responder	FEIBA NF®	FEIBA NF®
5 - 10	low responder	FVIII or FEIBA NF®	FEIBA NF®
5 - 10	high responder	FEIBA NF®	FEIBA NF®
< 10	low responder	FEIBA NF®	FEIBA NF®
> 10	high responder	FEIBA NF®	FEIBA NF®

[1]Bethesda Unit is defined as that amount of antibody that will inhibit 50% of the factor VIII activity of fresh plasma after incubation for 2 hours at 37 °C.

Dosage and Administration

Dosage is independent of the patient's inhibitor titre. As a general rule, a dose of 50 - 100 U FEIBA NF® per kilogram body weight is recommended. However, due to the risk of thrombosis, the total daily dose should not exceed 200 U/kg and, for any one dose, the infusion rate should not exceed 2 U/kg per minute. Due to varying response to treatment the following dosage recommendations are only guidelines.

Table 5.7: FEIBA NF® Dosing Guideline

Bleeding Indication	Dose[1] (U/kg)	Dose Frequency (day)	Treatment Duration
Prophylaxis[2]	70-100	alternate day	ongoing
Surgery	50-100	4	preoperatively and until wound healing
Mucous membrane[3]	50	4	until clinical improvement
Joint, muscle, soft tissue - mild to moderate	50-75	2	until clinical improvement
Joint, muscle, soft tissue - severe	100	2	until clinical improvement
Other severe[4] e.g., CNS	100	2	until clinical improvement

[1]Single doses of 100 U/kg and daily doses of 200 U/kg body weight should not be exceeded.
[2]Dose recommendations, based on body weight, are the same for paediatric patients as for adults.
[3]If bleeding is not controlled the dose may be increased to 100 U/kg, provided the maximum daily dose is not exceeded.
[4]In individual cases the frequency may be increased to 6-hourly until clinical improvement, provided the maximum daily dose is not exceeded.

Contraindications

FEIBA NF® is contraindicated in cardiac surgery involving cardiopulmonary bypass and procedures involving extracorporeal membrane oxygenation (ECMO) due to the high risk of thrombotic adverse events.

Precautions

- **Allergic reactions**
  FEIBA NF® has been associated with severe allergic and anaphylactoid reactions.

- **Anamnestic response**
  Administration of FEIBA NF® to patients with inhibitors may result in an initial anamnestic rise in inhibitor levels. Clinical data suggest that the efficacy of FEIBA NF® is not reduced. Inhibitor levels may decrease over time with continued administration of FEIBA NF®.

- **Laboratory tests**
  In vitro tests such as APTT, whole blood clotting time (WBCT) and thromboelastography (TEG) used to monitor efficacy may not correlate with clinical improvement. Attempts to normalise these values by increasing the dose of FEIBA NF® are discouraged and may induce DIC through overdosage.

- **Passive anti-HBs transfer**
  Administration of FEIBA NF® with a transitory rise of passively transferred hepatitis B surface antibodies may mislead the interpretation of positive serology test results.

- **Sodium**
  The maximum daily dose of FEIBA NF® may contain > 200 mg sodium and this should be taken into consideration for patients on a sodium-restricted diet and/or with renal impairment.

- **Thrombosis**
  Patients should not receive single doses of FEIBA NF® > 100 U/kg body weight or daily doses > 200 U/kg body weight as these may predispose venous and arterial thromboembolism, DIC, myocardial infarction or stroke. Patients receiving doses such as these should be monitored for the development of adverse events. The possible presence of risk factors for thromboembolism, even in patients with haemophilia, should always be considered.

Interactions with Other Medicines

The use of tranexamic acid, an antifibrinolytic agent, in combination with FEIBA NF® is not recommended due to an increased risk of thrombotic events. If treatment with both is indicated the products should be administered at least 12 hours apart. Concomitant use with recombinant factor VIIa may potentially result in an adverse thrombotic event.

5.1.5 RiaSTAP® (Fibrinogen)

RiaSTAP® does not have full New Zealand registration and is in limited supply so consultation with an NZBS Transfusion Medicine Specialist/Medical Officer is required prior to release of this product.

RiaSTAP® is a freeze-dried powder of purified human fibrinogen (factor I). Each 50 mL vial when reconstituted contains 1 g of human fibrinogen for intravenous administration.

Indications for Use

RiaSTAP® is indicated for:

- Prophylaxis and treatment of bleeding in patients with congenital fibrinogen deficiency including afibrinogenaemia and hypofibrinogenaemia

Dosage and Administration

The (functional) fibrinogen level should be determined in order to calculate individual dosage requirements. The frequency of administration should be determined on an individual patient basis by regular measurement of plasma fibrinogen and continuous monitoring of the clinical condition of the patient. Dosage recommendations in the treatment of children are the same as for adults.

$$\text{Dose of RiaSTAP® (mg/kg body weight)} = \frac{\text{target level (g/L)} - \text{measured level (g/L)}}{\text{0.017 (g/L per mg/kg body weight)}}$$

If the serum fibrinogen level is not known the recommended dose is 70 mg per kilogram body weight administered intravenously.

As a guide for subsequent dosing the target level of 1 g/L for minor events should be maintained for three days. The target level of 1.5 g/L for major events should be maintained for seven days.

Precautions

- **Thrombosis**
  There is a risk of thrombosis when patients with congenital fibrinogen deficiency are treated with human fibrinogen, particularly with high or repeat doses. Patients, particularly those with risk factors for thromboembolic disease including neonates, should be monitored closely for signs and symptoms of thrombosis.

- **Serum sodium**
  RiaSTAP® contains up to 164 mg (7.1 mmol) sodium per vial and this should be taken into consideration for patients on a sodium-restricted diet and/or with renal impairment.

Adverse Events

The following adverse reactions have been reported from clinical studies.

Table 5.8: Adverse Events Associated with Administration of RiaSTAP®

Event	Frequency
Urticaria, rash, fall in blood pressure, dyspnoea	≥ 1/10,000 and < 1/1,000
Increase in body temperature	≥ 1/10,000 and < 2/1,000
Headache	≥ 1/10,000 and < 1/1,000
Thromboembolic episodes	< 1/10,000

5.1.6 Fibrogammin® P (Factor XIII)

Fibrogammin® P does not have full New Zealand registration and so consultation with an NZBS Transfusion Medicine Specialist/Medical Officer is required prior to product release.

Fibrogammin® P is a freeze-dried powder of purified human factor XIII. Each vial when reconstituted contains 250 units of factor XIII.

Indications for Use

Fibrogammin® P is indicated for:

- The prophylaxis and treatment of bleeding associated with congenital FXIII deficiency
- Supportive therapy in the case of disturbance in wound healing associated with congenital FXIII deficiency, especially with venous ulcers or following extensive surgery
- The treatment of bleeding associated with acquired FXIII deficiency

Dosage and Administration

The following guideline is to assist in the immediate management of a patient until consultation with a specialist haematologist or NZBS Transfusion Medicine Specialist/ Medical Officer. The exact loading and maintenance dose and dosing interval should be based on the patient's clinical condition and response to therapy. It is recommended to monitor the increase in factor XIII activity. For major surgery and severe haemorrhage the aim is to obtain normal values.

Table 5.9: Fibrogammin® P Dosing Guideline

Indication	Dose (IU/kg)	Treatment Duration
Congenital FXIII deficiency		
Prophylaxis	10	approx. once per month, individualised to bleeding frequency
Moderate to severe haemorrhage[1]	10-20	daily for severe haemorrhage and until bleeding stops
Surgery		
■ Loading dose	35	preoperatively
■ Maintenance	10	daily until complete wound healing
Acquired FXIII deficiency		
Moderate to severe haemorrhage	15-20	daily until bleeding stops or normal FXIII levels achieved spontaneously
Disorder of wound healing		
Surgery[2]	10	preoperatively and then once daily for 3 days

[1]*Severe life threatening bleeding may initially require doses up to 50 IU/kg with an aim to achieve normal factor XIII levels.*
[2]*In high-risk patients the dose can be increased to 15 - 20 IU/kg.*

Precautions

- **Allergic reactions**
  Allergic reactions or fever are rarely observed. Depending on the nature of an adverse reaction, the rate of injection should be slowed or stopped to alleviate symptoms.
- **Antibodies to factor XIII**
  Patients with congenital deficiency may rarely develop neutralising alloantibodies (inhibitors) to factor XIII after repeated treatment.
- **Thrombosis**
  In cases of fresh thrombosis, caution should be exercised due to the fibrin-stabilising effect.

5.2 Natural Inhibitors of Coagulation

5.2.1 Thrombotrol®-VF (Antithrombin III)

Thrombotrol®-VF is a sterile, freeze-dried powder of purified human antithrombin III (ATIII). Each vial when reconstituted contains 1000 IU of ATIII for intravenous administration.

Indications for Use

Thrombotrol®-VF is indicated in patients with hereditary deficiency of antithrombin under the following circumstances:

- Prophylactic administration for the prevention of thromboembolism in surgery, pregnancy and during childbirth
- Therapeutic administration in thrombosis or pulmonary embolism

The dose should be based on pretreatment and desired ATIII levels. The dose can be calculated using the following formula which is based on an incremental in-vivo recovery of ATIII of 2.2% per IU/kg bodyweight using a functional ATIII assay.

$$\text{Dose (IU)} = \frac{[\text{Desired ATIII (IU)} - \text{Pretreatment ATIII level*(IU)}] \times \text{Wt (kg)}}{2.2}$$

** expressed as % normal level based on functional ATIII assay*

Under conditions of acute consumption, the biological half-life of ATIII may be reduced from 2.8 days to only a few hours. Following acute thrombosis where ATIII levels should be maintained ≥ 100% for 2 - 8 days, plasma ATIII levels determined several times per day may be used to guide replacement therapy.

ATIII replacement may also be given prophylactically to overcome heparin resistance and reduce the risk for circuit thrombosis in patients (particularly neonates) undergoing extracorporeal membrane oxygenation (ECMO) during cardiac surgery. In this situation acute consumption of ATIII may lead to low plasma ATIII levels and failure to achieve adequate anticoagulation despite increasing heparin infusion doses. ATIII is administered as either intermittent intravenous bolus doses, each over 10 - 20 minutes, or as a continuous infusion with the aim to maintain an activated clotting time (ACT) > 400 seconds together with a target ATIII level of 60 - 100%. The doses required are typically larger than those used for replacement in hereditary deficiency.

5.2.2 Ceprotin (Protein C)

Ceprotin does not have full New Zealand registration and so consultation with an NZBS Transfusion Medicine Specialist/Medical Officer is required prior to product release.

Ceprotin is a sterile, freeze-dried powder of purified human protein C. Each vial when reconstituted contains 1000 IU of protein C for intravenous administration.

Indications for Use

Ceprotin is indicated for:

- Prophylaxis and treatment of venous thrombosis and purpura fulminans in paediatric and adult patients with severe congenital protein C deficiency

Dosage and Administration

The loading and maintenance dose and dosing interval should be based on the clinical condition, the severity of the protein C deficiency (i.e., pretreatment level) and desired protein C level. It is recommended to monitor the increase in protein C activity. These guidelines are recommended for neonatal, paediatric and adult patients.

Table 5.10: Ceprotin Dosing Guideline[1]

Indication	Initial Dose (IU/kg)	Subsequent Doses (IU/kg)	Maintenance Dose (IU/kg)	Target Protein C (%) (IU/dL)
Acute episode/ Short term prophylaxis[2]	100-120	60-80 6 hourly for three doses	45-60 6-12 hourly	peak 100
Long term prophylaxis	-	-	45-60 12 hourly	trough >25

[1]Dosing should be adjusted according to the pharmokinetic profile for each individual.
[2]Ceprotin should be continued until desired anticoagulation is achieved.

Adverse Reactions

Common reactions include rash, itch and lightheadedness. Other reported reactions include restlessness and hyperhydrosis.

Precautions

- **Allergic reactions**
  Ceprotin may contain traces of mouse protein and/or heparin, to which allergic reactions cannot be ruled out.
- **Heparin**
  Ceprotin contains trace amounts of heparin which may lead to heparin-induced thrombocytopenia (HIT).
- **Sodium**
  Ceprotin contains > 200 mg sodium and this should be taken into account for patients on a sodium-restricted diet and/or with renal impairment.

5.3 Albumin Solutions

5.3.1 Albumex® 4 (Human albumin 4%)

Albumex® 4 contains 40 g/L albumin in solution for intravenous injection and is iso-oncotic with human serum. It is available in vials of 50 mL and 500 mL volume. When

infused into adequately hydrated patients its effect is to expand the circulating blood volume by an amount approximately equal to the volume of Albumex® 4 infused. It is prepared by a combination of Cohn cold-ethanol fractionation and chromatography. The manufacturing process of Albumex® 4 includes pasteurisation and cold temperature incubation to reduce the potential for viral transmission. The current procedures are effective for inactivation/removal of HIV, hepatitis A, hepatitis B, and hepatitis C and may also be of limited value against parvovirus B19.

Indications for Use

Table 5.11: Clinical Indications for Use of Albumex® 4

Indication	Comments
Hypovolaemia / Shock	■ Preservation of an adequate circulating blood volume should be the primary aim of therapy. Albumex® 4 may be the initial plasma expander of choice for shock associated with significant hypoalbuminaemia (plasma albumin < 25 g/L). ■ May also be useful following initial resuscitation with crystalloid or synthetic colloid solutions in patients in whom extended support of the intravascular volume is required such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome. ■ The use of albumin for fluid resuscitation of patients with traumatic brain injury is not recommended.
Cardiopulmonary Bypass	■ Priming the pump for cardiopulmonary bypass surgery for patients with poor left ventricular function and other complicating factors such as long bypass time, anaemia or repeat surgery.
Plasma Exchange	■ Indicated as a replacement solution in plasma exchange procedures, particularly when the volume exchanged exceeds 20 mL/kg body weight. ■ In patients with thrombotic thrombocytopenic purpura, fresh frozen plasma or cryosupernatant may be the preferred replacement solution.

Precautions

- **Adverse effects**
  Adverse reactions to albumin solutions are uncommon and are usually mild and transient. Chills, fever, urticaria, flushing, nausea, headache and dyspnoea may occur. More serious allergic events including hypotension and anaphylaxis are reported. In addition, hypotension has been reported in patients given albumin who are on angiotensin-converting enzyme (ACE) inhibitors.

- **Aluminium accumulation**
  Albumex® 4 contains trace amounts of aluminium (200 µg/L). Accumulation of aluminium in patients with chronic renal insufficiency has led to toxic manifestations such as hypercalcaemia, vitamin D-refractory osteodystrophy, anaemia and severe progressive encephalopathy. Therefore, when large

volumes of albumin are contemplated for administration to such patients, serious consideration should be given to these potential risks relative to the anticipated benefits.

- **Circulatory overload**
  Circulatory overload can be avoided by monitoring the rate and volume of infusion. Patients with cardiac failure, renal insufficiency, stabilised chronic anaemia or on cardiopulmonary bypass are at special risk of developing circulatory overload.

- **Compatibility with other fluids**
  Albumex® 4 should not be mixed with protein hydrolysates, amino acid solutions, solutions containing alcohol, or solutions containing drugs that bind to albumin such as calcium channel blockers.

- **Shock**
  Administration of albumin can aggravate myocardial depression when present in patients with shock.

Safety of Albumin for Fluid Resuscitation

In 2011 the Cochrane Injuries Group reported results of a meta-analysis of the available medical literature on "Human albumin solution for resuscitation and volume expansion in critically ill patients" and concluded that for patients with hypovolaemia there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline. Contributing significantly to this report were results from the SAFE trial (Saline vs Albumin Fluid Evaluation) which compared the safety and efficacy of albumin versus saline in Australasian intensive care units. The study concluded that albumin and saline should generally be considered clinically equivalent treatments for intravascular resuscitation in the ICU although further study is required for more highly selected populations of critically ill patients, for example those with brain injury. The Cochrane report also concluded that for patients with burns and hypoalbuminaemia there is no evidence that albumin reduces mortality. Due to the increased cost of albumin compared to alternatives such as saline, albumin should only be used within the context of further trials.

5.3.2 Albumex® 20 (Human albumin 20%)

Albumex® 20 contains 200 g/L albumin in solution for intravenous injection and is hyperoncotic and hypo-osmotic compared to human serum. It is available in vials of 10 mL and 100 mL volume. When infused it supplies the oncotic equivalent of approximately four times its volume of human plasma. Albumex® 20 has two main functions: maintenance of plasma colloid osmotic pressure and transport of intermediate products in the transport and exchange of tissue metabolites. It is prepared by a combination of Cohn cold-ethanol fractionation and chromatography. The manufacturing process of Albumex® 20 includes pasteurisation and cold temperature incubation to reduce the potential for viral transmission. The current procedures are effective for inactivation/removal of HIV, hepatitis A, hepatitis B, and hepatitis C and may also be of limited value against parvovirus B19.

Indications for Use

Table 5.12: Clinical Indications for Use of Albumex® 20

Indication	Comments
Hypoproteinaemia in acutely ill patients	■ Administered when there are (or it is anticipated) clinical problems or complications from reduced oncotic pressure, and/or as an adjunct to diuretic therapy.
Shock	■ May be used for the resuscitation of patients in shock due to acute loss of blood or plasma however 4% human albumin is preferred when available.
Burns	■ Extensive burns are followed by sequential shifts in the distribution of body water, salt and proteins resulting in hypovolaemic shock and circulatory failure. ■ Initially there is an increased vascular permeability leading to loss of water and proteins into the extravascular compartment leading to haemoconcentration. ■ Large volumes of crystalloid solutions should be infused to restore the constricted intravascular fluid space while smaller amounts of Albumex® 20 are required to maintain adequate plasma volume and colloid osmotic pressure.
Haemodialysis	■ May be used to assist with the rapid removal of excess extravascular fluid and to maintain perfusion pressure.
Adult Respiratory Distress Syndrome	■ ARDS, an acute inflammatory lung injury with diffuse alveolar damage and increased vascular permeability, is characterised by inadequate oxygenation secondary to non-cardiogenic pulmonary oedema. ■ Combination therapy with Albumex® 20 and diuretics may improve fluid balance, oxygenation, and haemodynamics. ■ In patients who have undergone abdominal surgery, intravenous administration of 20% albumin immediately after the operation has been shown to improve lung compliance and gaseous exchange.
Therapeutic plasma exchange	■ TPE is a procedure in which approximately one plasma volume is exchanged with a colloid replacement solution. The choice of replacement fluid and its concentration are determined by the particular clinical situation and the frequency of the procedure. ■ Iso-oncotic 4% albumin solution is the preferred replacement material. If the patient's serum albumin level is not maintained 20% albumin may be indicated. If exchange occurs less frequently than once a week, less concentrated colloids may be appropriate.

Precautions

- **Adverse effects**
  Adverse reactions to albumin solutions are uncommon and are usually mild and transient. Chills, fever, urticaria, flushing, nausea, headache and dyspnoea may occur. More serious allergic events including hypotension and anaphylaxis are reported. Hypotension has been reported in patients given albumin who are on angiotensin-converting enzyme (ACE) inhibitors.

- **Aluminium accumulation**
  Albumex® 20 contains trace amounts of aluminium (≤ 200 µg/L). Accumulation of aluminium in patients with chronic renal insufficiency has led to toxic manifestations such as hypercalcaemia, vitamin D-refractory osteodystrophy, anaemia and severe progressive encephalopathy. Therefore, when large volumes of albumin are contemplated for administration to such patients, serious consideration should be given to these potential risks relative to the anticipated benefits.

- **Circulatory overload**
  The colloid osmotic effect of Albumex® 20 is approximately four times that of plasma. Circulatory overload can be avoided by monitoring the rate and volume of infusion. Patients with cardiac failure, renal insufficiency or stabilised chronic anaemia often have an increased circulatory plasma volume and are at special risk of developing circulatory overload.

- **Compatibility with other fluids**
  Albumex® 20 should not be mixed with protein hydrolysates, amino acid solutions, solutions containing alcohol, or solutions containing drugs that bind to albumin such as calcium channel blockers.

- **Hyperoncotic effects**
  As Albumex® 20 is hyperoncotic, it must be diluted with or followed by crystalloid solution in the presence of dehydration or shock.

  If Albumex® 20 is diluted to an iso-oncotic protein concentration (4-5% albumin) prior to administration, this must be done with an iso-osmotic electrolyte solution such as 0.9% saline. Under no circumstances should water be used since the lower tonicity will lead to intravascular haemolysis.

- **Hypoproteinaemia**
  The infusion of Albumex® 20 is not justified in hypoproteinaemic states associated with chronic cirrhosis, malabsorption, protein losing enteropathies, pancreatic insufficiency, undernutrition. Albumex® 20 may be indicated as a temporising measure in selected cases awaiting liver transplantation.

- **Nephrosis**
  In chronic nephrosis, infused albumin is promptly excreted by the kidneys with no or limited relief of the chronic oedema. Albumex® 20 may be indicated as a temporising measure in selected cases awaiting renal transplantation.

- **Shock**
  Administration of albumin can aggravate myocardial depression when present in patients with shock.

- **Sodium levels**
  The sodium levels in this product are 48 - 100 mmol/L. This should be noted when the product is used in patients requiring sodium restriction.

5.4 Immunoglobulin Preparations

General Considerations

Immunoglobulin products are sterile, preservative-free solutions of concentrated IgG prepared by Cohn cold-ethanol fractionation and chromatography of human plasma. In the case of specific immunoglobulins, for example anti-D immunoglobulin and hepatitis B immunoglobulin, plasma is obtained from individuals with a high titre of the required antibody.

The manufacturing process contains two or more viral removal steps such as pasteurisation (inactivation) and viral filtration (nanofiltration) reducing the possibility of virus transmission. Currently available immunoglobulins have not been implicated in the transmission of viral infectious diseases including human immunodeficiency virus (HIV).

Precautions

- Immunoglobulin products approved for intramuscular injection must not be administered intravenously because of the potential for severe adverse reactions. They should be given slowly by deep intramuscular injection using an appropriate sized needle and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel.
- If an intramuscular dose of more than 5 mL is required, it is advisable to administer in divided doses at different sites. Hyaluronidase and/or a suitable local anaesthetic may be added to the injection if desired. When large doses of immunoglobulins are required, consider using an alternative product suitable for intravenous administration.
- Intramuscular injection of immunoglobulin products should be avoided in patients with a low platelet count. In these circumstances they may be given subcutaneously.
- Immunoglobulin products approved for subcutaneous infusion must not be administered intravenously because of the potential for severe adverse reactions.
- Immunoglobulin products should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations. In the case of allergic shock, treatment should follow recommended guidelines for managing anaphylaxis.

Contraindications

Immunoglobulin products are contraindicated in individuals:

- With isolated immunoglobulin A (IgA) deficiency, unless they have been tested and shown not to have circulating anti-IgA antibodies.
- Who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection.

Interactions with Other Drugs

- Immunoglobulin should not be mixed with other pharmaceutical products, except as indicated by the manufacturer.
- Passively acquired antibody can interfere with the response to live, attenuated virus vaccines. Therefore, administration of such vaccines, e.g., measles and varicella, should be deferred for at least 3 months after passive immunisation with immunoglobulin preparations and antibody-containing blood components, i.e., whole blood, resuspended red cells, plasma and platelets. *General Recommendations on Immunization* from the Advisory Committee on Immunization Practices (ACIP), including recommended deferral intervals, are available from the Centers for Disease Control and Prevention (CDC) at www.cdc.gov/vaccines/. Consultation with a NZBS Transfusion Medicine Specialist/ Medical Officer is recommended.
- By the same token, immunoglobulins and antibody-containing blood components should not be administered for at least two weeks after a live vaccine has been given.
- Inactivated vaccines may be administered concurrently with passive antibody (although in separate syringes) to induce active immunity, as is sometimes done for tetanus-prone wounds.

Passive Transfer of Antibodies and Interference with Serological Testing

After injection of immunoglobulin, the transient rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Although it has not been determined whether or not immunoglobulin products can transmit human parvovirus B19, they are known to contain antibodies to the virus.

Adverse Reactions

- Local tenderness, erythema and stiffness may occur at the site of injection and may persist for several hours. This may occur after any intramuscular injection.
- Mild pyrexia, malaise, drowsiness and urticaria have occasionally been reported after injections of immunoglobulins.
- True allergic responses are rare. Skin lesions, headache, dizziness, nausea, generalised hypersensitivity reactions and convulsions have been reported on rare occasions. These occur more frequently in patients who have a profound hypogammaglobulinaemia.

5.4.1 Normal Immunoglobulin-VF

Normal Immunoglobulin-VF is a sterile, preservative-free solution containing 160 mg/mL human plasma proteins with at least 98% being immunoglobulin (mainly IgG). Normal Immunoglobulin-VF is intended for intramuscular injection.

Indications for Use

Table 5.13: Clinical Indications for Use of Normal Immunoglobulin-VF

Indication	Comments
Primary hypogammaglobulinaemia	Congenital and acquired forms.
Secondary hypogammaglobulinaemia	Acquired hypogammaglobulinaemia, as seen in haematological malignancies, nephrosis or protein-losing enteropathy, complicated by recurrent infections.
Hepatitis A	Routine passive protection is recommended in those exposed less than two weeks previously for the following categories of individuals: ■ Household contacts of an index case who have not already had hepatitis A or have no evidence of immunity to the virus ■ Common source exposures (i.e., a vehicle such as food or water is identified as a common source of infection for multiple cases of hepatitis) where administration of Normal Immunoglobulin-VF should be considered for all those exposed ■ Institutional contacts ■ Staff in institutions where hepatitis is endemic ■ Newborn infants where the mother has developed acute hepatitis A from two weeks before birth to one week after birth Routine prophylaxis is not recommended for school, factory or hospital contacts. Active immunisation with hepatitis A vaccine is recommended in these circumstances. Vaccination is also recommended for those at risk of exposure to hepatitis A, such as persons travelling to areas of high or intermediate endemicity and staff at child day care centres. Immunoglobulin is no longer routinely recommended for pre-travel use however may be appropriate for providing optimal protection to adults aged over 40 years of age, immunocompromised individuals and those with chronic medical conditions including liver disease who are planning to depart in < 2 weeks. Travellers under 12 months of age and those unable or unwilling to receive vaccination should also receive immunoglobulin.

Table 5.13: Clinical Indications for Use of Normal Immunoglobulin-VF continued

Indication	Comments
Rubella	Although Normal Immunoglobulin-VF can prevent or modify the clinical disease in susceptible rubella contacts if given within 72 hours of exposure, it does not prevent viraemia in such patients. It should not be relied upon to prevent congenital malformations due to rubella if given to susceptible pregnant women during the first trimester. Therefore, routine use of Normal Immunoglobulin-VF for post-exposure prophylaxis of rubella in early pregnancy is not recommended. It may be considered if termination of the pregnancy is not an option but termination must be discussed when maternal infection is confirmed.
Measles	Recommended for the following contacts of measles cases: ■ Immune-compromised or immune-deficient children ■ Pregnant women ■ Immune-competent children aged under 15 months beyond 72 hours after exposure ■ People outside the 72-hour window for MMR who have not had a history of measles infection or vaccination For these individuals Normal Immunoglobulin-VF is given to attenuate disease and should be given as soon as possible, to a maximum of six days after exposure.
Poliomyelitis	Normal Immunoglobulin-VF is recommended for susceptible contacts not previously immunised against poliomyelitis.

In general, the earlier in the incubation period of hepatitis A, rubella, measles or poliomyelitis that normal immunoglobulin is given, the greater its effectiveness.

Dosage and Administration

Table 5.14: Dosage Recommendations for Normal Immunoglobulin-VF

Indication	Dose (mL/kg)	Dose Interval (months)
Hepatitis A		
■ Short-term prophylaxis (general)	0.03	
■ Long-term prophylaxis (general)	0.06	5 monthly[1]
■ Short term travel (< 3 months)	0.03	
■ Long term travel[2] (> 3 months)	0.06	Repeat 4-6 monthly
■ Institutional contacts[2]	0.06	
■ Institutions where hepatitis A endemic[2]	0.06	Repeat 6 monthly
Hypogammaglobulinaemia	0.6	Additional loading dose in first month, then monthly
Measles prophylaxis[3]	0.6	
Poliomyelitis	0.3	
Rubella	0.2	

[1]Perform serological checks to assess if active immunity has developed.
[2]Use of hepatitis A vaccine may be more appropriate for these individuals provided there is sufficient time for active immunity to develop (7–10 days).
[3]0.6 mL/kg to a maximum dose of 5 mL in immune-competent infants aged under 15 months and to a maximum dose of 15 mL, recommended as three 5 mL injections, in pregnant women, immune-competent adults and immune-compromised or immune-deficient children.

5.4.2 Hepatitis B Immunoglobulin-VF

Hepatitis B Immunoglobulin-VF is a sterile, preservative-free solution containing not less than 100 IU/mL neutralising hepatitis B antibodies. Donations used in the preparation of Hepatitis B Immunoglobulin-VF are selected on the basis that they contain high levels of specific antibodies against HBsAg. Hepatitis B Immunoglobulin-VF is provided as 400 IU vials, intended for intramuscular injection.

Indications for Use

Hepatitis B Immunoglobulin-VF is indicated for:

- Post-exposure prophylaxis in persons who did not receive prior vaccination or whose vaccination regimen is incomplete, or when the hepatitis B antibody level is inadequate (< 10 IU/L)
- Infants born to HBsAg-positive mothers, either chronic carriers or those who contract hepatitis B during pregnancy
- Patients with hepatitis B undergoing a liver transplant, to protect the transplanted liver

Post-exposure prophylaxis should be considered following percutaneous or permucosal exposure to HBsAg-positive or suspected HBsAg-positive material, for example, following needle stick injury, oral ingestion or sexual exposure.

Dosage and Administration

For maximum protective effect, Hepatitis B Immunoglobulin-VF should be given within 72 hours of exposure. Efficacy is greatly reduced if it is given after a longer interval.

Table 5.15: Prophylaxis with Hepatitis B Immunoglobulin-VF in Adults Following Percutaneous or Permucosal Exposure to HBsAg-positive or Suspected HBsAg-positive Material

Source material	Vaccination history	
	No prior vaccination or incomplete vaccination regimen	**Completed vaccination regimen**
Confirmed positive for HBsAg	A single dose of 400 IU hepatitis B immunoglobulin immediately and initiate hepatitis B vaccination regimen at the same time.	Test for anti-HBs. If level <10 IU/L, give a single dose of 400 IU hepatitis B immunoglobulin immediately plus a booster vaccination.
High risk for HBsAg but not confirmed	Initiate hepatitis B vaccination regimen. Test source material for HBsAg and, if positive, give a single dose of 400 IU hepatitis B immunoglobulin.	Test exposed person for HBs antibody. If level <10 IU/L, test source material for HBsAg and, if positive, give a single dose of 400 IU Hepatitis B Immunoglobulin-VF plus a booster vaccination.
Uncertain or low risk	Initiate hepatitis B vaccination regimen.	Nothing required.

Active immunisation with hepatitis B vaccine should always be commenced in conjunction with administration of Hepatitis B Immunoglobulin-VF in patients exposed to hepatitis B virus. Vaccination should be initiated simultaneously with the passive immunoglobulin, but administered at a different site.

Prophylaxis in Infants Born to HBsAg-positive Mothers

Where HyperHEP™ S/D is unavailable, give 100 IU Hepatitis B Immunoglobulin-VF to the infant at birth and initiate simultaneously a hepatitis B vaccination regime administered at a different site.

5.4.3 HyperHEP™ S/D

HyperHEP™ S/D is a sterile, preservative-free, solvent/detergent-treated solution containing not less than 220 IU/mL neutralising hepatitis B antibodies. Donations used in the preparation of HyperHEP™ S/D are selected on the basis that they contain high levels of specific antibodies against HBsAg. HyperHEP™ S/D is supplied as a 0.5 mL neonatal single-dose syringe containing at least 110 IU of hepatitis B immunoglobulin, intended for intramuscular injection.

Indications for Use

HyperHEP™ S/D is indicated for:

- Infants born to HBsAg-positive mothers, either chronic carriers or those who contract hepatitis B during pregnancy

Dosage and Administration

The infant should receive a single 110 IU neonatal dose of HyperHEP™ S/D at birth. The dose is preferably given within 12 hours of birth as efficacy decreases markedly if treatment is delayed beyond 48 hours. Hepatitis B vaccine should be administered concurrently with hepatitis B immunoglobulin (or at most within 7 days) but at a separate site. If administration of the first dose of hepatitis B vaccine is delayed for as long as 3 months, then a 0.5 mL dose of HyperHEP™ S/D should be repeated at 3 months. If vaccine is refused, the 0.5 mL dose of HyperHEP™ S/D should be repeated at 3 and 6 months.

5.4.4 Tetanus Immunoglobulin-VF

Tetanus Immunoglobulin-VF is a sterile, preservative-free, pasteurised solution with a tetanus antitoxin activity of not less than 100 IU/mL. Donations used in the preparation of tetanus immunoglobulin are selected on the basis that they contain high levels of specific antibodies against the toxin of Clostridium tetani. Tetanus Immunoglobulin-VF is intended for intramuscular injection.

Indications for Use

Tetanus Immunoglobulin-VF is indicated for:

- Passive protection of individuals who have sustained a tetanus-prone wound and who have either not been actively immunised against tetanus or whose immunisation history is doubtful
- Passive protection of fully immunised individuals with a tetanus-prone wound if more than 10 years have elapsed since the last dose of tetanus toxoid vaccine

In both of the above instances, active immunisation with tetanus vaccine should be commenced at the same time. Although tetanus immunoglobulin and vaccine can be given at the same time, they should be administered in opposite limbs, using separate syringes.

Table 5.16: Guide to Tetanus Prophylaxis in Wound Management

History of active immunisation	Type of wound			
	Clean, minor wound		All other wounds	
	Tetanus Vaccine[1]	Tetanus Immunoglobulin-VF	Tetanus Vaccine[1]	Tetanus Immunoglobulin-VF
Never immunised or < 3 doses	Yes	No	Yes	Yes
Immunised and ≥ 3 doses:				
< 5 years since last dose	No	No	No	No
5-10 years since last dose	No	No	Yes	No
> 10 years since last dose	Yes	No	Yes	Yes

[1]Children < 8 years old receive combined DTPa vaccine. Persons 8 years and older receive combined dT vaccine.

Dosage and Administration

Good medical care is essential in the prevention of tetanus from fresh wounds. Thorough cleansing and removal of all foreign and necrotic material from the site of injury is important.

The minimum routine prophylactic dose of Tetanus Immunoglobulin-VF for adults or children is 250 IU given slowly by deep intramuscular injection. The dose should be doubled to 500 IU if the wound is grossly contaminated or if more than 24 hours have elapsed since injury or if there is a risk of heavy contamination or following burns.

An intravenous preparation of tetanus antitoxin is appropriate for patients where large doses are indicated (i.e., treatment of tetanus), or when the patient has a significant haemostatic defect which may cause bleeding following intramuscular injection. In New Zealand, Intragam® P is used to provide intravenous tetanus immunoglobulin. As the level of immunoglobulin in each batch varies consultation with an NZBS Transfusion Medicine Specialist/Medical Officer is recommended prior to prescription.

Treatment of Suspected or Confirmed Clinical Tetanus

For the treatment of suspected or confirmed clinical tetanus it is recommended that a single dose Intragam® P containing 4000 IU tetanus immunoglobulin is given to cover the typical 4-6 week course of the illness. NZBS acknowledges that the optimal dose, which may be as low as 500 IU, is not yet defined.

5.4.5 Zoster Immunoglobulin-VF

Zoster Immunoglobulin-VF is a sterile, preservative-free solution containing not less than 200 IU/vial varicella-zoster antibody. Plasma for Zoster Immunoglobulin-VF is obtained from blood donors who have recently recovered from shingles or chickenpox. Donations are selected on the basis that they contain high levels of antibodies against Herpesvirus varicellae. Zoster Immunoglobulin-VF is intended for intramuscular injection.

Indications for Use

Zoster Immunoglobulin-VF is indicated for prophylaxis against varicella in patients who meet all of the following four criteria listed below.

Table 5.17: Clinical Indications for the Use of Zoster Immunoglobulin-VF

Criteria	Required Condition(s)
One of the following underlying illnesses or conditions:	■ Neoplastic disease (leukaemia or lymphoma) ■ Congenital or acquired immune compromise ■ Immunosuppressive therapy with steroids or antimetabolites ■ Pregnancy in non-immune woman
One of the following types of exposure to chickenpox or shingles patients:	■ Household contact ■ Playmate contact (> 1 hour play indoors) ■ Hospital contact (in same 2 to 4 bedroom or adjacent beds in a large ward) ■ Newborn contact (newborn of mother who develops chickenpox (but not zoster) from 7 days before to 7 days after delivery) ■ Premature infant ≥ 28 weeks gestation whose mother lacks a prior history of chickenpox ■ Premature infant < 28 weeks gestation or < 1000 g regardless of maternal history
Negative or unknown prior history of chickenpox	
Zoster Immunoglobulin-VF can be given within 96 hours[1] for best effect (however may be given up to 10 days post-exposure)	

[1]*For guidance on the management of both pregnant women exposed to varicella or zoster and newborns exposed to maternal perinatal varicella or zoster, including recommendations on the timing of Zoster Immunoglobulin-VF administration in these situations, refer to the NZ Ministry of Health Immunisation Handbook.*

The Starship Children's Health Clinical Guideline covering *Zoster Immunoglobulin* (2013) and the National Child Cancer Network Guideline for *Immunisation of Children During and After Cancer Therapy* (2013) provide additional specific detail on the use of zoster immunoglobulin in paediatric post-exposure prophylaxis and are summarised below. Consultation with a specialist paediatrician or NZBS Transfusion Medicine Specialist/ Medical Officer is recommended prior to prescription.

Table 5.18: Recommendations for the Use of Zoster Immunoglobulin in Children at Risk for Developing Serious Varicella Infection and Complications

At Risk Group	Comments
High dose corticosteroid therapy	Considered as > 0.5 mg/kg/day of prednisone or equivalent within the last three months.
Receiving immunosuppressive treatment or chemotherapy	All children regardless of VZV IgG status.
Completed immunosuppressive treatment or chemotherapy[1]	For 3 months after therapy if VZV IgG negative. Regardless of VZV IgG status: - for 6 months after autologous HPC transplant. - for 12 months[2] after allogeneic HPC transplant.
Malignancy	
Congenital immunodeficiency	
HIV positive; no prior history of chickenpox	

[1]Patients who have received antithymocyte globulin, alemtuzumab, fludarabine or other T-cell immunomodulation should be discussed with a paediatric oncologist.
[2]May be longer if chronic GVHD is present.

Varicella-zoster immunoglobulin is of no value in the treatment of established varicella or zoster infection. High levels of circulating antibody do not prevent dissemination of infection.

Dosage and Administration

The required dose is 125 IU per 10 kg bodyweight and rounded up to the nearest 200 IU to a maximum of 600 IU.

Table 5.19: Weight-Based Dosing Schedule for Zoster Immunoglobulin-VF

Weight of Patient (kg)	Dose (IU)	No. of Vials
0 - 10	125	1
10.1 - 20	250	2
20.1 - 30	375	2
30.1 - 40	500	3
>40	600	3

An intravenous preparation of varicella-zoster immunoglobulin is appropriate when the patient has a significant haemostatic defect which may cause bleeding following intramuscular injection. In New Zealand, Intragam® P is used to provide intravenous varicella-zoster immunoglobulin. As the level of immunoglobulin in each batch varies, consultation with an NZBS Transfusion Medicine Specialist/Medical Officer is recommended prior to prescription.

5.4.6 Berirab® P (Rabies immunoglobulin)

Berirab® P does not have full New Zealand registration and so consultation with an NZBS Transfusion Medicine Specialist/Medical Officer is required prior to product release.

Berirab® P is a sterile solution of anti-rabies immunoglobulin prepared from the plasma of individuals immunised with rabies vaccine. Donations are selected on the basis that they contain high levels of rabies antibody. Each 1 mL of Berirab® P contains a minimum of 150 IU/mL of rabies antibody. Berirab® P should be administered intramuscularly.

If anatomically feasible, the full dose should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration.

Indications for Use

Berirab® P is indicated for prophylaxis in individuals suspected of having exposure to rabies from:

- Bites, licks, scratches or other injuries caused by a suspected rabid animal
- Mucous membrane contamination with infectious tissue or saliva of suspected rabid animal
- Mucous membrane or new skin wound contact with rabies live attenuated vaccine (e.g., vaccination baits)

The exception to these indications is individuals who have previously been immunised, pre- or post-exposure, with rabies vaccine prepared from human diploid cells.

The recommended dose of Berirab® P is 20 IU per kg body weight which should be given in conjunction with rabies vaccine.

5.4.7 Rh(D) Immunoglobulin-VF (Anti-D immunoglobulin)

Rh(D) Immunoglobulin-VF is a sterile, preservative-free solution with an anti-D antibody content of either 625 IU or 250 IU per vial. Rh(D) Immunoglobulin-VF is prepared from plasma obtained from either New Zealand voluntary or USA remunerated donors who have been immunised to the RhD antigen. Rh(D) Immunoglobulin-VF is intended for deep intramuscular injection using an appropriate sized needle.

Anti-D immunoglobulin acts by suppressing the immune response of RhD negative individuals exposed to RhD positive red cells. Such exposure follows the passage of cells from the fetal to the maternal circulation or the transfusion of RhD positive red cells. Clinical studies indicate that the administration of anti-D immunoglobulin to a RhD negative mother within 72 hours of the birth of a RhD positive infant reduces

the incidence of RhD isoimmunisation from 12 - 13% to 1 - 2%. Studies have also shown that this number can be reduced to < 1.0% by antenatal prophylaxis with anti-D immunoglobulin administered at 28 and 34 weeks of pregnancy.

Indications for Use

Rh(D) Immunoglobulin-VF is indicated for:

- Prevention of RhD sensitisation in RhD negative females with child-bearing potential

Rh(D) Immunoglobulin-VF may, in certain circumstances, also be used for protection against the development of anti-D sensitisation when RhD positive donor red cells are transfused to RhD negative females without child-bearing potential and to RhD negative males.

Precautions

There is some evidence to suggest that intramuscular administration of anti-D immunoglobulin may be associated with an increased risk of lack of effect in patients with a body mass index (BMI) > 30. An Expert Panel Consensus Position Statement (available online at www.transfusion.com.au/node/612) provides recommendations regarding the use of anti-D immunoglobulin in these patients.

Contraindications

Rh(D) Immunoglobulin-VF should not be given to RhD positive individuals or to RhD negative individuals previously sensitised to the RhD antigen.

Rh(D) Immunoglobulin-VF should not be given to RhD negative women with detectable anti-D except where the antibody is passively acquired due to prior antenatal administration. If unsure whether the anti-D detected in the mother's blood is passively acquired or preformed, the treating clinician and/or a NZBS Transfusion Medicine Specialist/Medical Officer should be consulted. If there is continuing doubt, Rh(D) Immunoglobulin-VF should be administered. Although there is no benefit in administering Rh(D) Immunoglobulin-VF to a woman who is already sensitised to RhD antigen, there is no more risk than when it is given to a woman who is not sensitised.

Dosage and Administration: Antenatal and Postpartum Prophylaxis

The following table is based on the 2003 Australian National Blood Authority (NBA) *Guidelines on the Prophylactic Use of RhD Immunoglobulin (Anti-D) in Obstetrics* and the 2013 British Committee for Standards in Haematology *Guideline for the Use of Anti-D Immunoglobulin for the Prevention of HDFN.* The table below is reproduced, together with additional explanatory notes, in Section 6.8: *Hemolytic Disease of the Fetus and Newborn (HDFN)* of this Handbook. In 2011 the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) endorsed the 2003 NBA *Guidelines*, however it should be noted that the NZ Ministry of Health does not recommend routine antenatal anti-D prophylaxis (RAADP).

Table 5.20: Indications for the Use of Anti-D Immunoglobulin for the Prevention of HDFN (unless the fetus is confirmed to be RhD negative)

Timing	Clinical Indication
Routine antenatal prophylaxis[1]	A RhD negative woman, not previously immunised to produce anti-D; one dose at each of 28 and 34 weeks gestation.[2] **Anti-D immunoglobulin dose: 625 IU (125 µg)**
Potential sensitising event during first trimester up to and including 12 weeks gestation	A RhD negative woman, not previously immunised to produce anti-D, with an obstetric indication. ■ Uterine bleeding where this repeated, heavy or associated with abdominal pain[3] ■ Miscarriage[3] ■ Termination of pregnancy ■ Ectopic pregnancy ■ Molar pregnancy **Anti-D immunoglobulin dose: 250 IU (50 µg)**[4]
Potential sensitising event beyond first trimester[5]	A RhD negative woman, not previously immunised to produce anti-D, with an obstetric indication. ■ Amniocentesis, chorionic villus sampling, and intrauterine fetal blood sampling ■ Antepartum haemorrhage (or unexplained uterine pain) ■ External cephalic version (performed or attempted) ■ Abdominal trauma sufficient to cause FMH ■ Ectopic pregnancy ■ Molar pregnancy ■ Intrauterine death or stillbirth ■ Miscarriage, threatened miscarriage ■ Termination of pregnancy **Anti-D immunoglobulin dose: 625 IU (125 µg)**
Postpartum prophylaxis[6]	A RhD negative woman, not previously immunised to produce anti-D, who gives birth to a RhD positive baby. **Anti-D immunoglobulin dose: 625 IU (125 µg) with additional dose(s) indicated where fetomaternal haemorrhage is > 6 mL fetal red cells**

[1]Routine antenatal anti-D prophylaxis (RAADP) should be administered regardless of, and in addition to, prophylaxis given for a potentially sensitising event.
[2]A sample for antibody testing should be taken prior to administration of anti-D immunoglobulin at 28 weeks.
[3]Before 12 weeks gestation, in cases of either spontaneous complete miscarriage where the uterus is not instrumented or mild painless vaginal bleeding, the risk of fetomaternal haemorrhage is negligible.
[4]For multiple pregnancies the recommended anti-D immunoglobulin dose is 625 IU (125 µg).
[5]Routine antenatal prophylaxis does not preclude prophylaxis for a potentially sensitising event.
[6]Routine antenatal prophylaxis or prophylaxis for a potentially sensitising event does not preclude postpartum prophylaxis.

NZBS is aware that an alternative approach to RAADP may be to administer a single 1500 IU anti-D dose at 28 weeks, however this is currently not endorsed in NZ.

Dosage and Administration: Transfusion of RhD Positive Blood Components

The recommended dose of Rh(D) Immunoglobulin-VF is 100 IU per mL RhD positive red cells. A single 625 IU dose of Rh(D) Immunoglobulin-VF will therefore suppress the immune response induced by up to 6 mL of RhD positive red cells. Consultation with a NZBS Transfusion Medicine Specialist/Medical Officer is recommended in the event that a recipient has been transfused with a larger volume of RhD positive red cells.

The amount of red cell contamination in platelet components supplied by NZBS is less than 1 mL per unit and therefore adequately covered by a single 250 IU dose of Rh(D) Immunoglobulin-VF. A single 250 IU dose of Rh(D) Immunoglobulin-VF (administered subcutaneously in severely thrombocytopenic patients) is likely to be sufficient to cover up to five adult therapeutic doses of RhD positive platelets given within a 6-week period.

5.4.8 Rhophylac® (Anti-D immunoglobulin)

Rhophylac does not have full New Zealand registration and so consultation with an NZBS Transfusion Medicine Specialist is required prior to product release.

Rhophylac® is a sterile, preservative-free solution in a pre-filled 2 mL syringe containing 1500 IU (300 µg) anti-D IgG immunoglobulin. Rhophylac® is manufactured from plasma obtained from remunerated donors who have been immunised to the RhD antigen. It is important to note that this product is obtained from a screened and carefully monitored donor pool and has a similar safety profile to Rh(D) Immunoglobulin-VF. Rhophylac® may safely be administered intramuscularly or intravenously.

Indications for Use

Rhophylac® has similar indications and contraindications for use as other anti-D immunoglobulin products. While Rhophylac® is an acceptable alternative to Rh(D) Immunoglobulin-VF, it is supplied by NZBS only when stock of this product is unavailable, large doses of anti-D are indicated (i.e., > 2 vials 625 IU Rh(D) Immunoglobulin-VF), or when a product suitable for intravenous administration is required.

Dosage and Administration

A maximum dose of 15,000 IU is sufficient in the case of larger incompatible transfusions independent of whether the transfusion volume is greater than 300 mL of RhD positive red cells. Treatment can usually be given without preceding exchange transfusion when the transfused RhD positive blood represents less than 20% of the total circulating red blood cells. If the volume exceeds 20%, consideration should be given to red cell exchange transfusion to reduce the load of RhD positive cells prior to Rhophylac® administration.

Precautions

- Following a large fetomaternal bleed or incompatible transfusion, patients receiving large doses of anti-D immunoglobulin should be monitored, as there is a risk of haemolytic reaction. To reduce this risk, the maximum recommended dose administration rate is 3000 IU every 8 hours.
- Rhophylac® can contain antibodies to other Rh antigens and the passive transfer

of these antibodies may be detectable by serological testing methods.

- There is some evidence to suggest that intramuscular administration of anti-D immunoglobulin may be associated with an increased risk of lack of effect in patients with a body mass index (BMI) > 30. An Expert Panel Consensus Position Statement (available online at www.transfusion.com.au/node/612) provides recommendations regarding the use of anti-D immunoglobulin in these patients.

5.4.9 Intragam® P (Normal immunoglobulin, intravenous, IVIg)

Intragam® P is a sterile, preservative free solution containing 6 g of human protein and 10 g of maltose in each 100 mL, available in 10 mL (0.6 g), 50 mL (3 g) and 200 mL (12 g) vials. The solution has a pH of 4.25 and isotonicity is achieved by the addition of maltose. Intragam® P is made by chromatographic fractionation of large pools of human plasma obtained from New Zealand's voluntary and non-remunerated blood donors. Intragam® P is intended for intravenous administration.

The distribution of IgG subclasses present in Intragam® P is: IgG1 (61%), IgG2 (36%), IgG3 (3%) and IgG4 (1%). Intragam® P contains only trace amounts of IgA (typically <0.025 mg/mL). The actual amount of IgA in each batch is printed on the label.

The protein has not been chemically or enzymatically modified and the manufacturing process contains specific steps to reduce the possibility of virus transmission including pasteurisation (heating at 60°C for 10 hours) and incubation at low pH.

Indications for Use

Intragam® P is registered for use as replacement IgG therapy and immunomodulatory therapy for a number of conditions.

Table 5.21: Registered Indications for Use of Intragam® P

Indication	Comments
Replacement Therapy	
■ Primary immunodeficiency	Causing hypogammaglobulinaemia
■ Acquired hypogammaglobulinaemia	Symptomatic with recurrent infections
Immunomodulatory Therapy	
■ Primary immune thrombocytopaenia[1]	
■ Kawasaki disease	
■ Guillain-Barre syndrome	

[1]*Recommendations for the use of IVIg in immune thrombocytopaenia (ITP) can be found in the International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia in Blood 2010; 115: 168-186 and the American Society of Hematology (ASH) 2011 Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia.*

In addition, intravenous immunoglobulin has an established and emerging therapeutic role in a wide range of, and in some cases uncommon or rare, autoimmune and inflammatory diseases including chronic inflammatory demyelinating polyneuropathy,

inflammatory myopathies, Lambert–Eaton myasthenic syndrome, multifocal motor neuropathy, myasthenia gravis, and stiff-person syndrome. Intragam® P is not registered for these indications in New Zealand and issue of this product is subject to consultation between the specialist physician and a NZBS Transfusion Medicine Specialist/Medical Officer.

Comprehensive evidence-based guidelines for the use of IVIg are lacking. Substitutes, such as the 2012 Australian National Blood Authority *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia (2nd ed.)* and the 2011 UK Department of Health *Clinical Guidelines for Immunoglobulin Use (2nd ed. update)* provide information about the criteria for accessing IVIg and should be followed wherever possible to avoid the inappropriate utilisation of Intragam® P.

Dosage and Administration

Intragam® P may be infused undiluted. It may also be infused diluted with up to 2 parts of 0.9% saline or 5% glucose.

- The infusion should be commenced at the rate of 1 mL per minute.
- After 15 minutes the rate may be gradually increased to a maximum of 3 - 4 mL per minute over a further 15 minutes.
- Too rapid a rate of infusion may cause flushing and changes in heart rate and blood pressure.
- Patients naive to Intragam® P, switching from an alternative IVIg product, or who have not received IVIg for a long time, should be closely monitored during the first infusion.
- In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Replacement Therapy

- The optimal dose and frequency of administration of Intragam® P must be determined for each patient. Freedom from recurrent bacterial infections is usually achieved with a serum IgG level > 5 g/L.
- Most patients initially receive 400 mg IgG per kilogram body weight, followed by monthly maintenance doses of at least 200 mg per kilogram body weight.
- The monthly maintenance dose, guided by the patient's clinical status and pre-infusion (trough) serum IgG level, is often 300 - 450 mg of IgG per kilogram body weight.
- As catabolic rates vary, the IgG levels of new patients should be monitored regularly for several monthly cycles to determine the effective dose.

Immunomodulatory Therapy

Primary immune thrombocytopaenia

- Patients should receive up to a maximum total cumulative dose of 2.0 g IgG per kilogram body weight, over 2 - 5 days.

Kawasaki disease

- Patients should receive 1.6 - 2.0 g IgG per kilogram body weight, administered in divided doses over 2 - 5 days, or 2.0 g IgG per kilogram body weight as a single dose.

Guillain-Barre syndrome

- Patients should receive 0.4 g IgG per kilogram body weight per day for five days.

IVIg dosage recommendations for off-label indications are available in *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia (2nd ed.)*, developed by the Australian National Blood Authority (NBA) in 2012.

Contraindications

Intragam® P is contraindicated in individuals who have had a true anaphylactic reaction to the active substance or the excipient.

Precautions

- **Administration**
  Intragam® P should only be administered intravenously. It is possible that Intragam® P may, on rare occasions, cause a precipitous fall in blood pressure and a clinical picture of anaphylaxis. Therefore, adrenaline and oxygen should be available for the treatment of such an acute reaction.

- **Aseptic meningitis**
  Aseptic meningitis syndrome has been reported to occur infrequently in association with IVIg treatment.

- **IgA antibodies**
  Intragam® P contains trace amounts of IgA which may provoke anaphylaxis in patients with IgA antibodies, such as those with IgA deficiency.

- **Positive direct antiglobulin tests and red cell haemolysis**
  Positive direct antiglobulin tests and red cell haemolysis have been reported following high dose infusion of intravenous immunoglobulin due to the presence of anti-A, anti-B, and occasionally with anti-D or other erythrocyte antibodies in the product. Such red cell sensitisation may cause crossmatching difficulties and transient haemolytic anaemia.

- **Renal dysfunction**
  There have been reports of renal dysfunction and acute renal failure in patients receiving IVIg. Patients should be adequately hydrated prior to administration of IVIg.

- **Thromboemblism**
  Thrombotic events have been reported in association with IVIg therapy. Caution should be exercised in prescribing and administering Intragam® P in in patients with pre-existing risk factors for thrombotic events.

- **Thrombophlebitis**
  Prolonged administration (over 6 hours) using large doses (greater than 400 mg/kg) may result in thrombophlebitis at the infusion site.

Adverse Reactions

Reactions to intravenous immunoglobulin tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient's vital signs and general status be monitored regularly throughout the infusion.

The types of reactions that may occur include: malaise, abdominal pain, headache, chest-tightness, facial flushing or pallor, hot sensations, dyspnoea, non-urticarial skin rash, itching, arthralgia, tissue swelling, hypotension, nausea, or vomiting. Should any of these reactions develop during infusion of Intragam® P, the infusion should be temporarily stopped (5 - 10 minutes) until the patient improves clinically and then cautiously recommenced at a slower rate.

Allergic reactions are most likely to occur during the first hour of the infusion.

True hypersensitivity reactions to intravenous immunoglobulin such as urticaria, angioedema, bronchospasm or hypotension occur very rarely. Should an anaphylactic reaction to Intragam® P develop, the infusion should be stopped and immediate treatment instituted with adrenaline and oxygen.

Interactions with Other Medicines

Passively acquired antibody can interfere with the response to live attenuated virus vaccines such that vaccine administration should be deferred for at least 3 months. In the case of measles and varicella vaccines following IVIg products, the impairment may persist for up to 12 months. Where deferral is impractical, patients receiving such vaccines should have their antibody response checked. By the same token, immunoglobulins should not be administered for at least two weeks after live attenuated vaccines are given. Consultation with a NZBS Transfusion Medicine Specialist/Medical Officer is recommended.

Interaction with Capillary Glucose Measurement

Caution should be exercised when interpreting blood sugar levels in patients receiving Intragam® P. The maltose present in Intragam® P may result in falsely elevated capillary blood glucose levels with some types of glucose meters. If this measurement is used to guide treatment, hypoglycaemia may occur.

When monitoring glucose levels in patients receiving Intragam® P, consult the product information and/or manufacturer of the glucose meter and test strips (including those used at home by patients) to ensure that maltose does not interfere with the blood glucose reading.

5.4.10 Privigen® (Normal immunoglobulin, intravenous, IVIg)

Privigen® is a sterile, preservative free 10% solution containing 10 g of human protein in each 100 mL, available in 50 mL (5 g), 100 mL (10 g) and 200 mL (20 g) vials. The solution has a pH of 4.8 and is approximately isotonic. The product contains 250 mmol/L of L-proline as a stabiliser which is a physiological non-essential amino acid. It contains no carbohydrate stabiliser (e.g., sucrose, maltose) and has a low sodium content. Privigen® is made by a combination of cold ethanol fractionation, octanoic acid fractionation and anion exchange chromatography of large pools of human plasma obtained from blood donors in the United States and Europe. Privigen® is intended for intravenous administration.

The distribution of IgG subclasses present in Privigen® is: IgG1 (68%), IgG2 (29%), IgG3 (2%) and IgG4 (1%). Privigen® contains only trace amounts of IgA (typically <0.025 mg/mL).

The protein has not been chemically or enzymatically modified and the manufacturing process contains specific steps to reduce the possibility of virus transmission including filtration and incubation at low pH.

Indications for Use

Privigen® is registered for use as replacement IgG therapy and immunomodulatory therapy for a number of conditions.

Table 5.22: Registered Indications for Use of Privigen®

Indication	Comments
Replacement Therapy	
■ Primary immunodeficiency[1]	Causing hypogammaglobulinaemia
■ Acquired hypogammaglobulinaemia	Symptomatic with recurrent infections
Immunomodulatory Therapy[2]	
■ Primary immune thrombocytopaenia[3, 4]	
■ Kawasaki disease	
■ Guillain-Barré syndrome	
■ Chronic inflammatory demyelinating polyneuropathy	
■ Multifocal motor neuropathy	
■ Myasthenia gravis exacerbations	
■ Lambert-Eaton myasthenic syndrome	
■ Stiff person syndrome	

[1]The use of Privigen® has not been established in patients with primary immunodeficiency disorder under the age of 3 years.
[2]The use of Privigen® has not been established in patients with neurological indications under the age of 18 years.
[3]Recommendations for the use of IVIg in immune thrombocytopaenia (ITP) can be found in the International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia in Blood 2010; 115: 168-186 and the American Society of Hematology (ASH) 2011 Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia.
[4]The use of Privigen® has not been established in patients with ITP under the age of 15 years.

In addition, intravenous immunoglobulin has an established and emerging therapeutic role in a wide range of other, and in some cases also uncommon or rare, autoimmune and inflammatory diseases. Privigen® is not registered in New Zealand for indications other than those listed. For situations involving off-label indications, issue of this product is subject to consultation between the specialist physician and a NZBS Transfusion Medicine Specialist/Medical Officer.

Comprehensive evidence-based guidelines for the use of IVIg are lacking. Substitutes,

such as the 2012 Australian National Blood Authority *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia (2nd ed.)* and the 2011 UK Department of Health *Clinical Guidelines for Immunoglobulin Use (2nd ed. update)* provide information about the criteria for accessing IVIg and should be followed wherever possible to avoid the inappropriate utilisation of Privigen®.

Dosage and Administration

Privigen® may be infused undiluted. It may also be infused diluted with 5% glucose.

- Patients naive to Privigen®, switching from an alternative IVIg product, or who have not received IVIg for a long time, should be closely monitored during and for the first hour after the first infusion.
- In such patients, the infusion should be commenced at the rate of 0.3 mL per kilogram body weight per hour.
- If well tolerated, the rate may gradually be increased to 4.8 mL per kilogram body weight per hour.
- In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Replacement Therapy

- The optimal dose and frequency of administration of Privigen® must be determined for each patient.
- Most patients receive 400 mg IgG per kilogram body weight initially, followed by monthly maintenance doses of at least 200 mg per kilogram body weight.
- The monthly maintenance dose, guided by the patient's clinical status, is often 300 - 450 mg of IgG per kilogram body weight aiming for a pre-infusion (trough) serum IgG level of at least 4 - 6 g/L.
- As catabolic rates vary, the IgG levels of new patients should be monitored regularly for several monthly cycles to determine the effective dose. Three to six months are required for equilibration.

Immunomodulatory Therapy

Primary immune thrombocytopaenia

- Patients should receive up to a maximum total cumulative dose of 2.0 g IgG per kilogram body weight, over 2 - 5 days.

Kawasaki disease

- Patients should receive 1.6 - 2.0 g IgG per kilogram body weight, administered in divided doses over 2 - 5 days, or 2.0 g IgG per kilogram body weight as a single dose.

Guillain-Barre Syndrome

- Patients should receive 0.4 g IgG per kilogram body weight per day for five days.

Chronic inflammatory demyelinating polyneuropathy

- Patients should receive a starting dose of 2.0 g IgG per kilogram body weight, administered in divided doses over 2 - 5 days.
- Patients should receive a maintenance dose of 1.0 g IgG per kilogram body weight, administered every three weeks.

Multifocal motor neuropathy

- Patients should receive a starting dose of 2.0 g IgG per kilogram body weight, administered in divided doses over 2 - 5 days.
- Patients should receive a maintenance dose of 0.4 - 2.0 g IgG per kilogram body weight, administered every two to six weeks.

Myasthenia gravis exacerbations

- Prior to surgery or during myasthenic crisis, patients should receive an induction dose of 1.0 - 2.0 g IgG per kilogram body weight, administered in divided doses over 2 - 5 days.
- Patients should receive a maintenance dose of 0.4 - 1.0 g IgG per kilogram body weight, administered every four to six weeks.

Lambert-Eaton myasthenic syndrome

- Patients should receive a starting dose of 2.0 g IgG per kilogram body weight, administered in divided doses over 2 - 5 days.
- Patients should receive a maintenance dose of 0.4 - 1.0 g IgG per kilogram body weight, administered every two to six weeks.

Stiff person syndrome

- Patients should receive a starting dose of 2.0 g IgG per kilogram body weight, administered in divided doses over 2 - 5 days.
- Patients should receive a maintenance dose of 1.0 - 2.0 g IgG per kilogram body weight, administered every four to six weeks.

IVIg dosage recommendations for off-label indications are available in *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia (2nd ed.)*, developed by the Australian National Blood Authority (NBA) in 2012. In the case of allogeneic haematopoietic stem cell transplant, the following dosage recommendations for Privigen® have been used.

Treatment of infections and prophylaxis of graft-versus-host disease

- Patients should receive 0.5 g IgG per kilogram body weight weekly from 7 days before to 3 months after transplantation.

Persistent hypogammaglobulinaemia

- Patients should receive 0.5 g IgG per kilogram body weight monthly until antibody levels return to normal.

Contraindications

Privigen® is contraindicated in individuals who have had a true anaphylactic reaction to the active substance or the excipient and in those with hyperprolinaemia.

Precautions

- **Administration**
  Privigen® should only be administered intravenously. IVIg may, on rare occasions, cause a precipitous fall in blood pressure and a clinical picture of anaphylaxis. Therefore, adrenaline and oxygen should be available for the treatment of such an acute reaction.

- **Aseptic meningitis**
  Aseptic meningitis syndrome has been reported to occur infrequently in association with IVIg treatment.

- **IgA antibodies**
  Privigen® contains trace amounts of IgA which may provoke anaphylaxis in patients with IgA antibodies, such as those with IgA deficiency.

- **Positive direct antiglobulin tests and red cell haemolysis**
  Positive direct antiglobulin tests and red cell haemolysis have been reported following high dose infusion of intravenous immunoglobulin due to the presence of anti-A, anti-B, and occasionally with anti-D or other erythrocyte antibodies in the product. Such red cell sensitisation may cause crossmatching difficulties and transient haemolytic anaemia.

- **Renal dysfunction**
  There have been reports of renal dysfunction and acute renal failure in patients receiving IVIg. Patients should be adequately hydrated prior to administration of IVIg.

- **Thromboembolism**
  Thrombotic events have been reported in association with IVIg therapy. Caution should be exercised in prescribing and administering Privigen® in patients with pre-existing risk factors for thrombotic events.

Adverse Reactions

Reactions to intravenous immunoglobulin tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient's vital signs and general status be monitored regularly throughout the infusion.

The types of reactions that may occur include: malaise, abdominal pain, headache, chest-tightness, facial flushing or pallor, hot sensations, dyspnoea, non-urticarial skin rash, itching, arthralgia, tissue swelling, hypotension, nausea, or vomiting. Should any of these reactions develop during infusion of Privigen®, the infusion should be temporarily stopped (5-10 minutes) until the patient improves clinically and then cautiously recommenced at a slower rate.

Allergic reactions are most likely to occur during the first hour of the infusion.

True hypersensitivity reactions to intravenous immunoglobulin such as urticaria, angioedema, bronchospasm or hypotension occur very rarely. Should an anaphylactic reaction to Privigen® develop, the infusion should be stopped and immediate treatment instituted with adrenaline and oxygen.

Interactions with Other Medicines

Passively acquired antibody can interfere with the response to live attenuated virus vaccines such that vaccine administration should be deferred for at least 3 months. In the case of measles and varicella vaccines following IVIg products, the impairment may persist for up to 12 months. Where deferral is impractical, patients receiving such vaccines should have their antibody response checked. By the same token, immunoglobulins should not be administered for at least two weeks after live attenuated vaccines are given. Consultation with a NZBS Transfusion Medicine Specialist/Medical Officer is recommended.

5.4.11 Evogam® (Normal immunoglobulin, subcutaneous, SCIg)

Evogam® is a sterile, preservative free solution containing 16 g of human protein in each 100 mL, available in 5 mL (0.8 g) and 20 mL (3.2 g) vials. The solution has a pH of 6.6. As a stabiliser, Evogam® contains 2.25g of glycine in each 100mL. It does not contain a carbohydrate stabiliser (e.g., sucrose, maltose). Evogam® is made by chromatographic fractionation of large pools of human plasma obtained from New Zealand's voluntary and non-remunerated blood donors. Evogam® is intended for subcutaneous administration.

The distribution of IgG subclasses present in Evogam® is: IgG1 (48-58%), IgG2 (39-49%), IgG3 (1-2%) and IgG4 (1-2%). Evogam® contains only trace amounts of IgA (typically <0.025 mg/mL). The actual amount of IgA in each batch is printed on the label.

The protein has not been chemically or enzymatically modified and the manufacturing process contains specific steps to reduce the possibility of virus transmission including pasteurisation (heating at 60°C for 10 hours) and nanofiltration.

Indications for Use

Evogam® is indicated in adults and children for replacement therapy in:

- Primary immunodeficiency diseases (PID)
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment

Dosage and Administration

The dose and dosage interval must be individualised for each patient based on their measured IgG trough levels and ongoing clinical response. A weekly dose in the range 0.05 - 0.15 g/kg body weight is recommended, corresponding to a total monthly dose of Evogam® in the range of 0.2 - 0.6 g/kg body weight.

Evogam® should be brought to room temperature and administered via the subcutaneous route, optionally at several infusion sites (advisable for large > 20 mL doses) and preferentially into the upper outer arm, upper thigh, abdomen or lateral hip at an initial infusion rate of 10 mL/hour. The infusion rate may be gradually increased after the first completed infusion up to 20 mL/hour. The maximum rate administered during clinical trials was 40 mL/hour using two infusion pumps simultaneously. Evogam® must not be administered intravenously.

Contraindications

Evogam® is contraindicated in individuals who have had a true anaphylactic reaction to the active substance or to the excipient glycine.

Precautions

- **Administration**
  Evogam® must only be administered subcutaneously. Other routes of administration have not been evaluated. Evogam® administered intravenously could cause a clinical picture of anaphylaxis.

- **Aseptic meningitis**
  Aseptic meningitis syndrome has been reported to occur infrequently in association with human immunoglobulin treatment.

- **IgA antibodies**
  Evogam® contains trace amounts of IgA which may provoke anaphylaxis in patients with IgA antibodies, such as those with IgA deficiency.

- **Positive direct antiglobulin tests and red cell haemolysis**
  Evogam® can contain blood group antibodies causing a positive direct antiglobulin tests and rarely red cell haemolysis. Evogam® recipients should be monitored for clinical signs and symptoms of haemolysis.

- **Renal dysfunction**
  There have been occasional reports of renal dysfunction and acute renal failure in patients receiving IVIg. In cases of renal impairment with Evogam® use, discontinuation should be considered.

- **Thromboemblism**
  Thrombotic events have been reported in association with human immunoglobulin therapy. Caution should be exercised in prescribing and administering Evogam® in patients with pre-existing risk factors for thrombotic events.

Adverse Reactions

Local tolerability reactions of a mild to moderate intensity including infusion site pain, injection site haematoma or pruritis, erythema, local heat and/or induration are very commonly (≥1/10) reported at 8 to 12 hours after infusion. At 72 hours after infusion, the frequency of reported symptoms markedly decreases and the incidence of local reactions reduces with continued use of Evogam®. Other very commonly (≥ 1/10) reported reactions include headache, fever, nausea, diarrhoea and vomiting. Less common reactions include chills, back pain, arthralgia and hypotension.

Rarely, human immunoglobulin may cause allergic reactions and, in isolated cases, anaphylactic shock. Should an anaphylactic reaction to Evogam® develop, the infusion should be stopped and immediate treatment instituted with adrenaline and oxygen.

Interactions with Other Medicines

Passively acquired antibody can interfere with the response to live attenuated virus vaccines such that vaccine administration should be deferred for at least 3 months. In the case of measles and varicella vaccines following normal immunoglobulin products, the impairment may persist for up to 12 months. Where deferral is impractical, patients

receiving such vaccines should have their antibody response checked. By the same token, immunoglobulins should not be administered for at least two weeks after live attenuated vaccines are given. Consultation with a NZBS Transfusion Medicine Specialist/Medical Officer is recommended.

5.5 Other Products

5.5.1 Berinert® P (C1-esterase inhibitor)

Berinert® P does not have full New Zealand registration and so consultation with a NZBS Transfusion Medicine Specialist/Medical Officer is required prior to release of this product.

Berinert® P is a C1-esterase inhibitor concentrate supplied as 500 IU per vial (50 IU/mL). Berinert® P is intended for slow intravenous injection or infusion.

Indications for Use

Berinert® P is indicated for:

- The management of patients with C1-esterase inhibitor deficiency and/or hereditary angioedema (HAE)

Treatment should be initiated under the supervision of a physician experienced in the management of C1-esterase inhibitor deficiency.

The treatment of capillary leak syndrome with Berinert® P is not advised.

Dosage and Administration

The recommended dose is 20 IU per kilogram body weight, rounded to the nearest 500 IU. An additional dose may be required in less than 5% of patients with persistent or worsening clinical condition within a few hours of administration of the initial dose. It is recommended that Berinert® P be administered by slow intravenous injection 4 mL/minute.

5.5.2 Products from Australian Red Cross Blood Service (ARCBS)

From time to time there may be occasions when fractionated products prepared specifically from New Zealand plasma are unavailable or in short supply.

To ensure continuity of supply, NZBS may purchase supplementary stock of similar products from ARCBS. These products, manufactured by CSL Behring (using plasma from Australian donors) may be supplied in place of the equivalent New Zealand product. As they are unapproved medicines in New Zealand, a supply application is required under Section 29 of the Medicines Act 1981.

SPECIAL CIRCUMSTANCES

6.1 Management of Acute Blood Loss

Complications of major blood loss and massive transfusion associated with, for example, trauma, burns, surgery, obstetric haemorrhage and major gastrointestinal bleeding may jeopardise patients and challenge laboratory and blood transfusion resources. A successful outcome requires prompt action and good communication between clinical specialties, diagnostic laboratories, blood banks and NZBS.

Massive blood loss is usually defined as the loss of one blood volume within a 24 hour period (equivalent to 7% of ideal body weight in adults; 8 - 9% in children). Alternative definitions include the loss of 50% of blood volume within 3 hours and a rate of blood loss of 150 mL/minute. It is important that major blood loss is recognised early and appropriate action taken to prevent shock and its consequences.

The aim of treatment is the rapid and effective restoration of an adequate blood volume and to maintain blood composition within safe limits with regard to haemostasis, oxygen carrying capacity and biochemistry.

The essential features of management are:

- Restoring blood volume to maintain tissue perfusion and oxygenation.
- Achieving haemostasis by:
  - surgical control of bleeding.
  - correcting coagulopathy by expedient use of blood component therapy, based on results from early laboratory haemostasis screening.

The following table indicates likely crystalloid and blood transfusion requirements in response to acute blood loss, based on estimation of lost circulating volume.

Table 6.1: Transfusion Requirements in Response to Loss of Blood Volume

% Loss of Blood Volume	Action
15% (750 mL in an adult)	No need for transfusion unless blood loss is superimposed on pre-existing anaemia or when the patient is unable to compensate for this quantity of blood loss because of severe cardiac or respiratory disease.
15-30% (800-1500 mL in an adult)	Transfuse crystalloids. A requirement for red cell transfusion is unlikely unless the patient has a pre-existing anaemia, reduced cardiopulmonary reserve or if blood loss continues.
30-40% (1500-2000 mL in an adult)	Rapid volume replacement required with crystalloids. Red cell transfusion will probably be required.
>40% (>2000 mL in an adult)	Rapid volume replacement is required including red cell transfusion.

If bleeding continues after attempted surgical haemostasis and when the coagulation tests are abnormal or the platelet count reduced, then platelets, fresh frozen plasma, cryoprecipitate or a combination of these products may also be required.

In the setting of trauma-induced bleeding, early initiation of blood transfusion support with optimal ratios of plasma and platelets to red cell units may help achieve haemostasis and reduce the risk of exsanguination.

In trauma patients, use of the antifibrinolytic tranexamic acid is considered standard of care as an adjunct in arresting bleeding and should be administered as early as possible and within three hours of the trauma. The CRASH-2 trial included over 20,000 trauma patients, at least 16 years old, with significant haemorrhage (or at risk of) who were within 8 hours of initial injury. Compared to placebo, administration of tranexamic acid 1g loading dose over 10 minutes followed by 1g infusion over 8 hours reduced hospital mortality and death due to haemorrhage within 4 weeks of injury. No increase in the rate of vascular occlusion (myocardial infarction, stroke, pulmonary embolism) was seen with the use of tranexamic acid. For further information on the use of this antifibrinolytic agent see Section 8.7: *Tranexamic Acid*.

Clinical trials in humans have not demonstrated albumin solutions or other colloids to be superior to crystalloid in resuscitation, but larger quantities of crystalloid may be required. Synthetic colloids such as dextrans and hydroxyethyl starch should be avoided in patients at risk for acute kidney injury and otherwise limited to 1.5 litres per 24 hours in adults.

Aggressive volume resuscitation may cause problems with interstitial oedema, compartment syndrome, acute lung injury and, subsequent to haemodilution, exacerbations of anaemia, thrombocytopaenia and coagulopathy. A strategy of permissive hypotension, with minimal volume resuscitation and tolerating systolic blood pressures of 80-100 mmHg, is generally preferable while active bleeding is being controlled. Permissive hypotension is contraindicated in patients with traumatic brain injury and should be used with caution in the elderly.

Large quantities of saline may cause hyperchloraemic metabolic acidosis with subsequent complications and this has increasingly led to the use of physiologically buffered fluids such as Plasmalyte 148 and compound sodium lactate (Hartmann's or Ringer-Lactate).

Avoid saline in patients with severe liver disease for whom sodium overload is a risk. Specialist advice is recommended. For the same reason care should be taken with Albumex® 4 in these patients.

Table 6.2: *Transfusion Support for Major Bleeding* should be referred to in conjunction with a local massive transfusion protocol (MTP).

Table 6.2: Transfusion Support for Major Bleeding

Activity	Intervention	Comments
Restore circulating volume Note: in patients with major vessel or cardiac injury, it may be appropriate to restrict volume replacement after discussion with surgical team	■ Insert wide bore peripheral cannulae ■ Give adequate volumes of pre-warmed crystalloid +/- colloid ■ Aim to maintain normal BP and urine output >30 mL/hr in adults (or 0.5 mL/kg/hour)	■ Blood loss, including concealed blood loss, is often underestimated ■ Refer to local guidelines on resuscitation of trauma patients and use of red cell transfusion ■ Monitor CVP if haemodynamically unstable
Contact key personnel	■ Most appropriate surgical team ■ Duty anaesthetist ■ Blood Bank	■ A named senior person should take responsibility for communication and documentation
Arrest bleeding	■ Early surgical or obstetric intervention ■ Upper GI tract procedures ■ Interventional radiology ■ If appropriate, tranexamic acid, as a 1g loading dose over 10 minutes, followed by infusion of 1g over 8 hours	■ Following trauma, tranexamic acid should be administered as soon as possible and within 3 hours
Request laboratory investigations	■ FBC, PT/INR, APTT, fibrinogen, Blood Bank sample, biochemical profile, arterial blood gas ■ Ensure correct identity for transfusion samples ■ Repeat FBC, PT/INR, APTT, fibrinogen at least every 4 hours, or after one third blood volume replacement, or after FFP	■ Take samples at earliest opportunity as results may be affected by colloid infusion ■ Wrong blood in tube (WBIT) poses great risk for a transfusion-related adverse outcome ■ May need to give FFP and platelets, as per local MTP, before FBC and coagulation results available

Table 6.2: Transfusion Support for Major Bleeding continued

Activity	Intervention	Comments
Request suitable red cells	■ Maintain haemoglobin > 70 g/L ■ Blood needed immediately - use 'emergency stock' group O RhD negative ■ Blood needed in 15 to 45 minutes - uncrossmatched ABO group specific will be provided when blood group known (15 to 45 minutes from receipt of sample in laboratory) ■ Blood needed in 45 minutes or longer – crossmatch compatible units provided following completion of routine pretransfusion testing	■ Contact Blood Bank or on-call scientist ■ Collect sample for group and screen before using emergency stock ■ Emergency use of RhD positive blood is acceptable if patient is male or post menopausal female ■ Blood warmer indicated if large volumes are transfused rapidly ■ Consider use of cell salvage
Consider the use of platelets	■ Maintain platelet count > 50 x 10^9/L ■ Anticipate platelet count < 50 x 10^9/L after 2 x blood volume replacement ■ Dose: 10 mL/kg for a neonate or small child, otherwise one adult therapeutic dose	■ Target platelet count ≥ 100 x 10^9/L for multiple/ central nervous system trauma or with severe diffuse microvascular bleeding ■ May need to transfuse platelets before laboratory results are available, however take FBC sample first
Consider the use of FFP	■ Anticipate coagulation factor deficiency after blood loss of 1.5 x blood volume ■ Aim for PT/INR and APTT < 1.5 x mean control ■ Allow for 30 minutes thawing time ■ Dose: 12-15 mL/kg (equivalent to approximately 1 litre or 4 units for an average 70 kg adult)	■ PT/APTT > 1.5 x mean control correlates with increased microvascular bleeding ■ Take sample for PT/INR, APTT, fibrinogen before FFP transfused ■ May need to use FFP before laboratory results available ■ Maintain ionised Ca^{2+} > 1.13 mmol/L

Table 6.2: Transfusion Support for Major Bleeding continued

Activity	Intervention	Comments
Consider the use of cryoprecipitate	■ Maintain fibrinogen > 1.0 g/L ■ Allow for 30 minutes thawing time ■ Dose: 1 unit per 30 kg body weight in adults (or 5 mL/kg paediatrics) ■ In obstetric bleeding maintain fibrinogen > 2.0 g/L	■ Contains fibrinogen, FVIII, von Willebrand factor, FXIII, and fibronectin thereby complementing FFP in correcting multiple coagulation factor deficiencies
Suspect DIC	■ Treat underlying cause (shock, hypothermia, acidosis) if possible	■ DIC-related mortality is high

6.2 Massive Transfusion Protocol (MTP)

The MTP is a multidisciplinary process by which blood components are obtained rapidly for an exsanguinating patient. It is designed to provide clear guidance on the management of massive blood loss and facilitate communication between the clinical team and Blood Bank while streamlining the supply and administration of blood components to a patient during what may be a stressful situation. The clinical team is responsible for both activating the MTP and, when the crisis is over, inactivating the MTP. Activation of the MTP is really only indicated where the patient is bleeding so fast that goal-directed therapy is not practical.

The MTP instructs Blood Bank staff to prepare in advance a designated set or "box" of blood components, provides confidence that those components will be available for immediate release when required, and guides the clinical team in their administration. After release of each box, Blood Bank will then prepare the next box but will not release it until called for. The MTP also recommends additional components if certain thresholds are reached and the clinical team is responsible for requesting these.

Because hospitals serve unique patient populations and Blood Banks have differing blood component stocks and ability to re-supply, the MTP for each DHB and affiliated Blood Bank is specific, having been developed in consultation with local clinicians responsible for managing these events. The principle however remains the same and that is to provide the best possible transfusion support and ensure a common understanding.

Protocol Activation Criteria

The massive transfusion protocol may be activated for a specific patient when the following conditions are met:

- There is massive bleeding with either shock or abnormal coagulation
- The patient has been assessed as requiring the protocol by an experienced clinician

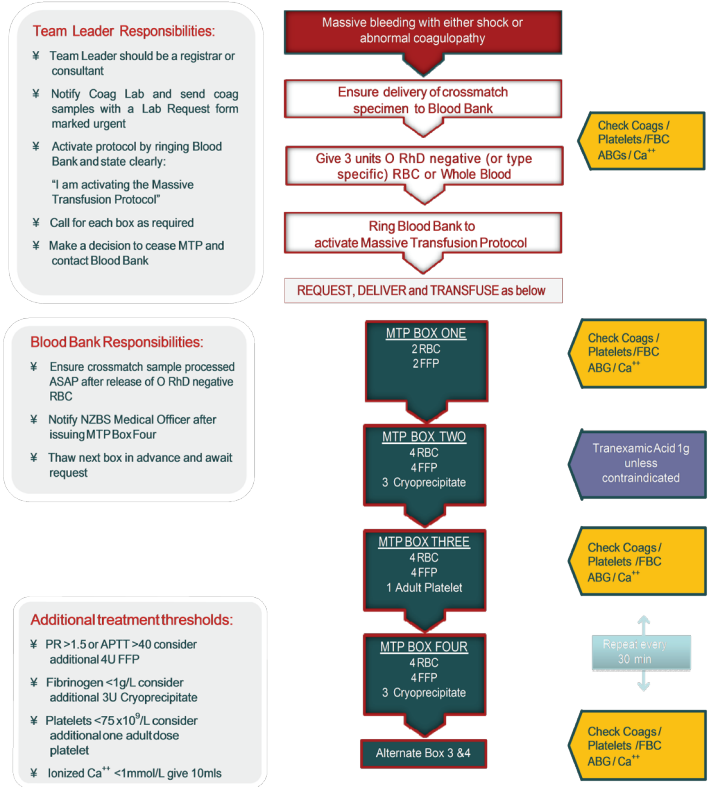
In the setting of massive blood loss the following steps should be followed to activate the massive transfusion protocol:

- The patient is assessed by an experienced clinician
- The patient is transfused 3 units of RBC or whole blood (either type-specific or emergency O RhD negative)
- The patient is reassessed and, if criteria are met, the MTP is activated
- The clinician (or delegate) must notify Blood Bank of the activation, informing them of the patient's name, NHI and clinical area
- The Blood Bank staff prepare and issue Box One and thereafter the MTP flow chart is followed
- Each MTP box will be made ready for issue upon release of the preceding box but will only be issued upon request

- To avoid delay in receiving the blood components an orderly or “designated runner” should be assigned
- Alongside regular clinical assessment of the patient, a full blood count, coagulation screen, ABG and serum calcium should be taken every 30 minutes
- Based upon laboratory results consider the use of specific blood components additional to those provided in standard MTP boxes
- Blood Bank must be informed when the patient is moved to another clinical department and/or the MTP is ceased.

Massive Transfusion Protocol Flowchart

Below is an example of a typical MTP flowchart. It is however important to be familiar with the MTP used at your local DHB as there may be variations.



The Australian National Blood Authority *(NBA) Patient Blood Management Guidelines* recommend early activation of the MTP and that fibrinogen is maintained > 2.0 g/L in obstetric patients. The role of permissive hypotension in these patients is uncertain as this may compromise fetal well-being and, in the postpartum period, uterine contraction.

6.3 Complications of Acute Blood Loss Associated with Large Volume Transfusions

When there is no pre-existing haemostatic problem, replacement of up to one blood volume (8-10 units of blood in an adult) using red cells and non-plasma fluids is unlikely to cause haemostatic problems due to dilution. Transfusion of much larger volumes may however lead to:

- **Microvascular bleeding**
  When major blood loss and massive transfusion is complicated by microvascular bleeding, with or without laboratory evidence of disseminated intravascular coagulation (DIC), the platelet count should be maintained > 50 x 10^9/L. With severe diffuse microvascular bleeding, a target platelet count ≥ 100 x 10^9/L is recommended.

  To avoid dilutional coagulopathy use of non-blood products should be restricted until laboratory evidence that any haemostatic failure is corrected. Fresh frozen plasma is indicated if the microvascular bleeding is accompanied by prolonged PT/APTT > 1.5 times the mean control or the fibrinogen is < 1.0 g/L (< 1.5 g/L with laboratory evidence of disseminated intravascular coagulation). With persisting severe hypofibrinogenemia despite FFP, administration of cryoprecipitate is recommended.

  While there is no evidence that the prophylactic transfusion of fresh frozen plasma or platelets to patients receiving large volume transfusions reduces the risk of microvascular bleeding, these blood components are included emperically in massive transfusion protocols in an attempt to maintain the platelet count > 50 x 10^9/L and PT/APTT < 1.5 times the mean control.

- **Hypocalcaemia**
  The citrate anticoagulant in some blood components (i.e., fresh frozen plasma) binds ionised calcium. It should be noted that red cells in additive solution contain only traces of citrate.

  Usually the rapid metabolism of citrate by the liver prevents lowering of plasma ionised calcium. In neonates and patients who are hypothermic, the combined effects of hypocalcaemia and hyperkalaemia may be cardiotoxic. If there is ECG or clinical evidence of hypocalcaemia, 5 mL of 10% calcium gluconate (for an adult) should be given intravenously. If necessary the dose should be repeated until the ECG is normal.

- **Hyperkalaemia**
  The plasma or additive solution in a unit of red cells or whole blood stored for four to five weeks may contain 5-10 mmol of potassium. In the presence of acidaemia and hypothermia this additional potassium load can lead to cardiac arrest. Keeping the patient warm best prevents this problem.

- **Hypothermia**
  The rapid transfusion of blood at 4°C can lower the body's core temperature by several degrees. Keeping the patient warm is the best safeguard to prevent this

problem. A blood warmer should be used in adults receiving large volumes of blood transfused at rates above 50 mL/kg/hour (in children above 15 mL/kg/hour).

It should be noted that hypothermic patients with a core body temperature < 35°C may be functionally coagulopathic even though coagulation tests performed in the laboratory at 37°C may be normal.

- **Acid-base disturbances**
  Despite the lactic acid content in transfused blood (1-2 mmol/unit), fluid resuscitation usually improves acidosis in a shocked patient. In practice, transfused citrate can contribute to metabolic alkalosis when large volumes of plasma components are transfused.

- **Adult respiratory distress syndrome**
  The risk is minimised if tissue oxygenation is optimised by good perfusion and over transfusion is avoided. The use of albumin solutions to maintain plasma oncotic pressure is often stated to be important but controlled studies have not proven any advantage of albumin solution over crystalloid fluids for resuscitation.

It should be noted that trauma (which may be the cause of major blood loss) is also known to cause or contribute to hypothermia, acidosis and coagulopathy, and therefore may lead to the problems described in association with massive transfusion.

6.4 Avoidable Haemostatic Problems in Elective Surgery

Any patient for whom elective surgery is planned must be asked about previous episodes of abnormal bleeding. Underlying medical conditions, the taking of medication that may be associated with impaired haemostatic function, or abnormal laboratory haemostasis test results may require the postponement of elective surgery until the abnormality has been identified or confirmed. Appropriate procedures including consultation with specialists in haematology, anaesthesiology and cardiology should be undertaken prior to surgery to minimise the perioperative risks for bleeding and, in the case of anticoagulant or antiplatelet withdrawal, thromboembolism.

Congenital abnormalities of haemostasis such as haemophilia should be managed in consultation with a specialist haemophilia centre.

6.4.1 Warfarin

Unless contraindicated, warfarin anticoagulation should be stopped early enough before elective surgery to allow the prothrombin time (or INR; International Normalised Ratio) to approach normal. This should be guided by a local protocol for preoperative anticoagulant management, taking into account patient-related risk factors for both thrombosis and bleeding. Bridging anticoagulation with either low molecular weight heparin or heparin infusion may be indicated for patients with at least a moderate risk of thrombosis. Prior to surgery where the INR is stable and therapeutic, withdrawal of warfarin for 3 - 5 days is generally adequate to achieve reversal sufficient for surgery. A longer period may be required in the presence of malnutrition or other factors predisposing to vitamin K deficiency. The Australasian Society of Thrombosis and Haemostasis (ASTH) has updated and published *Consensus Guidelines for Warfarin Reversal* in The Medical Journal of Australia 2013; 198 (4): 198-199. The *Guidelines* contain recommendations for the management of patients on long-term warfarin undergoing invasive procedures. Additionally, the NZBS *Reversing Warfarin* app developed by Health Obs Ltd, available for android and iPhone, provides guidance for managing patients undergoing elective and emergency surgery.

6.4.2 Non-Vitamin K-Dependent Oral Anticoagulants (NOAC)

The non-vitamin K-dependent oral anticoagulants, direct inhibitors of thrombin such as dabigatran (Pradaxa) or factor Xa such as rivaroxaban (Xarelto) and apixiban (Eliquis), should be stopped early enough before elective surgery to allow reversal of the anticoagulant effect. This should be guided by a local protocol for preoperative anticoagulant management with, in the case of dabigatran, particular attention paid to the patient's renal function and hence elimination of the drug. The Australasian Society of Thrombosis and Haemostasis has published *New Oral Anticoagulants: A Practical Guide on Prescription, Laboratory Testing and Peri-procedural/Bleeding Management* in The Internal Medicine Journal 2014; 44: 525-536. The *Guide* contains recommendations for the management of patients taking NOAC undergoing invasive procedures. Similarly, the Pharmaceutical Management Agency of the New Zealand Government (PHARMAC), has produced a concise document, *Guidelines for Testing and Perioperative Management of Dabigatran* (www.pharmac.govt.nz). Additionally, the *Rivaroxaban* app and the *Dabigatran* app developed by Health Obs Ltd, available for android and iPhone, provide guidance for managing patients undergoing elective and emergency surgery.

Table 6.3: Pharmacologic Properties of Non-Vitamin K-Dependent Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
Peak level	2 hours	1.5 - 4 hours	3 - 4 hours
Renal clearance	80%	66%	27%
Half-life	11 - 17 hours	5 - 9 hours	8 - 15 hours
	(longer in elderly and, especially dabigatran, with impaired renal function)		

Table 6.4: Suggested Approach for the Withdrawal of Non-Vitamin K-Dependent Oral Anticoagulants Prior to Elective Surgery

	Dabigatran	Rivaroxaban	Apixaban
Normal or mild renal impairment[1] (eGFR > 50 mL/min)	2 days	2 days	2 days
Moderate renal impairment[1] (eGFR 30 - 50 mL/min)	4 days	3 days	3 days
Severe renal impairment[2] (eGFR < 30 mL/min)	5 days	4 days	3 days

[1]For surgery with minimal bleeding risk, NOAC withdrawal may be shortened by 1 day. For surgery with high bleeding risk, NOAC withdrawal should be prolonged by 1 day.
[2]NOAC use is contraindicated or generally not recommended in the setting of severe renal impairment and should not be restarted post-operatively.

6.4.3 Aspirin

The antiplatelet effect of aspirin is mediated via irreversible acetylation of platelet cyclo-oxygenase, specifically COX-1, and the resulting inhibition of thromboxane A2 synthesis. Aspirin is indicated for the management of ischaemic atherosclerotic vascular disease including coronary artery and cerebrovascular disease and is used primarily in secondary prevention. Aspirin is used in combination with ADP-receptor inhibitors for the management of acute coronary syndromes (ACS) and for thromboprophylaxis following stent implantation. It may also be used for the management of some rheumatological disorders. While a single 75 mg dose of aspirin may impair platelet function for several days, the effect is less than with newer antiplatelet agents and most surgery can be performed after discontinuing aspirin at most the day prior to surgery. Prior to neurosurgery, transurethral prostatectomy or other invasive procedures with a major risk of bleeding or complications from bleeding, aspirin should (unless contraindicated) be stopped 3 days before planned surgery. If aspirin-induced platelet defect contributes to abnormal bleeding, desmopressin and tranexamic acid are likely to be effective in controlling haemostasis. Refer to Section 8.6: *Desmopressin* and Section 8.7: *Tranexamic* Acid for further information on these agents including dosing guidelines. Platelet transfusion is seldom necessary.

6.4.4 Non-steroidal Anti-inflammatory Drugs (NSAID)

Non-steroidal anti-inflammatory drugs cause reversible, but non-selective, inhibition of cyclo-oxygenase, both COX-1 and COX-2. The effects usually last for hours, as opposed to lasting days with aspirin. Normal platelet function is usually rapidly restored once the NSAID is stopped. The length of time that these medications should be stopped prior to an invasive procedure varies as the antiplatelet effect is dependent on the half-life of the NSAID being used. If NSAID-induced platelet defect contributes to abnormal bleeding, desmopressin and tranexamic acid may be effective in controlling haemostasis. Platelet transfusion is seldom necessary. The effect of both desmopression and platelet transfusion will be reduced in the presence of active drug.

6.4.5 $P2Y_{12}$ Adenosine Diphosphate (ADP) Receptor Inhibitors

Clopidogrel and the other thienopyridines, ticlopidine (not commonly in use) and prasugrel (Effient), irreversibly inhibit the $P2Y_{12}$ subtype of ADP receptor on platelet cell membranes. Ticagrelor (Brilinta), a cyclopentyltriazolopyrimidine reversibly inhibits the $P2Y_{12}$ ADP receptor. Clopidogrel is indicated for the management of ischaemic atherosclerotic vascular disease including coronary artery and cerebrovascular disease. The newer agents prasugrel and ticagrelor are indicated for the management of acute coronary syndromes (ACS) and as prophylaxis against stent thrombosis, usually in combination with aspirin. In some situations triple therapy in combination with an anticoagulant is indicated. $P2Y_{12}$ ADP receptor inhibitors should be used with caution in patients at increased risk of bleeding such as in the setting of trauma, surgery or other pathological conditions of haemostasis. Unless contraindicated, clopidogrel should be discontinued at least 5 days prior to surgery where an antiplatelet effect is undesirable. Prasugrel should be discontinued 7 days prior to surgery. Ticagrelor, although reversible, has a pronounced effect on platelet function and should be discontinued at least 3 days prior to semi-urgent surgery and 5 days prior to elective surgery. If $P2Y_{12}$ ADP receptor-induced platelet defect contributes to abnormal

bleeding, tranexamic acid together with a 1 - 2 unit platelet transfusion is likely to be effective in controlling haemostasis. Ticagrelor has a long half-life and inhibition of even transfused platelets may occur. An effect on transfused platelets may be seen for up to 6 hours following a loading dose of prasugrel. In patients with ACS who have recently received a coronary stent, platelet transfusion carries a risk of arterial and stent thrombosis and should therefore be restricted to situations involving serious bleeding or high bleeding risk.

6.4.6 Platelet Glycoprotein IIb (GPIIb) and IIIa (GPIIIa) Inhibitors

The platelet glycoproteins GPIIb and GPIIIa have important roles in normal haemostasis and pathological thrombosis. The peptides tirofiban (Aggrastat) and eptifibatide (Integrilin) and the monoclonal antibody abciximab (ReoPro) inhibit GPIIb and GPIIIa receptors. Inhibition of platelet aggregation occurs through blocking the final common pathway, the cross-bridging of platelets, following binding of fibrinogen to the activated GPIIb/IIIa receptor. These agents are indicated, in combination with aspirin and heparin anticoagulation, for the management of acute coronary syndromes (ACS) managed medically with or without percutaneous coronary intervention (PCI). Current applicability is however limited following the introduction of routine dual antiplatelet therapy using $P2Y_{12}$ ADP receptor blockers and percutaneous coronary stenting. Tirofiban and eptifibatide bind reversibly to GPIIb/IIIa receptors and the antiplatelet effect, in the absence of moderate renal impairment, recovers within 4 - 8 hours following cessation of treatment. In contrast, platelet binding by abciximab is irreversible and recovery of platelet function is delayed for 24 - 48 hours. By reducing thrombin burst generation, abciximab also inhibits normal coagulation and major bleeding may be observed within 12 hours of therapy, particularly following cardiac surgery. The antiplatelet effects of abciximab can be reversed by platelet transfusion. A small percentage of patients (≤ 1%) may experience acute severe thrombocytopenia following treatment with GPIIb/GPIIIa inhibitors.

Table 6.5: Pharmacologic Properties of Antiplatelet Agents

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Mode of action	Prodrug	Prodrug	Prodrug	Direct acting
Active drug $t_{1/2}$	2 - 4 hours	30 mins	7 hours[1]	7 - 9 hours
Prodrug $t_{1/2}$	NA[2]	6-8 hours	NA[2]	NA
Inhibition type	Irreversible[3]	Irreversible[3]	Irreversible[3]	Reversible[4]
Grade of effect	Mild	Moderate	Strong	Strong
Specific antidote	No	No	No	No

[1]Range 2 - 15 hours.
[2]Aspirin and prasugrel are rapidly converted to an active metabolite.
[3]The duration of inhibition is for the life span of the plalelet, i.e., 7-10 days. However, the effect on platelet-mediated haemostatic function declines more rapidly as approximately 10-15% of the circulating platelet pool is replaced daily.
[4]The duration of inhibition is dependent on the half-life ($t_{1/2}$). In general, it can be expected that after two half-lives the effect of ticagrelor has reduced to 25%. After four to five half-lives the remaining effect of ticagrelor is <5%.

Table 6.6: Managing Bleeding in Patients on Antiplatelet Agents

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Withdrawal pre-surgery	0 - 1 day[1]	5 days	7 days	5 days
Bleeding reversal[2]				
Tranexamic acid	Yes	Yes	Yes	Yes
Desmopressin	Yes	Possible effect	No effect	No effect
Platelets[3]	Seldom required	1 unit	2 units	2 units

[1]Prior to neurosurgery, transurethral prostatectomy or other invasive procedures with a major risk of bleeding or complications from bleeding, aspirin should (unless contraindicated) be stopped for 3 days.
[2]Where appropriate, local haemostatic measures should be used including mechanical compression, topical application of tranexamic acid and surgical/radiological intervention to identify sources of bleeding.
[3]Repeated doses may be required to achieve or maintain effect.

6.5 Oral Anticoagulant Induced Bleeding or Overdose

6.5.1 Warfarin

Withholding warfarin along with the judicious use of oral vitamin K_1 are the management options of choice unless rapid reversal of anticoagulation is required. Although intravenous administration of vitamin K_1 produces a more rapid response (onset within 6 - 8 hours), at 24 hours both routes achieve a similar correction of INR. The intravenous route may rarely be associated with anaphylaxis. The full effect of vitamin K_1 in reducing the INR takes up to 24 hours even when given in large doses. For immediate reversal of clinically significant bleeding, treatment with Prothrombinex®-VF covers the period until vitamin K_1 achieves full effect. Subsequent doses of vitamin K_1 may be necessary for maintaining correction of the INR achieved by coagulation factor replacement. Prothrombinex®-VF is a human prothrombin complex concentrate (PCC) containing factors II, IX and X together with only low levels of factor VII. The use of fresh frozen plasma should therefore be considered as a source of factor VII in life-threatening or critical organ bleeding. If no PCC is available, fresh frozen plasma should be transfused however this is less effective. The FFP dose for an adult in this setting is 15 mL/kg.

The ASTH has updated and published *Consensus Guidelines for Warfarin Reversal* in The Medical Journal of Australia, Med J Aust 2013; 198 (4): 198-199, from which the following table is adapted.

Table 6.7: Managing Overdose or Bleeding in Patients on Warfarin Therapy

Clinical setting	Action
INR greater than the therapeutic range but less than 4.5; no bleeding	■ Reduce or omit next dose of warfarin and resume therapy at a lower dose when INR approaches therapeutic range ■ If INR is only minimally above the therapeutic range (up to 10%) dose reduction may not be necessary
INR greater than 4.5 but less than 10.0; no bleeding	■ Stop warfarin and consider reasons for elevated INR ■ If bleeding risk is high[1], give vitamin K_1 1.0-2.0 mg orally or 0.5-1.0 mg intravenously ■ Measure the INR within 24 hours (vitamin K_1 effect on INR expected within 6-12 hours) and monitor closely for 1 week ■ Restart warfarin at a reduced dose once the INR approaches therapeutic range
INR greater than 10.0; no bleeding[2]	■ Stop warfarin ■ Give 3.0-5.0 mg vitamin K_1 orally or intravenously ■ If bleeding risk is high[1], consider Prothrombinex®-VF 15-30 IU/kg ■ Measure the INR within 24 hours (vitamin K_1 effect on INR expected within 6-12 hours) and monitor closely for 1 week ■ Restart warfarin at a reduced dose once the INR approaches therapeutic range
Life-threatening[3] **or critical organ bleeding with an INR ≥ 1.5**	■ Stop warfarin ■ Give 5.0-10.0 mg IV vitamin K_1, **and** Prothrombinex®-VF 50 IU/kg[4] **and** fresh frozen plasma 150-300 mL ■ If Prothrombinex®-VF is unavailable, administer fresh frozen plasma 15 mL/kg ■ Assess patient continuously until INR is reversed and bleeding stops
Clinically significant (non-life-threatening) bleeding with an INR ≥ 2.0	■ Stop warfarin ■ Give 5.0-10.0 mg IV vitamin K_1, **and** Prothrombinex®-VF 35-50 IU/kg ■ If Prothrombinex®-VF is unavailable, administer fresh frozen plasma 15 mL/kg ■ Assess patient continuously until INR is reversed and bleeding stops
Minor bleeding with any INR < 10.0	■ Omit warfarin and repeat INR the following day ■ Adjust warfarin dose to maintain INR in therapeutic range ■ If bleeding risk is high[1] or INR > 4.5, consider vitamin K_1 1.0-2.0 mg orally or 0.5-1.0 mg intravenously

[1]Risk factors for major bleeding include recent major bleed within previous four weeks, major surgery within previous two weeks, platelet count < 50 x 10^9/L, known liver disease, concurrent antiplatelet therapy.
[2]New Zealand laboratories generally report INR values up to 8.0. Above this, results are reported as INR > 8.0.
[3]Includes intracranial bleeding.
[4]Consider a Prothrombinex®-VF dose less than 50 IU/kg when INR is 1.5-1.9.

The NZBS *Reversing Warfarin* app developed by Health Obs Ltd, available for android and iPhone, also provides guidance for managing patients with bleeding.

6.5.2 Non-Vitamin K-Dependent Oral Anticoagulants (NOAC)

There is limited clinical data on reversal of the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban. As there is no specific reversal agent available, the mainstay of current management for drug-related bleeding is withholding NOAC together with best supportive care for local control of bleeding and maintenance of haemodynamic stability. The anticoagulant effect will not be reversed by the administration of vitamin K or infusion of plasma. Idarucizumab, a specific intravenous reversal agent for dabigatran, is showing promising early results in clinical trials. The antibody fragment completely reverses within minutes the anticoagulant effect of dabigatran.

The ASTH has published *New Oral Anticoagulants*: A *Practical Guide on Prescription, Laboratory Testing and Peri-procedural/Bleeding Management* in The Internal Medicine Journal 2014; 44: 525-536. The *Guide* contains recommendations for the management of patients taking NOAC with bleeding complications. Similarly, PHARMAC, has produced a concise document, *Guidelines for Management of Bleeding with Dabigatran* (www.pharmac.govt.nz). The recommendations may change as new evidence becomes available. Additionally, the *Rivaroxaban* app and the *Dabigatran* app developed by Health Obs Ltd, available for android and iPhone, provide guidance for managing patients with bleeding.

Table 6.8: Managing Bleeding in Patients on Non-Vitamin K-Dependent Oral Anticoagulant Therapy

Clinical setting	Action
General measures for any patient bleeding on NOAC therapy	■ Initiate standard resuscitation procedures as required ■ Take samples for FBC, creatinine, group and screen, routine coagulation studies ■ Dabigatran - APTT, thrombin time; consider dabigitran level using a dilute thrombin clotting time (Hemoclot) assay ■ Rivaroxaban - PT[1], drug specific anti-Xa level ■ Apixaban - drug specific anti-Xa level (if available)
Minor bleeding	■ Local haemostatic measures - mechanical compression - topical tranexamic acid ■ Delay next dose of NOAC ■ Consider appropriateness of continuing therapy in consultation with prescribing physician

Table 6.8: Managing Bleeding in Patients on Non-Vitamin K-Dependent Oral Anticoagulant Therapy continued

Clinical setting	Action
Clinically significant[2] **(non-life-threatening) bleeding**	■ Stop NOAC ■ Administer oral charcoal if NOAC ingestion < 2 h prior ■ Local haemostatic measures - mechanical compression - surgical/radiological intervention to identify and - treat source of bleeding ■ Maintain hydration to aid drug clearance ■ Transfusion support - RBC as indicated by haemoglobin - PLT if < 50 x 10^9/L or antiplatelet therapy - FFP only if concerned about dilutional coagulopathy ■ Consider use of tranexamic acid 15-30 mg/kg IV +/- infusion for mucosal bleeding
Life-threatening or critical organ bleeding[3]	■ Stop NOAC ■ Administer oral charcoal if NOAC ingestion < 2 h prior ■ Local haemostatic measures - mechanical compression - surgical/radiological intervention to identify and treat source of bleeding ■ Maintain hydration to aid drug clearance ■ Transfusion support - RBC as indicated by haemoglobin - PLT if < 100 x 10^9/L or antiplatelet therapy - FFP only if concerned about dilutional coagulopathy ■ Consider use of the following pro-haemostatic agents[4] - Tranexamic acid 15-30 mg/kg IV +/- infusion for mucosal bleeding - Prothrombinex®-VF 25-50 IU/kg - FEIBA 50 IU/kg ■ Consider dialysis for dabigatran-related bleeding[5] ■ Assess patient continuously until bleeding stops

[1]*Using a thromboplastin sensitive to rivaroxaban.*
[2]*Clinically significant bleeding - reduction in Hb ≥ 20 g/L, transfusion of ≥ 2 units of RBC.*
[3]*Life-threatening bleeding with hypotension not responding to resuscitation or bleeding in critical area or organ (intraocular, intracranial, intraspinal, compartment syndrome, retroperitoneal or pericardial).*
[4]*This is an off-license use of Prothrombinex®-VF and FEIBA and the risk of thrombotic complications with these agents when used for this indication is unclear. Their use is supported by laboratory data and clinical evidence in animals but clinical evidence in humans supporting an improvement in clinical outcomes is lacking.*
[5]*Dialysis is indicated if dabigatran level is high as indicated by excessively prolonged APTT > 80 sec or dabigatran level > 500 ng/mL and/or impaired renal function. Four hours of dialysis will reduce drug level by approximately 60%.*

6.6 Thrombolytic Therapy

Although bleeding is not a common complication of fibrinolytic therapy at normal doses, the risk is not predicted by laboratory monitoring. If there is serious bleeding, fresh frozen plasma and cryoprecipitate will raise a low fibrinogen level.

An anti-fibrinolytic agent such as tranexamic acid should only be used if life-threatening bleeding is encountered. As large clots may form at the site of bleeding, these agents are contraindicated in renal tract bleeding. It should however be noted that the use of anti-fibrinolytic agents is not contraindicated in the presence of intracranial bleeding following thrombolysis.

6.7 Disseminated Intravascular Coagulation (DIC)

In this syndrome there is generation of thrombin leading to consumption of circulating coagulation factors and platelets with subsequent fibrin deposition. Ischaemic organ damage particularly in the renal circulation can occur due to microthrombi. The treatment of DIC involves supportive care while treating the underlying primary condition. In the presence of active bleeding, or where there is a high risk of major bleeding such as prior to some invasive procedures, transfusion support to replace coagulation factors and platelets is likely to be appropriate. If the patient is bleeding and there are no problems with volume replacement, fresh frozen plasma is optimal as it contains a full spectrum of coagulation factors. Where real concern exists for intravascular fluid overload, Prothrombinex®-VF may be considered, as the reconstituted volume for infusion is smaller. Correction of the coagulation defect is however only likely to be partial and Prothrombinex®-VF is generally contraindicated in the presence of DIC. For bleeding patients with severe hypofibrinogenaemia despite FFP replacement, cryoprecipitate should be infused keeping the fibrinogen level > 1.5 g/L. Antithrombin concentrates may be considered where DIC is secondary to sepsis or in cases of thrombosis-predominant DIC treated with therapeutic dose heparin. A platelet count of 10 - 20 x 10^9/L can usually be tolerated in the absence of bleeding while transfusion is recommended with a platelet count < 50 x 10^9/L in the presence of active bleeding or prior to invasive procedures. Where the procedure is neuraxial a higher platelet is likely to be desirable.

The management of DIC requires careful coordination between the treating clinician and NZBS to ensure adequate supplies of blood components and plasma products are available and that these are used based upon relevant coagulation tests.

6.8 Cardiopulmonary Bypass

Cardiopulmonary bypass usually impairs haemostatic mechanisms and, as a result, bleeding complications may be severe. The effect is especially pronounced for patients who have been on prolonged bypass for more than 2 hours, in 'redo' operations or with surgery for infective endocarditis. A number of mechanisms are involved including haemodilution, effects on platelet function, reduced levels of coagulation factors, intraoperative heparin anticoagulation, induced hypothermia, acidosis, hyperfibrinolysis and preoperative anticoagulation or antiplatelet therapy.

Routine laboratory tests of coagulation do not accurately predict the full nature and clinical importance of the haemostatic defect. Intra-operative point-of-care testing with an activated clotting time (ACT) assay, together with viscoelastic global assessments

of coagulation using whole blood thromboelastography (TEG) or thromboelastometry (TEM), is increasingly being used alongside PT/APTT and fibrinogen results.

Platelet transfusion is indicated if, despite heparin reversal with protamine sulphate, there is diffuse microvascular bleeding with platelets < 100 x 10^9/L or suspected platelet dysfunction. In the presence of non-surgical bleeding, fresh frozen plasma and cryoprecipitate may help to correct prolonged clotting times, improve haemostasis and reduce transfusion requirements. The routine use of fresh frozen plasma, cryoprecipitate or platelets at the end of bypass does however not reduce transfusion requirements.

Aprotinin (Trasylol®) is no longer available due to concerns regarding effect on renal function. Tranexamic acid is commonly used as an antifibrinolytic and has been shown to reduce red cell transfusion requirement.

Red cell components for patients undergoing cardiac bypass surgery
Literature review provides no evidence supporting the use of fresh blood for cardiac bypass surgery. Accordingly, NZBS policy on the provision of red cell components, including whole blood, for use in recipients undergoing cardiopulmonary bypass surgery is as follows:

- Adult Cardiac Bypass Surgery
  Resuspended red cells less than 14 days old will normally be made available for adult patients as a replacement for blood loss. Resuspended red cells less than 10 days old will normally be made available for patients with renal impairment. It is the responsibility of the treating clinician to indicate this requirement to the Blood Bank.
- Paediatric Cardiac Bypass Surgery
  Resuspended red cells less than 5 days old will normally be made available for paediatric patients as a replacement for blood loss. Where possible, whole blood less than 2 days old will be provided for the purpose of bypass circuit priming.

6.9 Haemolytic Disease of the Fetus and Newborn (HDFN)

HDFN occurs when maternal IgG antibodies (most commonly anti-D) travel across the placenta and bind to fetal red cells having the corresponding antigen. The affected fetal red cells may be destroyed by the fetal reticuloendothelial system causing extravascular haemolysis and fetal anaemia.

The antibodies that cause HDFN are produced either as a consequence of earlier pregnancies (when fetal red cells with paternally derived antigens that the mother lacks, enter the maternal circulation during pregnancy) or because of a previous transfusion.

In the most severe cases of HDFN the fetus may die in utero or be born with severe anaemia that requires exchange transfusion. There may also be severe neurological damage (kernicterus) as a result of a high bilirubin level.

Anti-D, an antibody to the RhD antigen, is the most important cause of HDFN. Clinically significant IgG antibodies against other blood group antigens can also be responsible for causing HDFN for example anti-c, -K, -E, -Fya. These antibodies occur in about 0.5% of pregnancies and may occasionally cause severe haemolysis. Although ABO incompatibility between mother and fetus is common, severe HDFN due to IgG anti-A and anti-B antibodies is very rare in New Zealand.

Screening in Pregnancy

All pregnant women should have the following antenatal testing performed:

- ABO and RhD group following booking for antenatal care at 12 - 16 weeks. This identifies RhD negative mothers.
- Red cell antibody screen to test for antibodies that may cause HDFN. If an antibody is detected at booking, it should be monitored throughout the pregnancy in case the level of antibody increases.
- If a significant maternal antibody is found it may be useful to test the father's red cells to see if they carry the antigen against which the antibody is directed. If homozygous for the antigen concerned, the fetus will also be positive. If heterozygous, there is a 50% chance that the fetus will be positive.

Further information can be found in the ANZSBT/RANZCOG *Guidelines for Blood Grouping & Antibody Screening in the Antenatal and Perinatal Setting* (2007) upon which the following table is based.

Table 6.9: Timetable for Routine Antenatal Blood Group and Antibody Screen

Testing Requirements	Testing Interval / Comments
Blood Group - ABO and RhD	
All pregnancies	■ Initial visit and for pretransfusion testing
Antibody Screening	
All pregnancies	■ Initial visit and for pretransfusion testing
RhD negative females	■ For those RhD negative females who will receive anti-D immunoglobulin (at 28 weeks or at the time of any sensitising event), the blood sample must be collected prior to its administration
Antibody Identification	
All pregnancies	■ At initial antibody detection
Antibody Titration / Quantitation	
Rh antibodies and other potentially clinically significant antibodies capable of causing HDFN	■ In the event that clinically significant antibodies are detected, further testing is indicated at intervals no greater than 4 weeks ■ Seek specialist advice

Management of HDFN

It is important that women with potentially severe HDFN are referred without delay to a specialist obstetric unit. The referral should be made prior to 20 weeks in those patients who have had a previously affected baby. Management of an affected fetus may include intrauterine transfusion, early delivery, phototherapy and exchange transfusion.

Prevention of HDFN Due to Anti-D

The minimum volume of RhD positive red cells that will immunise a RhD negative woman is of the order of 0.1 - 0.25 mL. Clinical studies indicate that the administration of anti-D immunoglobulin to a RhD negative mother within 72 hours of the birth of a RhD positive infant reduces the incidence of Rh isoimmunisation from 12 - 13% to 1 - 2%. A small number (1.5 - 1.8%) of RhD negative mothers are immunised by their RhD positive fetus despite postpartum administration of anti-D immunoglobulin. Studies have also shown that this number can be reduced to < 1.0% by routine antenatal prophylaxis with anti-D immunoglobulin at 28 and 34 weeks of pregnancy. Although definitive studies have not been performed, guidelines promote the use of anti-D immunoglobulin for other potentially sensitising obstetric events in which fetomaternal haemorrhage is known to occur.

Anti-D immunoglobulin should not be given to RhD negative women with detectable anti-D except where the antibody is passively acquired due to prior antenatal administration. If unsure whether the anti-D detected in the mother's blood is passively acquired or preformed, the treating clinician and/or a NZBS Transfusion Medicine Specialist should be consulted. If there is continuing doubt, anti-D immunoglobulin should be administered. Although there is no benefit in administering anti-D immunoglobulin to a woman who is already sensitised to RhD antigen, there is no more risk than when it is given to a woman who is not sensitised.

The following table is based on the 2003 Australian NBA *Guidelines on the Prophylactic Use of RhD Immunoglobulin (Anti-D) in Obstetrics* and the 2013 BCSH *Guideline for the Use of Anti-D Immunoglobulin for the Prevention of HDFN.* In 2011 the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) endorsed the 2003 NBA Guidelines, however it should be noted that the NZ Ministry of Health does not recommend routine antenatal anti-D prophylaxis (RAADP).

Table 6.10: Indications for Use of Anti-D Immunoglobulin for the Prevention of HDFN (unless the fetus is confirmed to be RhD negative)

Timing	Clinical Indication
Routine antenatal prophylaxis[1]	A RhD negative woman, not previously immunised to produce anti-D; one dose at each of 28 and 34 weeks gestation.[2] **Anti-D immunoglobulin dose: 625 IU (125 µg)**
Potentially sensitising event during first trimester up to and including 12 weeks gestation	A RhD negative woman, not previously immunised to produce anti-D, with an obstetric indication. ■ Uterine bleeding where this is repeated, heavy or associated with abdominal pain[3] ■ Miscarriage[3] ■ Termination of pregnancy ■ Ectopic pregnancy ■ Molar pregnancy **Anti-D immunoglobulin dose: 250 IU (50 µg)**[4]

Table 6.10: Indications for Use of Anti-D Immunoglobulin for the Prevention of HDFN (unless the fetus is confirmed to be RhD negative) continued

Timing	Clinical Indication
Potentially sensitising event beyond first trimester[5]	A RhD negative woman, not previously immunised to produce anti-D, with an obstetric indication. ■ Amniocentesis, chorionic villus sampling, and intrauterine fetal blood sampling ■ Antepartum haemorrhage (or unexplained uterine pain) ■ External cephalic version (performed or attempted) ■ Abdominal trauma sufficient to cause FMH ■ Ectopic pregnancy ■ Molar pregnancy ■ Intrauterine death or stillbirth ■ Miscarriage, threatened miscarriage ■ Termination of pregnancy **Anti-D immunoglobulin dose: 625 IU (125 µg)**
Postpartum prophylaxis[6]	A RhD negative woman, not previously immunised to produce anti-D, who gives birth to a RhD positive baby. **Anti-D immunoglobulin dose: 625 IU (125 µg) with additional dose(s) indicated where fetomaternal haemorrhage is > 6 mL fetal red cells**

[1]Routine antenatal anti-D prophylaxis (RAADP) should be administered regardless of, and in addition to, prophylaxis given for a potentially sensitising event.
[2]A sample for antibody testing should be taken prior to administration of anti-D immunoglobulin at 28 weeks.
[3]Before 12 weeks gestation, in cases of either spontaneous complete miscarriage where the uterus is not instrumented or mild painless vaginal bleeding, the risk of fetomaternal haemorrhage is negligible.
[4] For multiple pregnancies the recommended anti-D immunoglobulin dose is 625 IU (125 µg).
[5]Routine antenatal prophylaxis does not preclude prophylaxis for a potentially sensitising event.
[6]Routine antenatal prophylaxis or prophylaxis for a potentially sensitising event does not preclude postpartum prophylaxis.

Laboratory Assessment of Fetomaternal Haemorrhage (FMH)

- The Kleihauer acid elution test is widely used to test for FMH and can detect bleeds of 0.1 mL or less. False results can occur with the test and it is less reliable in the first two trimesters of pregnancy when there is an increase in the level of fetal haemoglobin in the maternal red blood cells. Clinicians using this test should be aware of these limitations. Anti-D immunoglobulin should still be administered if a negative Kleihauer test is obtained.
- There is no need to assess the size of FMH in pregnancies of 20 weeks gestation or less, as the standard 250 IU (up to and including 12 weeks) and 625 IU (beyond 12 weeks, up to and including 20 weeks) dose of anti-D immunoglobulin will sufficiently cover the maximum likely FMH for the gestation.
- It is appropriate to assess the size of FMH after 20 weeks gestation. A blood sample should be taken from the mother as soon as possible after the potentially sensitising event and before the dose of anti-D immunoglobulin is given.

- Results reporting the fetal bleed in mL of red cells should be promptly available so that anti-D immunoglobulin can be given within 72 hours of the FMH.
- For large bleeds greater than 4 mL, repeat testing should be performed at 48 hours following each intravenous dose of anti-D or 72 hours following each intramuscular dose of anti-D immunoglobulin to check for clearance of fetal red cells and, if still positive, additional dose(s) given.
- Flow cytometry, a more accurate and reproducible method for measuring FMH, is not yet widely available.

Timing, Dose and Route of Anti-D Immunoglobulin

- Anti-D immunoglobulin prophylaxis should be given as soon as possible and always within 72 hours of a potentially sensitising event.
- If anti-D immunoglobulin has not been offered within 72 hours, a dose given within 10 days may provide some protection.
- A 625 IU dose of anti-D immunoglobulin will protect against a FMH of up to 6 mL of RhD positive red cells (equivalent to 12 mL of blood). Where testing shows that a FMH of greater than 6 mL has occurred, additional dose(s) of anti-D immunoglobulin must be administered. In this situation, the recommended minimum dose is 100 IU per mL RhD positive red cells.
- Where more than 1250 IU of anti-D immunoglobulin (two 625 IU vials of Rh(D) Immunoglobulin-VF) is indicated, consultation with a NZBS Transfusion Medicine Specialist is recommended.
- For bleeds requiring a large anti-D immunoglobulin dose, the maximum recommended administration rate is 3000 IU every 8 hours to reduce the risk of an adverse reaction arising from rapid clearance of fetal RhD positive red cells. As it is recommended that no more than 4 mL is injected intramuscularly at each site, Rhophylac®, an anti-D immunoglobulin product suitable for intravenous administration, may be an appropriate alternative.
- Recipients who have a moderate or severe thrombocytopenia should not receive intramuscular injections. The standard anti-D immunoglobulin provided by NZBS, Rh(D) Immunoglobulin-VF, is suitable for intramuscular use only. It may be given by intramuscular or subcutaneous route; it must not be given intravenously. Rhophylac, an anti-D immunoglobulin product suitable for intravenous administration is held at NZBS sites and can be obtained following consultation with a NZBS Transfusion Medicine Specialist/Medical Officer.
- There is some evidence to suggest that intramuscular administration of anti-D immunoglobulin may be associated with an increased risk of lack of effect in patients with a body mass index (BMI) > 30. An Expert Panel Consensus Position Statement (available online at www.transfusion.com.au/node/612) provides recommendations regarding the use of anti-D immunoglobulin in these patients.

The following is recommended where a woman has received an appropriate dose of anti-D immunoglobulin followed by a further risk event for immunisation.

- Where the previous dose was given 2 or more weeks before, a further dose(s) of anti-D immunoglobulin should be offered.

- Where the previous dose was given less than 2 weeks before, a further dose of anti-D immunoglobulin should be offered where the pregnancy is more than 20 weeks gestation. Where testing indicates a FMH greater than 6 mL, additional dose(s) of anti-D immunoglobulin must be administered.
- Where there is continual uterine bleeding that is judged clinically to represent the same risk event, further dose(s) of anti-D immunoglobulin should be offered at a minimum of 6 weekly intervals. In pregnancies > 20 weeks gestation, estimation of FMH should be undertaken at 2 weekly intervals and the presence of fetal cells should prompt an additional anti-D immunoglobulin dose to cover the volume of FMH.

Further observations and comment on the guidelines for the use of anti-D immunoglobulin are available in the NZBS Clinical Compendium.

Non-invasive Fetal Genotyping

A maternal blood sample may be used for non-invasive testing of cell-free fetal DNA to predict the fetal red cell phenotype. This has particular value in identifying a fetus that is unlikely to be at risk of HDFN. In the case of a sensitised RhD negative woman, the absence of the RhD gene predicts for a RhD negative fetus. As such, aggressive monitoring of the mother's anti-D titre and the health of the fetus is unnecessary. Fetal RhD status is also useful in determining whether anti-D immunoglobulin prophylaxis is required. Rarely, such as when genetic changes lead to gene silencing rather than deletion, genotype determination does not correlate with the antigen expression on the fetal red cells.

Certain criteria need to be met before obtaining fetal DNA for genotyping; the mother's serum contains an IgG antibody of potential clinical significance and the father is, or may be, heterozygous for the gene encoding the antigen of interest. Fetal genotyping for RhD, C, c, E and Kell is available for suitable patients. A NZBS Transfusion Medicine Specialist can be consulted on whether it is appropriate to refer samples for testing.

6.10 Intrauterine Transfusion (IUT)

Intrauterine red cell transfusion is used to correct fetal anaemia resulting from red cell alloimmunisation (most commonly due to anti-D followed in order of importance by anti-c and anti-K) and less commonly red cell aplasia due to fetal parvovirus infection. Similarly, intrauterine platelet transfusions are used to correct fetal thrombocytopenia due to platelet alloimmunisation. The goal of IUT is primarily to prevent (or treat) fetal hydrops, ensuring the fetus reaches a viable gestational age and can be delivered. Cellular components for IUT must be irradiated.

Consultation with a NZBS Transfusion Medicine Specialist is required to access these components. The specification for the component will be agreed in advance with the fetomaternal specialist and information on the actual composition of the component provided at the time of delivery of the product.

The general specification for red cell and platelet components for use in IUT are as follows:

Table 6.11: Component Requirements for IUT

Component	Requirements
Red cells[1]	■ Group O (low titre IgG anti-A, -B) or ABO identical with fetus (if group known) ■ RhD negative (if HDFN due to anti-c or other antibodies, may be RhD positive) ■ IAT crossmatch compatible with maternal plasma (antigen negative for relevant antigen) ■ < 5 days old ■ CMV negative ■ Irradiated ■ Haematocrit 0.75 - 0.90
Platelets	■ Group O (low titre IgG anti-A, -B) or group specific/compatible with maternal antibody ■ HPA-compatible with maternal antibody ■ Collected by apheresis where possible ■ CMV negative ■ Irradiated ■ Volume required (mL) = $\frac{\text{Desired plt increment}}{\text{Plt count of concentrate}}$ x Feto-placental BV[2] ■ Concentrated to platelet count 2000 - 4000 x 10^9/L ■ Rate of transfusion 1 - 5 mL/min

[1]*See Table 4.5: Red Cell Components Available from NZBS.*
[2]*Blood Volume (BV).*

6.11 Transfusion of the Newborn

Red Cells

Normal blood volume at birth varies according to gestational age and timing of clamping of the cord. For term infants the average blood volume is 80 mL/kg whilst in pre-term infants it is higher at 106 mL/kg. The newborn bone marrow does not respond as rapidly as an adult and any uncorrected blood loss can rapidly lead to anaemia.

A significant cause of anaemia in neonates is iatrogenic blood loss associated with laboratory testing. Neonates are also at increased risk of infection and these factors must influence transfusion medicine practice, especially in premature infants.

The volume of red cells to be transfused in newborns depends on the weight of the baby and local policy. International guidelines recommend a volume for top-up transfusion of 10 - 20 mL/kg (although some neonatal units use the range 8 - 12 mL/kg) at an infusion rate of 5 mL/kg/hr. Frusemide given at a dose of 1 mg/kg halfway through the transfusion may sometimes be required to minimise volume load.

In some centres it is practice to minimise the number of donors to which a newborn is exposed. NZBS provides small volume 'neonatal' red cell units (each typically containing 70 mL) which are produced by separating an adult 'plasma-reduced' red cell donation into a number of equal-sized aliquots. All (or some) of the individual aliquots from one

adult unit can be reserved for sequential transfusions to the same baby over the full 35-day shelf life of the red cells. Fresh frozen plasma and platelet concentrates are also available in neonatal volumes.

Compatibility Testing

The normal rules for ABO and RhD compatibility apply. However, for infants up to the age of 4 months, maternal blood may be used for pretransfusion testing provided the ABO groups of mother and infant are compatible since any clinically significant red cell antibody present in the infant's circulation will have come from the mother. Blood components selected for transfusion should be compatible with any ABO or other red cell antibody present in the maternal or infant plasma. Repeated transfusions during the infant's first 4 months of life do not require further compatibility testing if there are no atypical maternal red cell antibodies in the maternal or infant plasma. However, if the antibody screen is positive, full pretransfusion testing and crossmatching will be necessary.

Pretransfusion testing of infants 4 months or older should be performed on a sample from the infant.

Exchange Transfusion

For severe cases of HDFN, neonatal exchange transfusion may be required.

Table 6.12: Red Cell Component Requirements for Neonatal Exchange Transfusion

Red Cell Requirements For Exchange Transfusion[1]
■ Group O or ABO compatible with maternal and infant plasma
■ RhD negative (or RhD identical with the infant)
■ Negative for red cell antigens against which maternal antibody is directed
■ IAT crossmatch compatible with maternal plasma
■ < 5 days old
■ CMV negative
■ Irradiated, especially if infant has previously received IUT
■ Haematocrit 0.5 - 0.60
■ Transfusion volume: 80 - 160 mL/kg for term infants and 100 - 200 mL/kg for preterm infants, guided by clinical indication

[1]*See Table 4.5: Red Cell Components Available from NZBS.*

Special Requirements

Neonates less than 1500 g in weight or immunosuppressed for other reasons should be given 'CMV safer' blood components as an added precaution. The use of either prestorage leucodepletion or selection of CMV-antibody negative blood components significantly reduces the risk of CMV transmission and CMV disease in susceptible recipients. However, neither method alone or in combination can completely avoid transmission from the occasional donor with CMV viraemia in the "window" period prior to the development of antibodies following acute infection or when reactivation of latent infection occurs.

In some situations irradiated blood components may be indicated for neonatal transfusions. Irradiation removes the small risk of transfusion-associated graft-vs-host disease (TA-GVHD) in at-risk patients by inactivating donor lymphocytes.

When there is clinical suspicion of a congenital cellular immunodeficiency state such as severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia or partial deletion of chromosome 22 (del 22q11.2), use of irradiated components is mandatory. Features associated with immunodeficiency states include cardiac defects, dysmorphic features, craniofacial abnormalities, hypocalcaemia and lymphopenia.

Irradiated components are not indicated for 'top-up' transfusions of premature or term infants unless there has been a previous IUT, in which case irradiated components should be administered until 6 months after the 40 week gestation date.

Irradiated components may also be appropriate for extreme low body weight neonates less than 28 weeks who are at increased risk of TA-GVHD due to physiological immune incompetence. Evidence suggests that the risk is greatest in those < 900 g in body weight.

As a result of gamma irradiation, red cells lose potassium during storage. While this is not normally a problem with small volume neonatal top-up transfusions, for larger volume and exchange transfusions irradiated red cells must be transfused within 24 hours of irradiation.

Use of Erythropoeitin

In some infants erythropoietin (EPO) may be used to reduce transfusion requirements. Specialist advice on dose and frequency should be obtained.

Platelets

There is an increased risk of haemorrhage in preterm infants with moderate thrombocytopenia < 50 x 10^9/L and in full-term infants with platelet counts less than 20 - 30 x 10^9/L. The risk is increased if sepsis or coagulopathy are present. The recommended volume for top-up transfusion is 10 mL/kg to a maximum of one neonatal unit. A single neonatal platelet unit will normally provide an acceptable platelet increment in children under 10 kg in body weight. At higher body weights, one single neonatal platelet unit per 10 kg of body weight followed by a post-transfusion platelet count and reassessment of the patient is recommended. If the plasma volume of the platelet concentrate is excessive, the blood bank may be asked in advance for advice regarding the need to remove plasma to a minimum volume of 10 - 15 mL per platelet concentrate.

6.12 Neonatal Autoimmune Thrombocytopenia

Neonates with thrombocytopenia associated with maternal autoimmune disease (e.g., immune thrombocytopenia or systemic lupus erythematosis) generally have a benign postnatal course without bleeding complications and one in which often a nadir is reached by day 2 - 3, followed by a spontaneous rise in platelet count by the seventh day. In a small number of cases treatment is warranted due to persistent severe thrombocytopenia. Most neonates respond well to intravenous immunoglobulin in a dose of 2 g/kg body weight. Platelet transfusions have no value in prophylaxis of this condition but may be useful if there is bleeding.

6.13 Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

FNAIT is a rare but serious condition which arises from maternal alloimmunisation to fetal platelet antigens of paternal origin and which affects approximately 1:1,100 pregnancies. FNAIT is the platelet equivalent of HDFN, where maternal IgG antibodies cross the placenta and may destroy fetal platelets, leading to thrombocytopenia and an increased risk of bleeding. The most serious consequence, estimated to occur in 10 - 20% of untreated pregnancies and presenting at any time from 20 weeks gestation until a few days after birth, is intracranial haemorrhage (ICH) which may be fatal or lead to long-term neurological problems.

The most common alloantibody responsible for FNAIT in Caucasians is anti-HPA-1a (80 - 90% of cases) followed by anti-HPA-5b (5 - 15%), with other HPA antibody specificities are infrequently seen. In Maori and Asian mothers, consideration should be given to other antibodies including those within the HPA-4 system.

There may or may not be a history of thrombocytopenia in a previous infant. Unlike HDFN, FNAIT can occur during a first pregnancy and in fact almost half of the clinically evident cases are discovered in the first live-born infant.

Treatment

The management of FNAIT is overseen by a fetal medicine specialist along with input from a specialist haematologist and/or NZBS Transfusion Medicine Specialist.

In the neonatal period the condition is self-limiting often resolving within two weeks after birth although occasionally persisting for up to eight weeks. The treatment of choice is platelet transfusion for which platelets lacking the specific HPA antigen should be selected. In the absence of suitable donor platelets, the mother's platelets may be used. These must be washed to remove the plasma that contains the platelet antibody and must be irradiated. Such a selected donation must follow the usual procedures for collecting, testing, storing, handling and transfusing of the unit that apply to non-selected blood donations.

For well neonates with suspected FNAIT, no evidence of haemorrhage, and where the platelet count is $< 30 \times 10^9$/L, prompt transfusion of platelets negative for both HPA-1a and HPA-5b antigens is recommended. Following the results of serological testing, directed donations negative for the implicated antigen are recommended.

Where there is evidence of ICH or other major haemorrhage, a higher platelet threshold 50 - 100 x 10^9/L should be used. The platelet count should be maintained > 50 x 10^9/L at least until the end of the first week of life. In view of the poor outcome of FNAIT-associated ICH, if HPA antigen-negative or washed maternal platelets cannot be provided, current BCSH guidelines recommend the transfusion of randomly selected platelets (irrespective of their HPA status). Intravenous immunoglobulin (IVIg) is an alternative therapy, although there is often a 24 to 48 hour delay in response, and may be used in combination with platelet transfusion. Treatment of the neonate with high dose intravenous immunoglobulin (2 g/kg body weight) is effective in about 65% of cases and can reduce the period of dependence on compatible platelets.

For women with a history of FNAIT, management of the fetus during a subsequent pregnancy includes assessment of ICH risk (including paternal HPA zygosity +/- fetal HPA genotyping), antenatal administration of IVIg 1 - 2 g/kg/week from as early as 12 weeks, and/or corticosteroids. Despite immune modulating therapy, there remains

an increased risk of fetal ICH. For cases considered to be at high risk of ICH (such as a previous child with FNAIT-associated ICH), prophylactic intrauterine fetal platelet transfusions may be included in the management.

6.14 Individuals Refusing Blood Transfusion

Some patients may refuse to receive transfusion for personal, religious or cultural reasons. For example, Jehovah's Witnesses may hold beliefs that preclude transfusion of blood components or fractionated products. These wishes and beliefs must be respected and patients treated in a non-emotional and logical way.

Some patients will refuse all blood transfusions while others will accept fractionated products. Others will accept autologous blood collection and transfusion, cell salvage and auto-transfusion of blood collected during surgery. Some patients do not wish their relatives or peers to know that they have been transfused.

When a patient indicates that they do not wish to receive a transfusion there should be close and confidential discussion with the patient as to their exact requirements and what they will and will not accept. This information should be recorded in their notes.

It is advisable that the matter is discussed with the clinical leader of the unit concerned. Where there are areas of difficulty or dissension, the Chief Medical Officer (CMO) of the hospital should be contacted for further advice and guidance as to management of the patient. The CMO will have access to the DHB solicitor and appropriate patient advocate groups. Additional consultation may be necessary with anaesthetists and surgeons to ensure the best possible care is given to the patient when blood transfusion cannot be provided despite clear clinical indication.

For children, the same procedure should be followed with careful consultation of the parents and noting any comments or opinions from the child. For babies and infants, the clinical leader should be closely involved in the decision-making. In cases where the parents, whanau or guardians refuse consent for transfusion deemed necessary to save life, prevent permanent injury or prolonged and avoidable pain and suffering, the consultant responsible needs to consult with the CMO to discuss appropriate further action. Such action may involve meeting with a solicitor to discuss the need for legal action. If court action is deemed necessary, an *inter partes* hearing may be appropriate.

It is mandatory that a very careful procedure be followed, with full documentation and consultation with the relevant people, prior to any transfusion.

ADVERSE EFFECTS OF TRANSFUSION

7.1 Overview

Transfusion, like other treatments, can both benefit and harm the patient. Good clinical practice depends on understanding both the benefits and risks that transfusion may carry. Also, it is essential to consider the potential benefits and risks of not using a blood component or fractionated product, or of using an alternative.

Blood transfusion has become safer as infectious hazards have been identified and donor selection procedures, viral screening tests and platelet pre-release bacterial culture systems have been introduced. There has also been continuous improvement in manufacturing processes for fractionated products.

Although much effort is placed into ensuring the safety of transfusion, preventable clerical error and inappropriate transfusion still account for a significant proportion of reported transfusion-related adverse events.

Data on the occurrence of adverse reactions and other adverse events associated with the transfusion process are collected through NZBS Haemovigilance.

7.2 Reporting Adverse Reactions and Events

Serious or life-threatening acute reactions are rare but new or unexpected symptoms that appear while the patient is being transfused must not be overlooked, as they may be early warning signs of a serious reaction.

Severe reactions are most likely to occur within 15 minutes of starting a transfusion. It is important to monitor the patient closely during this initial period and thereafter at regular intervals according to local hospital policy. Serious events should be discussed with a NZBS Transfusion Medicine Specialist/Medical Officer or specialist haematologist for advice on further management of the patient, laboratory investigations and future transfusion requirements.

Adverse reactions to blood components

If the patient experiences an adverse reaction during or following transfusion of a blood component, clinical staff must report this to the blood bank as soon as possible. NZBS supplies a *Transfusion-related Adverse Reaction Notification* form that has guidelines for the management of adverse transfusion reactions to assist clinical staff in the immediate care of the patient.

The completed form should be sent to the blood bank along with remnants of the transfused components and laboratory samples required for full investigation of the reaction. Refer to Table 10.1: *Samples Required for Pretransfusion Testing* for further information.

Adverse reactions to fractionated products

If the patient experiences an adverse reaction to a fractionated plasma product this must be reported to the blood bank as soon as possible, for example by sending a NZBS *Transfusion-related Adverse Reaction Notification* form. The blood bank will then initiate completion of a NZBS *Notification of Adverse Reaction to a Fractionated Product* form together with information obtained from the patient's clinician.

In accordance with pharmacovigilance requirements, NZBS reports the occurrence of adverse reactions to fractionated products to the relevant manufacturer, for example CSL Behring. Where clusters of similar adverse reactions occur, these are reported to the New Zealand regulator, Medsafe. Both Medsafe and the Centre for Adverse Reactions Monitoring (CARM) are provided with an annual NZBS Haemovigilance Report.

Adverse events associated with transfusion

The blood bank should be notified as soon as possible if it is believed that the patient has received a wrong blood component or fractionated product, received one intended for another patient, that the transfusion did not meet requirements or that the transfusion was inappropriate. It should be noted that the patient may not always experience or show a 'reaction' in these situations.

7.3 Guidelines for the Management of Adverse Transfusion Reactions

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions

Reaction/Cause	Signs & Symptoms	Prevention	Management
Febrile Non-Haemolytic Transfusion Reaction (FNHTR) **Frequency:** 1-3:100 (higher in multi-transfused recipients) ▪ Common ▪ Onset during or within 4 hours following transfusion ➢ Reaction induced by cytokines ➢ Alloimmune reaction to leucocyte antigens ➢ Other causes may exist	▪ **Mild:** unexplained fever ≥38°C and a temperature rise of at least 1°C but <1.5°C from pretransfusion baseline, occurring in the absence of chills, rigors, respiratory distress and haemodynamic instability ▪ **Moderate:** unexplained fever ≥38°C and a temperature rise of at least 1°C but not meeting criteria for either mild or severe FNHTR ▪ **Severe:** unexplained fever >39°C and a temperature rise ≥2.0°C from pretransfusion baseline and chills/rigors ▪ Associated or secondary symptoms may be present: tachycardia, headache, nausea, flushing, anxiety, hypertension or occasionally hypotension ▪ In some cases: marked apprehension, loin pain, and/or angina	▪ Check for history of previous transfusion reactions. Consider pretransfusion antipyretic Paracetamol 1g po where repeated minor reactions occur and further transfusions are required ▪ Consult TMS if recurrent reactions occur ▪ Note: All blood components are depleted of leucocytes during production and further leucodepletion at the bedside is not required	▪ Check label and recipient identity ▪ Slow the transfusion if reaction is mild and MO elects to continue transfusion ▪ Send Haemovigilance notification to Blood Bank ▪ Antipyretic Paracetamol 1g po and monitor closely ▪ Steroids are not appropriate treatment for FNHTR

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Allergic Reaction (minor) **Frequency:** 1:100 – 1:500 ▪ More common with plasma and platelet components ▪ Onset during or within 4 hours following transfusion ➢ Recipient may have an antibody reacting with plasma protein or leucocyte antigen (HLA or other) in the transfused component or fractionated product	**Minor or localised reaction:** ▪ Flushed skin ▪ Morbilliform rash with itching ▪ Urticaria (hives) ▪ Localised angioedema ▪ Periorbital itch, erythema and oedema ▪ Conjunctival oedema ▪ Minor oedema of lips, tongue and uvula	▪ For recurrent mild reactions prophylaxis with antihistamine to alleviate symptoms, e.g., Loratadine 10mg or Cetirizine 10mg po ▪ Routine prophylaxis for all recipients before transfusion is not indicated	▪ Slow transfusion ▪ Check label and recipient identity ▪ Antihistamine, e.g., Loratadine 10mg or Cetirizine 10mg po if symptoms are troublesome ▪ If symptoms mild and transient, transfusion may resume ▪ Continue transfusion at a slower rate with increased monitoring, e.g., BP/TPR every 15-30 min ▪ Send Haemovigilance notification to Blood Bank ▪ If symptoms increase treat as a moderate or severe reaction

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Allergic Reaction (moderate) **Frequency:** 1:500 – 1:5,000 ▪ Onset usually within first 50-100mL infused and within 4 hours of transfusion ➢ Recipient may have an antibody reacting with a plasma protein or leucocyte antigen (HLA or other) in the transfused component or fractionated product	**Moderate or widespread reaction:** ▪ Symptoms as for minor reactions, plus: ▪ Cough ▪ Mild hypotension or tachycardia ▪ Dyspnoea and oxygen desaturation are common ▪ Chills and rigors ▪ Loin pain and angina ▪ Severe anxiety	▪ Discuss with TMS if recurrent ▪ Note: Prophylactic treatment with an antihistamine or hydrocortisone will not reliably prevent moderate and severe allergic reactions but may alleviate symptoms when present	▪ Stop transfusion ▪ Check label and recipient identity ▪ Replace IV set and give saline to keep vein open and/or maintain BP ▪ Monitor closely and treat symptomatically as required with IV fluids, oxygen and antihistamine, e.g., Promethazine 25-50mg IV (max rate 25mg/min) or Loratadine 10mg or Cetirizine 10mg po. Hydrocortisone may be considered ▪ Send Haemovigilance notification to Blood Bank ▪ Discuss moderate reactions with TMS

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Anaphylactic / Anaphylactoid Allergic Reaction (severe) **Frequency:** 1:20,000 – 1:50,000 ▪ Rapid onset ➢ Recipient may have an antibody reacting with a plasma protein in the transfused component or fractionated product, e.g., IgA, haptoglobin or other plasma protein	**Life-threatening reaction:** ▪ Symptoms as for moderate reactions, plus: ▪ Severe hypotension, shock and tachycardia ▪ Widespread urticaria with skin flushing and itching ▪ Wheezing, stridor, change in voice ▪ Severe anxiety ▪ Note: Respiratory symptoms may dominate in anaesthetised recipients	Discuss with TMS before requesting: ▪ IgA deficient blood/ blood products may be appropriate if recipient is known to have absolute IgA deficiency and to have anti-IgA ▪ Washed cellular components may be indicated where the cause of the reaction is not identified	▪ Stop transfusion ▪ Check label and recipient identity ▪ Follow Anaphylaxis Guidelines: • Adrenalin 1:1000 IM and repeat at 5-10 min intervals if required: ➢ Adult: 0.5mg/0.5mL ➢ Children 0.01mg/kg IM; min dose 0.1mL, max dose 0.5mL • Replace IV set and give rapid IV colloid or saline, e.g., adults 2L, children 20mL/kg, until SBP >90mmHg, then titrate • Consider Hydrocortisone 4mg/kg (200-400mg IV) • Consider H1-antihistamine, e.g., Loratadine or Cetirizine 10mg po for itch or angioedema • H2-antihistamine, e.g., Ranitidine may be added for severe reactions • Note: Sedating antihistamines, e.g., Promethazine are contraindicated ▪ CPAP ventilation, chest x-ray ▪ ICU liaison ▪ Follow NZRC Guidelines if no pulse present and for symptoms that persist after initial treatment ▪ Collect serum tryptase sample within 1-2 hours if anaphylaxis may be present (returns to normal within 6-8 hours) ▪ Send Haemovigilance notification to Blood Bank ▪ Discuss severe reactions with TMS

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Hypotensive Reaction **Frequency:** 1-2:1,000 ■ Onset during or within 1 hour of transfusion ➢ Often idiosyncratic reaction ➢ Possible increased risk with ACE-inhibitor therapy	■ Hypotension – fall in systolic BP >30mmHg during or within 1 hour of completing transfusion **and** systolic BP <80mmHg		■ Stop transfusion ■ Replace the IV infusion set and infuse saline to manage BP ■ Symptomatic management until resolved ■ Send Haemovigilance notification to Blood Bank

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Acute Haemolytic Transfusion Reaction **Frequency:** 1:12,000 – 1:100,000 ▪ Onset within 24 hours, usually immediate ➢ ABO or other incompatible red cell transfusion reaction caused by complement-fixing antibodies ➢ Rarely, ABO antibodies in a platelet or plasma component ➢ Improper handling, storage or administration of red cell component	*Some or all of –* ▪ Unexplained fever >1°C ▪ Chills, rigors ▪ Pain up arm ▪ Chest, abdominal or low back pain ▪ Dyspnoea ▪ Tachycardia ▪ Hypotension, shock ▪ Haemoglobinaemia and haemoglobinuria ▪ Oliguria with dark urine or anuria ▪ Nausea, vomiting ▪ Diarrhoea ▪ Pallor, jaundice ▪ Bleeding (due to DIC)	▪ Meticulous checking of recipient's ID and labelling of pretransfusion blood sample at recipient's side ▪ Meticulous two-person checking of ID of intended recipient of blood component and component label ▪ Careful monitoring of recipient for first 15 min of each unit transfused ▪ Store and handle blood components within specifications ▪ Proper administration of blood components	▪ Stop transfusion ▪ Check label and recipient identify ▪ Replace IV set and start normal saline ▪ Treat shock and maintain blood pressure with IV saline infusion ▪ Investigate possible DIC and treat if clinically significant bleeding ▪ Diuretic, e.g., Frusemide 1-2mg/kg IV and/or Mannitol, may help maintain urine flow ▪ Hydrocortisone may be considered ▪ Samples to assess renal and liver function, DIC and haemolysis, e.g., full blood count, unconjugated bilirubin, LDH and haptoglobin ▪ Send Haemovigilance notification to Blood Bank

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Delayed Haemolytic Transfusion Reaction **Frequency:** Estimated 1:5,000 but recognized and reported events 1:35,000 ■ Onset usually 1-7 days post-transfusion but may be up to 28 days ➢ Recipient has previously been sensitised to a blood group antigen, usually by transfusion or pregnancy. Transfusion with red cells expressing the relevant antigen produces a secondary immune response and results in haemolysis of transfused antigen-positive red cells	■ Worsening anaemia and jaundice from destruction of red cells ■ Often asymptomatic but rarely splenomegaly, haemoglobinaemia and haemoglobinuria ■ Renal impairment may occur in severe cases ■ Blood screen shows unexpected anaemia and spherocytes may be present on film	■ Blood group antibodies are recorded on the NZ Blood Service national database so that compatible red cell components can be provided for future transfusions ■ Note: Delay may occur in providing compatible red cells for transfusion	■ Investigate haemolysis: ■ Full blood count with film comment ■ Direct antiglobulin test (may be negative when most red cells cleared) ■ Blood group antibody screen (may be negative until red cells cleared) ■ Liver function tests ■ Haptoglobin concentration falls while haemolysis is occurring ■ LDH ■ Send Haemovigilance notification to Blood Bank if reaction is suspected

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Bacterial Sepsis **Frequency:** Platelet components: <1:10,000 Red cell components: <1:250,000 ■ Rapid onset ➢ Blood component contains bacteria that have grown to a high concentration ➢ Most commonly affects platelet components; rarely affects red cells ➢ If gram negative bacteria are present, endotoxin levels may be very high	■ Rigor, chills, fever ■ Shock, usually within minutes of starting transfusion ■ Respiratory distress, wheezing and oxygen desaturation ■ Pain up arm ■ Chest and back / loin pain ■ Nausea, vomiting ■ Explosive diarrhoea may occur with *Yersinia enterocolitica* sepsis ■ Most common infecting agents: staphylococcal species (platelet components), gram negative species (red cell components)	■ Collect, store and handle blood components within specifications ■ Inspect products for any visual abnormality or defect in unit container before transfusing: • a visibly clumped platelet component • an unusually dark red cell component • punctured or leaking bag	■ Stop transfusion ■ Replace IV set; give saline to maintain BP and/or keep vein open ■ Send Haemovigilance notification to Blood Bank ■ Notify Blood Bank by phone and contact TMS urgently ■ Obtain blood cultures from recipient if sepsis suspected ■ Give antibiotics: a broad-spectrum penicillin or cephalosporin and gentamicin 5mg/kg ■ Note: Blood Bank will arrange urgent Gram stain and cultures on blood component and report any positive findings

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
TACO: Transfusion-Associated Circulatory Overload **Frequency**: 1:100 – 1:1,000 red cell transfusion episodes ■ Onset during or within 6 hours following transfusion ➢ Main risk factors: • Elderly recipient with impaired cardiovascular or renal function • Transfusion too rapid for recipient • Volume transfused too great for recipient, especially if normovolaemic	■ Acute respiratory distress along with some or all of the following: dyspnoea, oxygen desaturation, productive cough with pink frothy sputum, nausea, restlessness and anxiety ■ Tachycardia ■ Increased blood pressure ■ Acute or worsening pulmonary oedema on chest xray ■ Enlarged cardiac silhouette on chest xray ■ Evidence of fluid overload such as positive fluid balance, raised JVP and/or CVP ■ Note: Hypotension may occur in cases of acute cardiac collapse	■ Restrictive transfusion practice ■ Monitor fluid balance esp. in elderly and children, and recipients with cardiovascular or renal disease ■ Transfuse at a rate appropriate for recipient ■ Give a diuretic immediately prior to a transfusion if cardiovascular reserve is impaired or a large transfusion is required ■ Avoid elective transfusions at night ■ Always prescribe paediatric transfusion dose in mL, **not** in Units	■ Stop transfusion ■ Seek urgent medical assessment ■ Sit recipient upright with legs over side of bed, administer oxygen, diuretic (Frusemide 1-2mg/kg IV), CPAP ventilation ■ Phlebotomy may be necessary ■ Send Haemovigilance notification to Blood Bank

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Post-transfusion Purpura **Frequency:** <1:100,000 (mostly occurs in women who have been pregnant) ■ Onset about 5-12 days after transfusion of cellular blood components ➢ Recipient has produced an antibody to a human platelet-specific antigen (HPA). The antibody forms immune complexes with transfused platelet antigens resulting in clearance of most circulating platelets	■ Severe thrombocytopenia often with purpura and possibly other bleeding ■ Thrombocytopenia will persist for 1-2 weeks	■ Restrictive transfusion practice ■ Notify Blood Bank and TMS promptly so that relevant investigations can be initiated ■ Further transfusions may require selected components ■ Note: Delay may occur in providing further cellular blood components	■ Consult TMS or haematologist if a recipient of cellular blood components develops an unexpected severe thrombocytopenia in the following 1-2 weeks ■ Test for HPA antibodies ■ If not bleeding – monitor ■ If severe thrombocytopenia or clinically significant bleeding – intravenous immunoglobulin is recommended ■ Corticosteroids and plasma exchange are recognised additional treatments ■ If life-threatening bleeding – platelet components lacking the relevant HPA antigen are desirable ■ Avoid random-donor platelet transfusion

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
TRALI: Transfusion-Related Acute Lung Injury **Frequency:** <1:5,000 ■ Onset within 6 hours following transfusion of plasma or plasma-containing cellular components ➢ A complex group of disorders indistinguishable clinically from ARDS ➢ One recognised mechanism involves a donor antibody reacting with recipient leucocyte (HLA) or neutrophil (HNA) antigens causing cell activation that results in acute severe microvascular lung injury ➢ Other contributing factors likely exist	■ Acute respiratory distress (often proceeding to respiratory failure) along with some or all of the following: dyspnoea, oxygen desaturation, non-productive cough, chills, fever and hypo- or hypertension. ■ Bilateral infiltrates on chest xray ■ Absence of left atrial hypertension (as in circulatory overload) ■ If the reaction occurs during anaesthesia the lungs become very stiff from rapidly developing pulmonary exudate ■ Distinguish from: • TACO • other causes of acute lung injury (ALI)	■ Restrictive transfusion practice ■ NZ case-rate from FFP and platelet components has been reduced by supply of: • Male-only FFP • HLA-antibody testing of apheresis platelet donors • Pooled platelets are suspended in platelet additive solution (PAS) and have minimal residual plasma ■ Notify Blood Bank so that donor(s) can be assessed for relevant antibodies and implicated donor(s) withdrawn from the active donor panel	■ Intensive care management for respiratory failure ■ Diuretics are not usually helpful ■ Send Haemovigilance notification to Blood Bank ■ Notify Blood Bank by phone and contact TMS urgently ■ Tissue typing samples will be required

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD) **Frequency:** Rare but fatal ■ Onset 1-6 weeks following transfusion ➢ Well-defined risk factors include: • Congenital cellular immune deficiency • Intrauterine transfusion and neonatal exchange transfusion • Hodgkin lymphoma • Autologous and allogeneic HSCT • Directed donation from blood relative • HLA-matched apheresis platelets • Granulocyte transfusion • Purine nucleoside analogue therapy • Alemtuzumab therapy	■ Clinical syndrome with fever, rash, liver dysfunction, diarrhoea and pancytopenia	■ Irradiate cellular blood components to inactivate residual lymphocytes ■ When notified of a patient requiring irradiation of cellular components, NZBS attaches a protocol to the patient's transfusion record	■ Consult TMS or haematologist to investigate and establish diagnosis ■ Send Haemovigilance notification to Blood Bank

Table 7.1: Guidelines for the Management of Adverse Transfusion Reactions continued

Reaction/Cause	Signs & Symptoms	Prevention	Management
Cooling **Frequency: no data** ■ Progressive onset during rapid infusion of large volumes of cold fluids, including blood products (more than 50mL/kg/h in adults or 15mL/kg/h in children)	■ Reduced temperature ■ May be associated with cardiac rhythm irregularity and a negative inotropic effect ■ Impaired platelet function and coagulation	■ Give large fluid infusions through a warmer designed for rapid infusion of blood components and follow the manufacturer's instructions ■ Equipment must be properly maintained and validated to ensure the correct temperature is achieved as excessive temperature will produce haemolysis	■ Limit heat loss from the recipient and monitor BP/TPR ■ If further blood components required, infuse through a warmer ■ Note: Reliable determination of temperature requires core temperature measurement

7.4 Febrile Non-Haemolytic Transfusion Reaction

Fever or rigors during red cell transfusion affect 1 - 3% of recipients and in the past were usually attributed to the transfusion of white cells present in blood components. Febrile non-haemolytic transfusion reactions (FNHTR) generally occur more frequently in patients who have been alloimmunised to leucocyte antigens as a result of pregnancy or recurrent transfusion. The use of leucocyte-depleted blood components has undoubtedly reduced the occurrence of FNHTR, however the relatively large number of reactions still seen suggests the involvement of other mechanisms and risk factors. Febrile reactions during platelet transfusion have been attributed to leucocyte- and platelet-derived cytokines that accumulate in the product during storage.

Classical symptoms of FNHTR are shivering, usually 30 - 60 minutes after the start of the transfusion, followed by fever. Most reactions can be managed by slowing or stopping the transfusion and giving an antipyretic such as paracetamol. FNHTR, although unpleasant, are not life-threatening, however it is important to remember fever or rigors can also be the early symptoms of a severe acute haemolytic transfusion reaction or transfusion of bacterially contaminated blood.

Recurrent severe FNHTR in patients who require repeated transfusion of red cells or platelets may be prevented by the use of washed cellular components.

Premedication

While treatment of FNHTR with antipyretics such as paracetamol for a symptomatic rise in temperature may be justified, routine premedication with antipyretics and/or antihistamines prior to transfusion is not advised as it is both unnecessary and may modify important signs of a transfusion reaction. Steroids are not appropriate for the treatment or prevention of FNHTR.

7.5 Allergic & Anaphylactic Reaction

Allergic reactions represent a spectrum of severity from mild, where the patient simply experiences isolated urticaria or a rash, though to fatal anaphylactic shock.

Allergic reaction

These are typified by one or more of the following: urticaria, rash, allergic dyspnoea (stridor, cyanosis, wheezing), localised angioedema or generalised pruritis without hypotension during or within 4 hours of transfusion. These reactions are commonly associated with transfusion of components with large volumes of plasma, for example platelets and FFP. Since the introduction of platelets suspended in platelet additive solution (PAS), the frequency of allergic reactions has reduced.

Symptoms usually subside if the transfusion is slowed and parenteral antihistamine is given. The transfusion may be continued if there is no progression of symptoms after 30 minutes.

A rise of mast cell tryptase can support the diagnosis of an allergic reaction.

Anaphylactic reaction

These are rare but life-threatening complications usually occurring during or very shortly after transfusion and are differentiated from mild/moderate allergic reactions by severity where, in addition to mucocutaneous features, there is airway compromise

or severe hypotension requiring vasopressor treatment (or associated symptoms like hypotonia or syncope).

Anaphylaxis may occasionally be associated with antibodies against IgA in patients who have extremely low levels of IgA in their plasma or other genetic variants of plasma proteins. If this is the suspected cause the patient should, if possible, not be transfused. Special components will be needed in consultation with an NZBS Transfusion Medicine Specialist.

Premedication

Treatment with an antihistamine or hydrocortisone for generalised allergic reactions is justified. Premedication may be appropriate before transfusing a patient who has previously experienced repeated allergic reactions. Routine premedication with antihistamines prior to transfusion is however not advised, as it is both unnecessary and may modify important signs of a transfusion reaction.

7.6 Hypotensive Transfusion Reaction

Hypotensive transfusion reactions are defined as a drop in systolic blood pressure ≥ 30 mmHg during or within one hour of transfusion together with a systolic blood pressure ≤ 80 mm Hg. Most reactions occur very rapidly within minutes of starting the transfusion and respond to ceasing the transfusion together with supportive care. The underlying condition of the patient must have been excluded as an explanation for the reaction. These may occur more frequently in patients receiving angiotensin-converting enzyme (ACE) inhibitor therapy.

7.7 Acute Haemolytic Transfusion Reaction

Incompatible transfused red cells react with the patient's anti-A or anti-B antibodies and cause an acute haemolytic transfusion reaction (AHTR). Such a reaction can activate complement and cause disseminated intravascular coagulation (DIC) and acute renal failure. The reaction is usually most severe if group A red cells are transfused to a group O patient. Transfusion of ABO-incompatible blood almost always arises from pretransfusion sample labelling errors or from failure to perform required checks prior to giving the transfusion. If red cells are administered to the wrong patient (i.e., any patient other than the one for whom the red cells were supplied) the chances of ABO-incompatibility are about 1 in 3. Rarely, AHTR is due to a non-A, non-B, complement-fixing antibody. Such reactions reported most commonly involve the Kell, Duffy and Kidd antigen group systems.

Acute haemolysis may also occur following transfusion of plasma-rich blood components such as platelets or FFP from donors with high titres of anti-A or anti-B that react with patient red cells.

In a conscious patient even a few millilitres of incompatible blood may cause symptoms within a few minutes of starting the transfusion. The patient may become restless or distressed and experience pain at the infusion site, fever, flushing, breathlessness, or abdominal, flank or substernal chest pain. The severity varies widely as it is dependent on the titre of blood group antibody in the recipient, the quantity of blood transfused and other factors such as age. In an unconscious or anaesthetised patient, hypotension and uncontrollable bleeding due to DIC may be the only signs of an incompatible transfusion. Oliguria is common and is often followed by acute renal failure.

If AHTR is suspected, the transfusion must be stopped, the line maintained with intravenous saline and urgent steps taken to confirm or exclude this possibility.

Signs and symptoms of AHTR may be similar to a severe allergic reaction or bacterial contamination. In addition, autoimmune haemolytic anaemia due to erythrocyte autoantibodies in the recipient and non-immune (mechanical) causes must be part of the differential diagnosis.

7.8 Delayed Haemolytic Transfusion Reaction

A delayed haemolytic transfusion reaction (DHTR) is one in which evidence of increased red cell destruction develops, usually between 24 hours and 28 days, following a transfusion. The symptoms and clinical or laboratory signs are similar to AHTR but are usually less severe, often manifesting as an inadequate rise or unexplained fall in the post-transfusion haemoglobin. Whilst clinically significant DHTR are rare and seldom fatal, they can cause additional problems for a patient who is already seriously ill.

DHTR occur in a patient immunised to a red cell antigen by an earlier transfusion or pregnancy. The level of antibody may be so low that it cannot be detected in the pretransfusion sample. After transfusion of red cells bearing the target antigen, a rapid secondary immune response boosts the antibody level so that, after a few days, transfused red cells bearing the relevant antigen may be rapidly destroyed. Antibodies of the Kidd and Rh systems are the most frequent cause of DHTR.

7.9 Bacterial Sepsis

Bacterial sepsis, whilst rare, is the leading microbial cause of transfusion mortality. Sources of bacteria in blood components may include contamination from skin organisms at the phlebotomy site due to ineffective skin disinfection, skin plugs introduced to units during phlebotomy, transient bacteremia in donors and, rarely, contamination during handling and processing of components.

Bacterial contamination is more likely in components stored at room temperature (20 - 24°C) such as platelets, than with red cells (stored at 2 - 6°C). Common organisms associated with contamination include *Staphylococcus epidermidis, Staphylococcus aureus, Bacillus cereus*, Group B streptococci, *Escherichia coli*, Pseudomonas species and other gram-negative organisms. Sepsis due to contaminated platelets is thought to be both under recognised and under reported. Platelet-associated sepsis is not normally catastrophic and can occur several hours or longer post-transfusion making it difficult to associate with transfusion and thereby diagnose. This is in contrast to the sepsis and toxaemia from bacterially contaminated red cells which is often rapid and catastrophic, with reported mortality rates of up to 60%.

Septic and toxic reactions may be life threatening. If bacterial contamination is suspected, the transfusion must be stopped immediately and institutional guidelines for investigating a reaction strictly followed. Usual investigation will include urgent patient and blood unit culture and Gram stain. Initial treatment involves managing the haemodynamic complications of sepsis and administration of intravenous antibiotics covering the usual pathogens associated with transfusion-related sepsis.

A number of measures are used by NZBS to minimise the risk of bacterial contamination in blood components. These include:

- Predonation identification and deferral of potentially bacteraemic donors
- Enhanced disinfection of the skin at the phlebotomy site
- Diversion of the initial 10 - 40 mL blood collected into a separate container
- Bacterial monitoring of platelet components using an automated bacterial detection system

Visual inspection of the blood component for abnormal appearance (such as discoloration or haemolysis) should be carried out both prior to release from the Blood Bank and before administration. Blood components must not be transfused beyond their expiry date.

7.10 Post-transfusion Purpura

Post-transfusion purpura (PTP) is a rare but potentially lethal complication of transfusion of red cells and platelets. It is characterised by the sudden onset of severe thrombocytopenia, typically 5 - 12 days following transfusion, often associated with haemorrhage. PTP is most often seen in females (90% of cases) and in particular those with a history of pregnancy.

Transfusion causes an anamnestic response boosting human platelet-specific antigen (HPA) antibodies previously stimulated by pregnancy or earlier transfusion. The resulting thrombocytopenia is due to alloantibody-mediated destruction of the transfused platelets as well as "bystander" destruction of the patient's own platelets.

Treatment of choice is high dose intravenous immunoglobulin, 2 g/kg body weight, administered in divided doses over 2 - 5 consecutive days.

Plasma exchange and corticosteroids have been used in the past but an increase in platelet count is significantly delayed when compared to intravenous immunoglobulin. If platelet transfusion is unavoidable, platelets that are compatible with the patient's antibody should be used although survival of the platelets may be impaired during the acute phase of the syndrome. If future transfusions are planned, red cell or platelet components from donors negative for the implicated HPA antigen(s) should be selected wherever possible.

Expert advice from a NZBS Transfusion Medicine Specialist or specialist haematologist is needed when managing PTP.

7.11 Transfusion-Associated Circulatory Overload

When too much fluid is transfused or the transfusion is too rapid for a patient, fluid overload can lead to systemic and pulmonary venous engorgement. Cardiogenic pulmonary oedema and acute respiratory failure may follow.

The features of transfusion-associated circulatory overload (TACO) include acute respiratory distress, tachycardia, increased blood pressure, evidence of fluid overload, an enlarged cardiac silhouette and new or worsening pulmonary oedema in the chest xray. TACO usually occurs within 6 hours of completion of the transfusion. Evidence of fluid overload may include a documented positive fluid balance and/or a clinical response to diuretic therapy. Diagnosis is supported by an elevated serum B-type natriuretic peptide (BNP) or the accompanying N-terminal fragment (NT-pro BNP) to

more than 1.5 times the pretransfusion value (if available) and/or an increase in mean arterial pressure or increase pulmonary wedge pressure.

Standard medical treatment includes stopping the transfusion, sitting the patient upright, administering oxygen and diuretic therapy. Where necessary, vasodilator therapy and/or non-invasive ventilatory support with continuous positive airways pressure (CPAP) may be helpful. Venesection can also be considered.

TACO is most commonly seen in patients with low body weight, the elderly, infants or children, those with a history of cardiac, respiratory or renal insufficiency, and in the setting of red cell transfusion for chronic anaemia. Volume overload is a special risk with albumin solutions.

Patients with chronic anaemia are normovolaemic or hypervolaemic and may have signs of cardiac failure before any fluid is infused. Each unit should be given slowly and the patient closely observed. Preemptive diuretic therapy may be helpful.

7.12 Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a significant transfusion-related event. Although poorly recognised and undoubtedly underreported, international haemovigilance data indicates that it is one of the most common causes of fatal transfusion reactions.

TRALI is characterised by acute respiratory distress due to non-cardiogenic pulmonary oedema, developing during or within 6 hours of transfusion. Typically, plasma components containing antibodies against the patient's white blood cells are implicated. Transfusion is followed by a (usually) severe reaction with acute respiratory distress, accompanied by chills and/or fever. The chest xray shows numerous, mainly perihilar, nodules with infiltration of the lower lung fields without cardiac enlargement or engorgement of the vessels. A transient leucopenia or neutropenia may be seen. The implicated donors are almost always alloimmunised multiparous women. However the number of reactions seen where antibodies are either not identified or serologically cannot be implicated suggests the involvement of other mechanisms and risk factors.

The diagnosis of TRALI is therefore a clinical and radiographic diagnosis and is not dependent on the results of laboratory tests or any proposed pathophysiologic mechanisms. TRALI should be considered a clinical syndrome rather than a disease with single cause. Treatment usually involves intensive care respiratory support.

Reporting to the NZBS Transfusion Medicine Specialist is essential so that an implicated donor can be removed from the panel.

Testing of donors implicated in TRALI events

One proposed mechanism for TRALI is the interaction between human leucocyte antigen (HLA) or neutrophil-specific (HNA) antibodies of donor origin and the recipient's white cells. NZBS has developed a standard procedure for investigating TRALI events, including relevant serological testing. The investigation includes testing of the donor(s) and recipient for HLA class I and II antibodies (identifying specificity if detected) and for HNA antibodies. Antibody detection and identification is complemented by HLA typing to confirm presence of the corresponding antigen(s). A crossmatch between donor serum and recipient white cells is also useful, with a positive result strongly implicating the particular donor(s).

TRALI risk reduction

A number of countries, including New Zealand, have introduced a strategy for reducing the frequency of TRALI involving the use of FFP manufactured from plasma collected only from male donors. The use of male-only donors for FFP appears to reduce the incidence of TRALI. In addition, female plateletpheresis donors with a history of pregnancy to > 20 weeks gestation are tested for the presence of HLA antibodies. Where positive, donors are deferred from donating apheresis platelets and whole blood donations are excluded from processing to platelet pools.

The differential diagnosis of TACO and TRALI

Acute respiratory distress during or shortly following transfusion may be due to TACO, TRALI, a severe allergic reaction or the patient's underlying condition. Unfortunately, many of the early signs and symptoms are not discriminatory and can occur in other types of transfusion reactions. Most FNHTR and allergic reactions can however be readily identified as such.

It is important to distinguish between TACO and TRALI because of the relatively high mortality for TRALI. Invasive measurements such as central venous and pulmonary wedge pressures may be useful (elevated in TACO) but are not consistently diagnostic or readily available, particularly in less severe cases. It has been suggested that measurement of serum B-type natriuretic peptide (BNP) or the accompanying N-terminal fragment (NT-pro BNP) might be useful in the differential diagnosis of TACO. BNP is secreted from the cardiac ventricles as a result of ventricular pressure overload and volume expansion, such as occurs with TACO. Low levels of BNP can help exclude TACO however, whilst high levels may favour TACO they do not necessarily exclude TRALI or allergic reactions, as these can co-exist.

7.13 Transfusion-Associated Dyspnoea

Only a minority of transfusion reactions are associated with predominantly respiratory features however these are some of the most serious transfusion-related adverse events. Included in this group are TACO, TRALI and allergic reactions, particularly of the more severe type.

The term transfusion-associated dyspnoea (TAD) is used by haemovigilance programmes to record events with significant respiratory distress, occurring within 24 hours of transfusion, that do not meet the criteria of TRALI, TACO or allergic reaction nor are explained by the patient's underlying condition.

7.14 Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of transfusion caused by engraftment and proliferation of transfused donor T-lymphocytes which destroy recipient cells carrying "foreign" human leucocyte antigens (HLA). Immunodeficient patients such as allogeneic bone marrow transplant recipients receiving cellular components and fetuses receiving intrauterine transfusions are at special risk for this disease. TA-GVHD has also occurred in immunologically normal patients after transfusion of blood from a relative.

TA-GVHD is fatal in almost all cases. Acute TA-GVHD begins from 4 - 40 days after transfusion with high fever followed by a diffuse erythematous skin rash progressing to erythroderma and desquamation. Gastrointestinal and liver dysfunction occur and, unlike GVHD following stem cell transplants, pancytopenia is common.

TA-GVHD is prevented by gamma irradiation of cellular blood components (red cells and platelets) to a minimum dose of 25 Gray (Gy) targeted to the central position of the container and 15 Gy to all other parts of the container. The irradiation dose must not exceed 50 Gy.

For further information regarding irradiation of blood components see Section 4.6: *Irradiation*.

7.15 Iron Overload / Haemosiderosis

Transfusion-dependent patients receiving red cells over a long period become overloaded with iron. Chelation therapy may be used to minimise or reverse accumulation of iron for these patients.

7.16 Transfusion-Related Immunosuppression

Allogeneic blood transfusion has been shown to cause suppression of the recipient's immune system. However, the mechanism behind the effect and the consequences resulting from such transfusion-related immunomodulation (TRIM) remain unclear, with contradictory evidence provided by both individual studies and metanalyses performed to date.

Evidence from a number of studies suggests that allogeneic blood transfusion enhances the survival of renal allografts, increases the recurrence rate of resected malignancies, increases the incidence of postoperative bacterial infections and increases the postoperative mortality rate from causes other than postoperative infection.

7.17 Transfusion-Transmitted Infection

The perception of the risks of transfusion have been greatly influenced by HIV transmissions that occurred before today's safer testing procedures were available.

Blood donors, like anyone else, can occasionally carry an infectious agent, sometimes for a long period, without having any clinical signs or symptoms. For this reason donors are interviewed at each and every visit and laboratory tests are performed on every blood donation. No part of the donation can be released until all these tests are known to be clear. Computer blood management systems (BMS) are used to ensure that this process is strictly adhered to.

There is very good evidence that with the donor selection and testing procedures used by NZBS, the risk in New Zealand of infection through the contamination of blood components and fractionated products is extremely small.

Table 7.2: Estimated Residual Risk of Transfusion-Transmitted Infection in New Zealand

Agent	Mean Window Period (days)	Residual Risk (with 95% prediction intervals)
HIV	5.6	1 in 9.2 million donations (2.5 - 33 million)
HCV	3.1	1 in 6.9 million donations (3.6 - 12 million)
HBV[1]	23.9	1 in 0.8 million donations (0.4 - 1.4 million)

[1]HBV residual risk does not take into account the risk from occult HBV nor the proportion of recipients who are HBV-immune from vaccination or past infection.

7.18 Other Infectious Agents

There are a number of other viral and parasitic infections that can be transmitted by transfusion, for example malaria (*Plasmodium* species), Chagas disease (*Trypanosoma cruzi*), Dengue, Zika and West Nile viruses. These are not endemic in New Zealand but a blood donor may be exposed or become infected during travel or residence abroad. The risk of acquiring Creutzfeldt-Jakob disease (CJD) and variant CJD from blood transfusion remains very low and neither has ever been reported in New Zealand. Rare cases have been reported in the UK.

It is important for NZBS to identify at-risk donors who will then either be selectively deferred from donating or tested for evidence of infection.

7.19 Adverse Event Data

The NZBS National Haemovigilance Programme has been collecting data regarding transfusion-related adverse events (TRAE) since 2005. The imputability scores of adverse events have been recorded since 2008. From January 2008 to December 2013, a total of 2756 events having an imputability score ≥3 were reported for transfusions involving 207,361 recipients who between them received 918,918 red cell, platelet or frozen plasma components. The following table outlines the type and frequency of TRAE during the period 2008 - 2013.

Table 7.3: Frequency of Transfusion-Related Adverse Events (Imputability[1] ≥3) Reported to New Zealand Haemovigilance 2008 - 2013

Event	Number	Per 100,000 Components Transfused	Per 10,000 Recipients Transfused
FNHTR	1152	125.4	55.6
Allergic	920	100.1	44.4
UCT	179	19.5	8.6
TACO	119	13.0	5.7
IBCT	84	9.1	4.1
TAD	76	8.3	3.7
DSTR	60	6.5	2.9
Hypotension	60	6.5	2.9
DHTR	36	3.9	1.7
Inappropriate transfusion	26	2.8	1.3
TRALI	13	1.4	0.6
Acute reaction[2]	12	1.3	0.6
Pain	10	1.1	0.5
TTI	9	1.0	0.4
All Events	**2,756**	**299.9**	**133.0**

[1]Imputability ≥3: the event is possibly, probably or certainly attributable to transfusion.
[2]Includes acute haemolytic and other severe acute transfusion reactions.

Key

FNHTR	*Febrile non-haemolytic transfusion reaction*
Allergic	*Allergic transfusion reaction*
TACO	*Transfusion-associated circulatory overload*
IBCT	*Incorrect blood component transfused*
UCT	*Unclassifiable complication of transfusion*
TAD	Transfusion-associated dyspnoea
DSTR	*Delayed serologic transfusion reaction*
DHTR	*Delayed haemolytic transfusion reaction*
TRALI	*Transfusion-related acute lung injury*
TTI	*Transfusion-transmitted infection*

7.20 Other Complications

Complications associated with large volume transfusions including hypocalcaemia, hyperkalaemia, hypothermia, disturbances of acid base balance and adult respiratory distress syndrome are considered in Section 6.3: *Complications of Acute Blood Loss Associated with Large Volume Transfusions*.

CLINICAL ALTERNATIVES AND APPLICATIONS

There are no effective alternatives to red cells, platelets, white cells, haemopoietic progenitor cells, plasma and most fractionated products.

In this section, the emphasis, with some exceptions, is directed towards minimising exposure to allogeneic blood components. One such option is the collection and transfusion of autologous blood components, namely red cells, platelets, fresh or frozen plasma and some blood constituents such as serum eye drops. Practices which include preoperative collection, acute normovolaemic haemodilution (ANH) and perioperative salvage are all essentially modifications of routine blood transfusion practice. However, the circumstances where these procedures are indicated or applicable are limited.

8.1 Autologous Blood Collection and Transfusion

Using autologous blood will avoid the risks of alloimmune complications of transfusion and may reduce the risk of many transfusion-transmitted infections. Autologous transfusion does not however reduce the risk of bacterial infection associated with transfusion.

Autologous blood can be collected several ways, including:

- **Preoperative collection** where blood is collected from the patient during the weeks leading up to their surgical procedure. This should only be performed in exceptional clinical circumstances. In general, this is limited to patients undergoing an elective procedure normally requiring a blood transfusion (otherwise units of blood collected are likely to be wasted) where there are clinical, religious or cultural reasons for preferring autologous blood. The inevitable reduction in preoperative hemoglobin level increases the likelihood that any intra- or post-operative blood transfusion (autologous or allogeneic) may be required.

  Autologous blood components obtained by preoperative donation are collected, prepared and stored under the same conditions as allogeneic blood. Acceptance of these individuals may vary from that of regular donors for allogeneic use, particularly with reference to age. The preferred programme for obtaining up to four units of blood involves collections at weekly intervals from approximately four weeks before surgery, with the last unit collected no later than one week before surgery. Most patients will require supplementary iron during the period of autologous collections to maintain the haemoglobin > 110 g/L. The patient will be required to pay for autologous collections unless this is undertaken for clinical, religious or cultural reasons. The charge covers the costs of collection, processing and testing of the units. Patients wishing to donate autologous blood prior to surgery should initially discuss this with their surgeon who should in turn liaise with a NZBS Transfusion Medicine Specialist.

- **Frozen autologous blood** where red cells and platelets are collected from patients with rare blood groups or multiple antibodies and then frozen for future use.

- **Acute normovolaemic haemodilution (ANH)** where a patient donates whole blood immediately before surgery, which is then replaced with intravenous colloid or crystalloid solution to maintain normovolemia. The removed whole blood is usually returned within several hours, for example at wound closure, providing fresh clotting factors and platelets.

- **Red cell salvage**

  Intraoperative blood salvage: where blood is collected from the surgical site using a cell-saver machine and reinfused after processing (washing and filtering) during or after surgery.

  Post-operative blood salvage: where blood is collected from wound drains and reinfused. The salvaged blood may be processed before reinfusion to minimise potential coagulation problems sometimes seen with unprocessed blood.

  ANH and red cell salvage are usually performed under the supervision and the responsibility of anaesthetists and/or surgeons.

8.2 Non-Blood Plasma Volume Expanders

The judicious use of plasma volume expanders can result in adequate restoration of blood volume at an economic cost.

It should be noted however that positive fluid balance is an independent predictor of poor outcome in ICU patients and this, together with the increasing adoption of permissive hypotension (hypotensive resuscitation) in a number of clinical settings, is leading to more restrictive intravenous fluid administration in the critically ill than has been used in the past.

Crystalloid Solutions

Initial resuscitation should be with 1 - 3 litres of a crystalloid solution such as Plasmalyte 148, pH 7.4 (an isotonic non-calcium containing 'balanced' solution buffered with acetate) or 0.9% sodium chloride ('normal' saline). Adequate crystalloid resuscitation may often avert the need for other plasma expanders. Colloid products can then be used in the recommended doses. If prolonged volume expansion is required, such as in a severely ill trauma patient, then the use of albumin solutions rather than synthetic colloids is likely to be justified.

Plasmalyte 148 in 5% glucose, dextrose solutions and compound sodium lactate (CSL) solutions, e.g., Hartmann's or Ringer-Lactate, must not be administered simultaneously with a red cell infusion as the solutions are not compatible. No drugs or additives, other than 0.9 % sodium chloride intravenous infusion, are recommended to be mixed with red cells before or during transfusion.

Synthetic Colloid Solutions

Colloids should only be used if crystalloids are insufficient to stabilise a patient. Due to the risk for acute renal damage and a requirement for dialysis, the use of synthetic colloids, particularly starch solutions, should be avoided in critically ill patients and those with sepsis or pre-existing renal dysfunction. In these situations, and where colloids are required, the use of albumin solutions is likely to be justified.

Gelatin Solutions (Gelofusal®)

Gelofusal® is a 4% solution of succinylated gelatin prepared from heat degraded cattle bone gelatin. It has an average molecular weight of 30,000 Dalton. Gelofusal® has a volume-expansion effect that lasts three to four hours. The frequency of severe acute reactions, which are usually anaphylactic, is < 1/10,000 and patients should be closely monitored at least while the first 20 - 30 mL are infused. The maximum volume

that can be infused has not been determined but is at least 3 - 5 litres. Apart from a dilutional effect on coagulation proteins, haemostasis is not affected. Gelofusal® does not interfere with blood group analysis and cross-matching procedures.

Gelofusal® must not be administered simultaneously with a red cell infusion, as the solution is not compatible.

Hydroxyethyl Starch (Voluven® 6%; Volulyte® 6%)

Hydroxyethyl starch (HES) solutions provide an alternative colloidal fluid to albumin and plasma for use in plasma volume expansion. HES solutions are prepared from chemically modified amylopectin.

Voluven® 6% and Volulyte® 6% are solutions of HES in 0.9% sodium chloride. The average molecular weight is 110,000 - 150,000 Dalton. Infusion results in a plasma volume increase of approximately 100% of the infused volume and the effect lasts four to six hours. The frequency of severe acute reactions, which are usually anaphylactoid, is 1/10,000 - 1/1000 and patients should be closely monitored at least while the first 10 - 20 mL are infused. With the administration of Voluven disturbances of blood coagulation, beyond dilutional effects, can occur. The maximum volume recommended before this product interferes with coagulation is about one litre per day.

8.3 Oxygen Carrying Compounds

Although red cell substitutes in the form of haemoglobin-based oxygen carriers, including polymerised haemoglobin and haemoglobin conjugated with polyethylene glycol, and perfluorocarbon oxygen carriers have been under investigation for many years, there is no indication that these compounds will be widely available for routine use in the near future.

8.4 Haemopoietic Growth Factors

Genetically engineered haemopoietic growth factors are expected to have an increasing impact on the use of allogeneic blood components. These should only be used by clinicians with relevant expertise.

Recombinant Human Erythropoietin (r-HuEPO)

- Epoetin alfa - Eprex®, Binocrit®
- Epoetin beta - NeoRecormon®

Administration of r-HuEPO can increase the rate of red cell production, principally through its proliferative effect on erythroid precursors.

The use of r-HuEPO in patients with chronic renal failure has seen a significant reduction in the requirement for repeated transfusion of red cells, allowing them to live virtually transfusion-free and without symptomatic anemia. The benefit is seen prior to dialysis and in dialysis-dependent patients. For patients awaiting renal transplantation, reducing allogeneic red cell exposure may reduce the risk of adverse outcomes from immune modulation and/or transfusional hemosiderosis.

Patients experiencing chronic anaemia with reduced levels of circulating erythropoietin may require fewer red cell transfusions if treated with r-HuEPO. They include those with:

- chronic inflammatory diseases such as rheumatoid arthritis
- cancer, with or without chemotherapy treatment
- myelodysplastic syndromes

There is evidence that the use of r-HuEPO along with iron supplements can reduce transfusion requirements for anaemia of prematurity seen in infants with very low birthweight (< 1000 g). However, studies have shown that the benefits are only seen when treatment with r-HuEPO is initiated after two to four (or more) weeks of life. Before this, the major factor affecting transfusion requirements for sick neonates is iatrogenic blood loss, for which treatment with r-HuEPO is ineffective.

Eprex® and Binocrit® have the following indications:

- Severe symptomatic anaemia of renal origin in patients with renal insufficiency not yet undergoing dialysis.
- Anaemia associated with chronic renal failure in paediatric and adult patients on dialysis.
- Chemotherapy-induced anaemia in patients with non-myeloid malignancies.
- Adult patients with mild-to-moderate anaemia (haemoglobin 100 - 130 g/L) scheduled for elective surgery with an expected moderate blood loss (i.e., 2 - 4 units or 900 - 1800 mL), to reduce exposure to allogeneic blood transfusion and to facilitate erythropoietic recovery.
- To augment autologous blood collection in anaemic adult patients undergoing major surgery who are not expected to deposit preoperatively their complete perioperative blood needs.

Granulocyte-Colony Stimulating Factor (G-CSF)

- Filgrastim - Zarzio®, Neupogen®
- Pegfilgrastim - Neulastim®

G-CSF is accepted therapy in the management of patients with severe neutropenia associated with chemotherapy-induced bone marrow failure, autoimmune and drug-induced disorders, congenital agranulocytosis and to increase the level of haemopoietic progenitor cells (HPC) in the circulation prior to collection by apheresis for autologous and allogeneic HPC transplantation.

CXCR4 Chemokine Receptor Antagonist

- Plerixafor - Mozobil®

Plerixafor, an antagonist of the CXCR4 chemokine receptor, is used in combination with G-CSF to enhance mobilisation of haematopoietic stem cells in adult patients with myeloma and lymphoma whose cells mobilise poorly.

Thrombopoietin Receptor Agonist

- Eltrombopag olamine - Revolade®

Eltrombopag binds to the thrombopoietin receptor (TPO-R) inducing proliferation and differentiation of megakaryocytes with subsequent platelet production. Revolade® is

indicated for the treatment of adult patients with chronic immune thrombocytopenic purpura (ITP) refractory to corticosteroids and immunoglobulins, and for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Promising results following the use of eltrombopag in other clinical areas including myelodysplasia, severe aplastic anaemia refractory to immunosuppressive therapy, non-myeloablative chemotherapy and thrombocytopenia due to HIV and liver disease are the subject of ongoing research.

8.5 Recombinant Coagulation Factors

These products should only be used by clinicians with relevant expertise.

Recombinant Factor VIII (rFVIII)

- Moroctocog alfa - Xyntha®
- Octocog alfa - Kogenate® FS, Advate, Recombinate™

rFVIII has similar efficacy to plasma-derived factor VIII in the management of bleeding and a similar rate of development of inhibitors associated with deficiency of circulating factor VIII (haemophilia A). It contains no von Willebrand factor (vWF) and therefore should not be used for improving haemostasis in von Willebrand disease (vWD). Unlike other rFVIII products, Recombinate™ contains human albumin, added to stabilise the factor VIII and therefore could theoretically transmit blood-borne infections.

Recombinant Factor IX (rFIX)

- Nonacog alfa - BeneFIX®
- Nonacog gamma - Rixubis
- Eftrenonacog alfa - Alprolix

rFIX has similar efficacy to plasma-derived factor IX in the management of bleeding and a similar rate of development of inhibitors associated with deficiency of circulating factor IX (haemophilia B, Christmas Disease). No human protein is added to stabilise the product.

Recombinant Factor VIIa (rFVIIa)

- Eptacog alfa - NovoSeven® RT

NovoSeven® RT is licensed for the treatment of bleeding episodes in patients with haemophilia A or B who have inhibitors to factors VIII and IX respectively, in patients with congenital factor VII deficiency and in patients with Glanzmann's thrombasthenia refractory to platelet transfusion due to GPIIb-IIIa and/or HLA antibodies.

8.6 Desmopressin acetate (Octostim®, Minirin®)

Desmopressin should only be used by clinicians with relevant expertise. It is a synthetic analogue of the antidiuretic hormone vasopressin. When administered in high doses of 0.3 mcg/kg it releases factor VIII (FVIII) and von Willebrand factor (vWF) from endothelial storage sites with a three to five-fold rise in plasma FVIII coagulant activity (FVIII:C) and a three to four-fold rise in vWF level. Desmopressin has also been shown to lead to improvement in, or normalisation of, assays of platelet function, including the bleeding time, in patients with uremia, liver cirrhosis, congenital or substance-induced platelet dysfunction. The effect of desmopressin on FVIII:C lasts for six to eight hours while the effect on bleeding time is for a shorter period of one to three hours.

Indications for use

- Mild to moderate Haemophilia A
- von Willebrand disease (vWD)
  - In most patients with type I vWD administration of desmopressin will increase von Willebrand factor-antigen (vWF:Ag) level three to four-fold and shorten or normalises the bleeding time.
  - Some but not all type IIA vWD patients respond to desmopressin.
  - In type IIB vWD administration of desmopressin is generally contraindicated as it fails to shorten the bleeding time and may produce a severe transient thrombocytopenia.
  - Desmopressin is also contraindicated in pseudo von Willebrand's disease.
  - Type III vWD does not respond to desmopressin.
- Congenital platelet function defects
- Acquired platelet function defects
- Uraemia
- Hepatic cirrhosis

Contraindications

- Habitual and psychogenic polydipsia
- Unstable angina, myocardial infarction or stroke
- Decompensated cardiac failure
- Type IIB von Willebrand's disease

Precautions

- Hyponatraemia; with repeated doses, fluid restriction and monitoring of sodium levels are recommended
- Patients at risk for raised intracranial pressure, including closed head injury
- Caution when using in children under 2 years of age
- Caution when using in patients > 70 years of age, especially those with a history of vascular disease

Presentation

The product is presented as 1 mL ampoules containing 15 mcg (Octostim®) or 4 mcg (Minirin®) of desmopressin acetate. Administration is either by intravenous or subcutaneous injection. A suitable intranasal preparation is not currently available in New Zealand.

Dosage and administration

Desmopressin acetate 0.3 mcg/kg for intravenous administration can be diluted in 50 - 100 mL of isotonic saline and given no more than one hour before surgery. The first 5 mL is given over five minutes and, provided the patient does not show marked tachycardia or other adverse reactions, the remainder of the dose may be given over the next 15 - 30 minutes. When administered subcutaneously, Octostim® should be given one hour preoperatively.

If a positive effect is obtained, the initial dose may, if necessary, be repeated once after 24 hours, with sodium monitoring and fluid restriction, and no more than two doses in any five day period. Octostim® given subcutaneously and once daily is the preferred method to achieve adequate release of FVIII and vWF while minimising side effects.

Patients may become progressively unresponsive to desmopressin with repeated daily doses over two to three days. Responsiveness will return when the drug has been discontinued for two days. For this reason it is not recommended to perform a desmopressin trial within four days of planned surgery.

8.7 Tranexamic Acid (Cyklokapron®)

Tranexamic acid is an inhibitor of fibrinolysis. Initially this compound was used primarily to reduce mucosal bleeding in patients with haemophilia and von Willebrand disease. Currently it is also used to decrease blood loss in cardiopulmonary bypass and joint surgery, trauma-related bleeding, obstetric complications, severe hypoproliferative thrombocytopenia, disorders of platelet dysfunction (e.g., Glanzmann's thrombasthenia), following treatment with anti-platelet medications and in conditions associated with increased fibrinolysis including menorrhagia, prostatectomy, cervical conisation, gastrointestinal bleeding, dental extraction and epistaxis. Additionally, tranexamic acid has a role in the management of hereditary angioedema.

Use of tranexamic acid carries a risk of clot formation resistant to fibrinolytic therapy and is therefore generally contraindicated in thromboembolic disease and in DIC. Due to the risk of clot-induced hydronephrosis, tranexamic acid is contraindicated with haematuria/bleeding from renal parenchyma.

Dose adjustment is required with even mild renal impairment.

Presentation

Cyklokapron® is presented as 500mg oral tablets or 5 mL ampoules containing 500 mg tranexamic acid. Administration of the latter is either by IV injection or, in the case of epistaxis or dental surgery, topical via application of soaked gauze.

Dosage and administration

The recommended standard dose of tranexamic acid is 1000 - 1500 mg orally or 500 - 1000 mg IV at a rate of 1 mL/minute, two to three times per day. In general, the use of tranexamic acid intravenously is recommended only when adequate doses cannot be administered orally.

In the setting of surgery, tranexamic acid 10 - 15 mg/kg administered IV over 10 minutes may be given as preoperative prophylaxis or as therapy for bleeding. Further intravenous infusion or bolus IV doses of 500 - 1000 mg, every 8 hours, may be given.

Oral doses up to 1500 mg, administered three to four times daily, may be used for up to 14 days to cover the post-operative period.

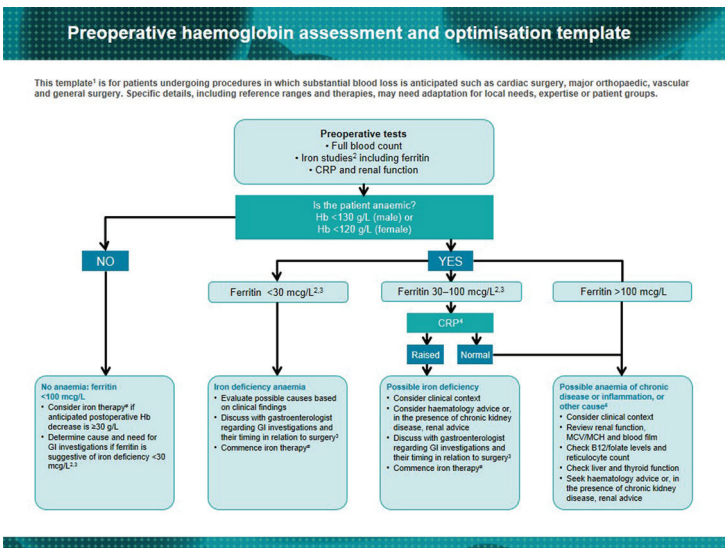
For trauma-related bleeding, tranexamic acid should be initiated within 3 hours of the event.

For oral mucosal bleeding, experience suggests clinical effect can be achieved from the use of a crude mouth wash made by dispersing 500 mg tranexamic acid tablet to a slurry in 10 - 15 mL water and swirling the total preparation around the mouth for two minutes before expelling. This is used four times daily for up to seven days.

8.8 Iron Supplementation

Preoperative identification and treatment of iron deficiency anaemia may avoid pre- and/or post-operative red cell transfusion in elective surgery. Correction of iron deficiency, even in the absence of anaemia, may improve erythropoietic recovery and reduce the risk for red cell transfusion in post-operative patients. Where red cell transfusion is required (e.g., for cardiac compromise), iron therapy should always follow, as transfusion fails to replenish deficient iron stores.

The following algorithm is adapted from the Australian National Blood Authority (NBA) *Preoperative Haemoglobin Assessment and Optimisation Template* of the *Perioperative (2012) Patient Blood Management Guidelines.*



Preoperative haemoglobin assessment and optimisation template

 # Iron therapy

Oral iron in divided daily doses. Evaluate response after 1 month. Provide patient information material.

IV iron if oral iron contraindicated, is not tolerated or effective; and consider if rapid iron repletion is clinically important (e.g. <2 months to non deferrable surgery).

NOTE: 1 mcg/L of ferritin is equivalent to 8–10 mg of storage iron. It will take approximately 165 mg of storage iron to reconstitute 10 g/L of Hb in a 70 kg adult. If preoperative ferritin is <100 mcg/L, blood loss resulting in a postoperative Hb drop of ≥30 g/L would deplete iron stores.

In patients not receiving preoperative iron therapy, if unanticipated blood loss is encountered, 150 mg IV iron per 10g/L Hb drop may be given to compensate for bleeding related iron loss (1 ml blood contains ~0.5 mg elemental iron)

Abbreviations
CRP = C-reactive protein
GI = gastrointestinal
Hb = haemoglobin
IV = intravenous
MCV = mean cell/corpuscular volume (fL)
MCH = mean cell/corpuscular haemoglobin (pg)

Footnotes:

1. Anaemia may be multifactorial, especially in the elderly or in those with chronic disease, renal impairment, nutritional deficiencies or malabsorption.
2. In an anaemic adult, a ferritin level <15 mcg/L is diagnostic of iron deficiency, and levels between 15–30 mcg/L are highly suggestive. However, ferritin is elevated in inflammation, infection, liver disease and malignancy. This can result in misleadingly elevated ferritin levels in iron-deficient patients with coexisting systemic illness. In the elderly or in patients with inflammation, iron deficiency may still be present with ferritin values up to 60–100 mcg/L.
3. Patients without a clear physiological explanation for iron deficiency (especially men and postmenopausal women) should be evaluated by gastroscopy/colonoscopy to exclude a source of GI bleeding, particularly a malignant lesion. Determine possible causes based on history and examination; initiate iron therapy; screen for coeliac disease; discuss timing of scopes with a gastroenterologist.
4. CRP may be normal in the presence of chronic disease and inflammation.
5. Consider thalassaemia if MCH or MCV is low and not explained by iron deficiency, or if long standing. Check B12/folate if macrocytic or if there are risk factors for deficiency (e.g. decreased intake or absorption), or if anaemia is unexplained. Consider blood loss or haemolysis if reticulocyte count is increased. Seek haematology advice or, in presence of chronic kidney disease, nephrology advice

For more information on the diagnosis, investigation and management of iron deficiency anaemia refer to Pasricha SR, Flecknoe-Brown SC, Allen KJ et al. Diagnosis and management of iron deficiency anaemia: a clinical update. *Med J Aust*, 2010, 193(9):525–532.

Disclaimer
The information above, developed by consensus, can be used as a guide. Any algorithm should always take into account the patient's history and clinical assessment, and the nature of the proposed surgical procedure.

9.1 Therapeutic Apheresis

Some NZBS centres provide therapeutic apheresis programmes using a centrifugal cell separator. Procedures may be carried out in a hospital ward or, if there is a medical officer on site and patients are mobile and in good health, at a NZBS blood centre.

Therapeutic plasma exchange (TPE) is an established first-line treatment in some conditions and second-line treatment in several others. TPE may be combined with other medical therapy in managing diverse conditions such as hyperviscosity syndromes, Guillain-Barré syndrome, thrombotic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, familial hypercholesterolaemia and renal transplant rejection. It is also sometimes used for the treatment of myasthenia gravis, polymyositis, SLE and other autoimmune disorders. The potential hazards of plasma exchange should be taken into account when considering this treatment.

Leucopheresis may be used to reduce leucostasis in patients with very high white cell counts. Similarly, plateletpheresis may occasionally be used for patients with complications due to thrombocytosis.

Replacement fluids used for TPE usually include albumin or fresh frozen plasma (FFP). Saline, usually in combination with albumin, can also be used in certain conditions such as hyperleucocytosis and thrombocytosis. FFP is occasionally used to correct a deficiency of coagulation factors and cryosupernatant may be used for patients with thrombotic thrombocytopenic purpura.

Complications of therapeutic apheresis include allergic reactions to FFP or cryosupernatant, volume overload or hypovolaemia, air embolism, haemolysis, extracorporeal clotting, citrate toxicity, coagulopathy and vasovagal attacks. However, present procedural methods appear to minimise these complications.

To request therapeutic apheresis, contact a NZBS Transfusion Medicine Specialist/ Medical Officer.

9.2 Therapeutic Venesection

Whole blood therapeutic venesection is available for patients with medical conditions where regular venesection is beneficial such as haemochromatosis, polycythaemia and porphyria cutanea tarda.

Blood collected from an individual with genetic haemochromatosis may potentially be used to prepare therapeutic blood components and fractionated products if the patient meets all normal donor selection criteria and is registered as a blood donor. See Section 2.7: *Haemochromatosis* for further information.

In the case of polycythaemia vera managed by venesection in combination with cytoreductive medication, the referring doctor remains responsible for the management of the patient's underlying condition and should regularly review the patient (at least every 12 weeks), as well as providing instructions concerning the frequency of venesection. NZBS is responsible for the venesection collection and for ensuring the safety of the patient during the procedure. For patients with polycythaemia managed by venesection alone, and following clear instruction from the referring doctor, it may be

possible for NZBS to monitor the haematocrit and adjust the frequency of venesection accordingly. In such cases, review by the referring doctor at intervals greater than 12 weeks may be appropriate.

A similar arrangement for the monitoring of ferritin levels and titration of therapeutic venesection may be made for patients with porphyria cutanea tarda.

9.3 Tissue Bank

The NZBS Tissue Banks provide:

- Cadaver split skin, sourced locally and from international tissue banks, used as a physiological dressing to treat victims of burns.
- Donated or autologous bone, mostly femoral heads, used in reconstructive orthopaedic surgery.
- Autologous cranial bone flaps held for neurosurgical patients until reimplantation weeks to months later.

NZBS Tissue Banks are located in the NZBS centres in Auckland, Hamilton, Palmerston North, Wellington, Christchurch and Dunedin. Cadaver skin is only available from the Auckland centre. Donated bone is held at the NZBS sites as well as a number of DHB-managed blood banks.

All donations are voluntary. Written consent is required from the donor or, in the case of skin, from next of kin. All donations are tested for infectious diseases and bacterial contamination. Frozen tissue is generally stored frozen and held for up to five years.

All tissue is issued frozen to a named patient and is only for that patient. An information sheet is available from Tissue Bank for consenting patients. Unused frozen tissue should be returned to the Tissue Bank. Unused thawed tissue must be discarded.

9.4 Autologous Serum Eye Drops

Autologous serum eye drops (SED), a blood component prepared by NZBS, is used for treating dry eyes and corneal epithelial defects. It is not normally first-line treatment due to the cost and requirement that patients donate blood. However, in selected patients, SED have proven to be a successful treatment modality.

Conditions for which SED can be used include severe Sjögren's syndrome, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, some causes of epithelial limbal stem cell deficiency such as chemical or thermal ocular surface burns and other severe ocular surface disorders that do not respond to conventional therapies. SED may also be useful in acute management of severe sight threatening ocular surface chemical or thermal burns.

Although not fully defined, it is believed that epidermal growth factor, transforming growth factor ß, vitamin A, platelet-derived growth factor and fibronectin are important serum constituents that promote healing of the ocular surface.

SED is prepared from a single blood donation and contains no added preservatives or antimicrobial agents. It has the potential to transmit infectious diseases or become contaminated with microorganisms. Accordingly, blood collected for SED must meet

standard safety requirements. This includes a donor health assessment and screening of the blood donation to exclude evidence of human immunodeficiency virus, hepatitis B virus and hepatitis C virus. Following manufacture of SED, a proportion of the eye drop bottles are cultured for 14 days to confirm bacterial sterility.

To access the service, ophthalmologists complete a specific request form that is forwarded to NZBS. As this constitutes a prescription, it is valid for three months only, as per the Medicines Act, although blood is only collected every six months. Due to the time required for manufacturing and sterility testing, 18 working days are normally required from donation to issuing of SED. In exceptional circumstances and with the patient's consent, the ophthalmologist may request that SED are issued prior to completion of the sterility testing.

Appropriate storage of SED vials is essential to minimise the risk of bacterial contamination. Vials are stored frozen in a NZBS facility or hospital blood bank and are dispensed in quantities necessary to cover a 4 week period. The dispensed vials should be kept frozen until needed, usually in the patient's domestic freezer. Each vial usually lasts one week and should be stored in a refrigerator once thawed. Any adverse events should be reported to NZBS for investigation.

For patients where blood cannot safely be donated or where allogeneic SED are the preferred product, for example in ligneous conjunctivitis, NZBS can, on a named patient basis, prepare SED from an allogeneic donation. NZBS does not hold this as a stock item.

9.5 Reference Laboratory (Immunohaematology)

The NZBS Reference Laboratory is located in the NZBS Auckland centre and offers a national immunohaematology testing service as well as clinical and technical advice for resolving problems encountered during pretransfusion and antenatal testing such as:

- blood grouping, antibody screening and crossmatching
- antibody identification/confirmation and resolution of difficult antibody mixtures
- antibody titration (antenatal, cold agglutinins and isoagglutinins)
- adsorption and elution studies for patients with autoantibodies
- red cell phenotyping and genotyping

9.6 Tissue Typing Laboratory

The NZBS Tissue Typing Laboratory is also located in the NZBS Auckland centre and is responsible for tissue typing tests in support of New Zealand's bone marrow and solid organ transplant programmes. The laboratory also carries out testing for disease association markers, for antibodies implicated in transfusion-related reactions, for antibodies against platelet antigens and is responsible for the provision of compatible or matched platelets for transfusion.

The following provides an indication of the wide range of white cell and platelet-related investigations undertaken:

- HLA Class I and Class II typing

- HLA-antibody screening
- T- and B-lymphocyte crossmatching
- platelet-associated antibody testing
- serum platelet antibody testing
- platelet crossmatching
- fetal and neonatal alloimmune thrombocytopenia (FNAIT) investigation
- platelet genotyping

NZBS SAMPLE REQUIREMENTS

It is not possible to overemphasise the importance of proper patient identification. Most errors relating to transfusion practice arise from administrative and clerical error. These errors can have serious consequences for patients and are sometimes fatal.

Collection and labelling of blood samples for pretransfusion testing is described in Section 3.6: *Collecting Blood Samples for Pretransfusion Testing*.

The sample acceptance criteria used by NZBS are based on the 2016 Australian & New Zealand Society of Blood Transfusion (ANZSBT) *Guidelines for Transfusion, Pre and Postnatal Immunohaematology Testing*. Blood Bank staff are not authorised to accept samples which do not meet labelling requirements. Where necessary these will be rejected and new samples requested. Where a dispute arises in relation to a sample, the final decision on suitability for testing will lie with an NZBS Transfusion Medicine Specialist/Medical Officer.

The following tables provide a brief guide to the types of samples NZBS requires for laboratory investigations. Specific guidance can be obtained from the individual laboratories and NZBS Transfusion Medicine or Nurse Specialists.

Table 10.1: Samples Required for Pretransfusion Testing[1]

Test	Comment	Sample Required	Tube Top
ABO / RhD group	Normally performed as part of a 'Group & Screen'	1 x 6 mL EDTA[2]	Pink
Group & screen	A positive antibody screen in pretransfusion testing will require antibody identification which may delay the provision of blood	1 x 6 mL EDTA	Pink
Red cell antibody identification		1 x 6 mL EDTA	Pink
Transfusion reaction investigation	Reactions observed with transfusion of blood components only, not fractionated products	1 x 6 mL EDTA pre-transfusion sample	Pink
		1 x 6 mL EDTA post-transfusion sample	Pink
		Giving set/remnants from transfused unit(s)	N/A
Autoimmune haemolytic anaemia	Presence of autoantibodies may require adsorption techniques to detect underlying alloantibodies which may delay provision of blood	2 x 6 mL EDTA	Pink

[1]*Contact the Blood Bank or Transfusion Medicine Specialist for specific sample requirements or if further information is required.*
[2]*Ethylenediaminetetraacetic acid.*

Table 10.2: Samples Required for Diagnostic Testing[1]

Test	Comment	Sample Required	Tube Top
Antenatal screening		1 x 6 mL EDTA	Pink
Antenatal antibody titration		1 x 6 mL EDTA	Pink
Group & DAT on cord blood sample	Tested for maternal blood contamination	1 x 6 mL or 4 mL EDTA	Pink or lavender
Direct antiglobulin test (DAT)		1 x 6 mL or 4 mL or 0.5 mL[2] EDTA	Pink or lavender
Cold agglutinin screen and titration	Maintain and transport samples at 37°C	1 x 6 mL EDTA	Pink

[1]*Contact the Blood Bank or Transfusion Medicine Specialist for specific sample requirements or if further information is required.*
[2]*0.5 mL pink top microcontainer for use in infants only.*

Table 10.3: Samples Required for Reference Laboratory Diagnostic Testing[1]

Test	Comment	Sample Required	Tube Top
Alloantibody investigation		2 x 6 mL EDTA	Pink
ABO / Rh grouping problem		1 x 6 mL EDTA	Pink
Extended RBC phenotype		1 x 6 mL EDTA	Pink
AIHA[2] with positive DAT		2 x 6 mL EDTA	Pink
Transfusion reaction investigation		1 x 6 mL EDTA pre-transfusion sample	Pink
		1 x 6 mL EDTA post-transfusion sample	Pink
		Giving set/remnants from transfused unit(s)	N/A
Compatibility testing		1 x 6 mL EDTA	Pink
Fetal D genotyping from maternal blood[3]	Pregnancies beyond 16 weeks	1 x 6 mL EDTA	Pink
Haemolytic disease of the newborn	Cord blood sample	1 x 6 mL or 4 mL EDTA	Pink or lavender
Paternal phenotyping: HDFN[4] and FNAIT[5]		1 x 6 mL EDTA	Pink

[1]Contact the Reference Laboratory or Transfusion Medicine Specialist for specific sample requirements or if further information is required.
[2]Autoimmune haemolytic anaemia.
[3]Prior discussion with Transfusion Medicine Specialist required
[4]Haemolytic disease of the fetus and newborn.
[5]Fetal and neonatal alloimmune thrombocytopaenia.

Table 10.4: Samples Required for Tissue Typing Laboratory[1]

Test	Comment	Sample Required[2]	Tube Top
HLA typing (initial or confirmatory)	Haematopoietic progenitor cell (HPC) or solid organ transplant patient or potential donor and apheresis platelet donor	4 x 10 mL CPDA[3] 1 x 10 mL clotted 1 x 6 mL EDTA	Yellow Red Pink
Disease association	e.g., ankylosing spondylitis, coeliac disease, narcolepsy	1 x 10mL CPDA	Yellow
Monthly serum tray	HLA antibodies Patients awaiting cadaveric renal transplant	1 x 10mL clotted	Red
HLA antibody screen		1 x 10mL clotted	Red
Lymphocyte crossmatch	Solid organ transplant patient or potential donor	4 x 10 mL CPDA 1 x 10 mL clotted 1 x 6 mL EDTA	Yellow Red Pink
Platelet antibody screen / crossmatch	Platelet and platelet-associated antibody	4 x 10 mL CPDA 1 x 10 mL clotted	Yellow Red
Platelet antigen (HPA) genotyping		1 x 10mL CPDA	Yellow
Patients refractory to platelets		4 x 10 mL CPDA 2 x 10 mL clotted	Yellow Red
TRALI investigation	Donor	2 x 10 mL clotted	Red
	Patient	2 x 10 mL CPDA	Yellow

[1]*Contact the Tissue Typing Laboratory or Transfusion Medicine Specialist for specific sample requirements or if further information is required.*
[2]*Clotted samples may alternatively be sent in 3 x 5 mL or 2 x 7 mL red top tubes. EDTA samples may alternatively be sent in 7 mL lavender EDTA tubes.*
[3]*Citrate phosphate dextrose adenine.*

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