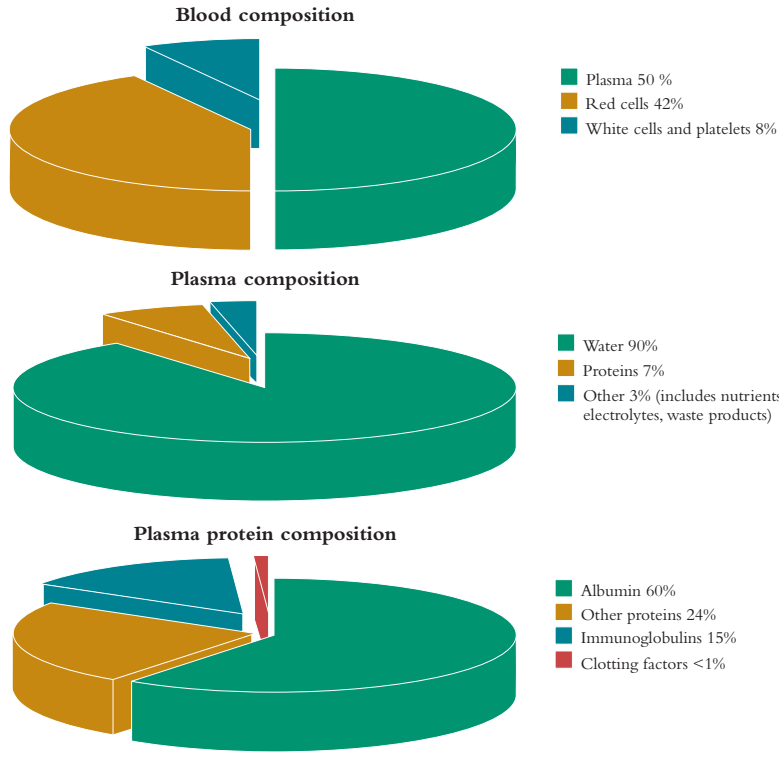
Chapter 1
Plasma and its applications in medicine

Throughout human history, blood has been imbued with many different cultural, religious and social meanings. Its use in medicine, however, is relatively recent. Scientific discoveries in the early part of the twentieth century made possible the collection, preservation and transfusion of blood and blood components. These developments revolutionised medical practice and have saved countless lives. Over 400 000 Australians receive a blood product each year, and more than 50% of Australians will require blood or a blood product in their lifetime.[1]

Composition of blood

Blood is a liquid, contained within blood vessels. Its major functions are to supply nutrients (such as oxygen, glucose, vitamins and minerals) to other tissues, to transport waste products (such as carbon dioxide and lactic acid), to protect the body

Fig. 1.1 The constituents of blood, plasma, and plasma proteins



Source: Adapted from information in: World Federation of Hemophilia, *Contract Fractionation*, Facts and Figures, no. 5, rev. edn, World Federation of Hemophilia, Montreal, 2004, p. 2; also available online at http://www.wfh.org/2/docs/Publications/Treatment_Products /Monographs/FF-5_English_Fractionation.pdf.

1 These estimates, provided by the Australian Red Cross Blood Service, relate to the full range of blood and blood-related products, including fresh blood products, plasma products, blood-derived diagnostic products used in laboratory testing, and products that use human albumin as a stabiliser (e.g. some recombinant products and vaccines).

from invasion by foreign organisms and to recognise and reject foreign tissues. Blood also functions as a regulator of body temperature. The cellular components of blood are red blood cells, white blood cells, and platelets.

Red blood cells (erythrocytes), which are cells without nuclei, contain the protein haemoglobin. Haemoglobin carries oxygen, in the form of oxyhaemoglobin, from the lungs to the tissues, and is also partly responsible for the transport of carbon dioxide, produced by metabolic activity, from the tissues to the lungs, where the CO_2 is breathed out.

White blood cells (leucocytes) protect against bacterial and viral infections and mediate immune responses.

Platelets (thrombocytes) are non-nucleated blood cell fragments that maintain the integrity of the blood vessel wall by adhering to sites of injury and aggregating to form a haemostatic plug. The surface and the interior of the haemostatic plug allow the interaction of coagulation factors; this process results in the formation of a fibrin clot, which consolidates the platelet plug.

Plasma is the straw-coloured liquid in which red blood cells, white blood cells, and platelets are suspended. Plasma contains a large number of biologically critical proteins, which have multiple physiological functions. The separation of plasma into its constituent proteins for medical use is called fractionation.

Figure 1.1 identifies the components of blood, plasma, and plasma proteins. It is important to note that the proportions indicated vary to some extent, and should not be regarded as constant values.

Plasma collection methods

Plasma is collected from donors by either of two methods: whole blood donation or apheresis. Plasma that is obtained by separation from whole blood donations is referred to as recovered plasma. Plasma collected via apheresis is referred to as source plasma.

The most common form of plasma collection by apheresis is plasmapheresis, which is a procedure whereby the donor's blood is extracted from the body and centrifuged in a closed and sterile system, so that the plasma in the blood is separated from the cells. The cells are then immediately returned to the body. The plasma is collected into sterile containers and subsequently fractionated.

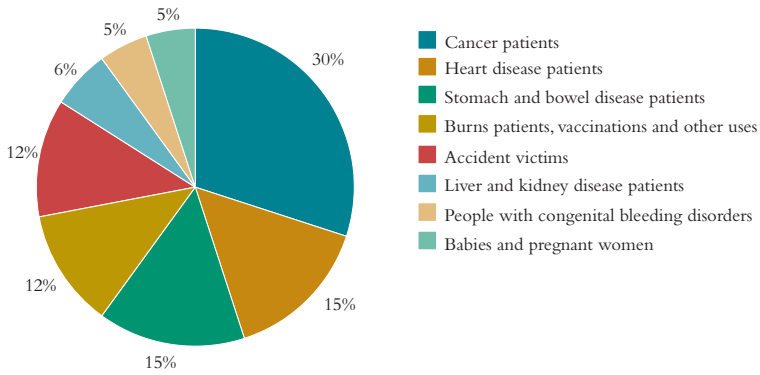
Approximately 650 millilitres of plasma per donation can be obtained using plasmapheresis, compared to approximately 250 millilitres of plasma from a whole blood donation.

The primary reason for the use of other forms of apheresis is to separate platelets for transfusion, or stem cells for bone marrow transplantation.[2] In these procedures, particularly the former, plasma is collected as a secondary product.

Figure 1.2 identifies the areas in which donated blood is used. The percentages shown account both for fresh blood products and for plasma derived products.

2 Stem cells can also be harvested from bone marrow, although at the present time these cells are more commonly harvested from blood.

Fig. 1.2 The various patient categories for whom donated blood is used



Source: Adapted from information in: Australian Red Cross Blood Service, ***How Donated Blood Is Used***, Australian Red Cross Blood Service, 2006, http://www.arcbs.redcross.org.au/Donor/aboutblood/ howused.asp.

Comparative aspects of plasma collection methods

Plasmapheresis donations can be made more frequently than whole blood donations, because in plasmapheresis the donor's red cells are returned and anaemia caused by red cell loss is largely avoided. Under Australian Red Cross Blood Service (ARCBS) procedures as set by Australia's national medicines regulatory agency, the Therapeutic Goods Administration (TGA), plasmapheresis donations can be made as often as every three weeks, whereas the minimum interval between donations of whole blood is 12 weeks.

Although plasmapheresis allows the collection of plasma from donors in larger amounts, and more frequently, an important point with respect to plasma fractionation is that source plasma provides lower overall yields of plasma proteins than does recovered plasma, mainly because of the shorter intervals between plasmapheresis donations – these intervals do not allow time for full recovery of the lost protein components of donors' plasma.

In addition, compared with whole blood donation the plasmapheresis process is a lengthier one. It normally takes approximately 45 minutes, to which must be added waiting time, time for the donor to rest after donating, and travel time to and from the office or home; for many plasmapheresis donors, the total time involved is between two and two and a half hours. From a donor's perspective, the process may be perceived as more taxing than whole blood donation.

Plasmapheresis also imposes extra costs, including those for staffing.

Plasma products

Plasma products can be grouped into three major categories:

- **Albumin:** Albumin is a low-molecular-weight protein that is essential for the maintenance of blood volume and thus for the stability of the circulation. Loss of albumin, through injury such as severe burns, may result in the collapse of the circulation. In some forms of kidney disease, there is loss of albumin via the urine, and severe liver disease can result in a failure to synthesise albumin. In all three

conditions, water and electrolytes exit from the circulation into tissues, causing swelling. Large blood or plasma losses following traumatic injury (including burns) or extensive surgery can result in hypotension (low blood pressure). Replacement albumin may be required in these various circumstances.

- **Immunoglobulins:** Immunoglobulins are proteins that provide protection against infection and modulate the immune system. Immunoglobulin products contain antibodies – complex protein substances that are a key component of the immune system. Hyperimmune immunoglobulins are plasma products that contain a high concentration of specific antibodies capable of combatting particular infections or antigens (substances that cause the formation of antibodies).
- **Clotting factors** (also termed 'coagulation factors'[3]): Clotting factors are proteins that when activated function as enzymes, leading to the production of thrombin and then fibrin, which together with platelets prevent loss of blood after vessel injury. Clotting factor concentrates are used to treat haemophilia and other conditions that require treatment to promote normal control of bleeding.

Other plasma derivatives include wound-healing products (fibrin sealants) and human alpha-1 antitrypsin, which is used in pulmonary disease therapy.

Recombinant products

Recombinant clotting factors are not produced by fractionating plasma. Instead, they are made using recombinant technology (genetic engineering) in a laboratory environment. Recombinant products are made by isolating a human clotting factor gene and inserting it into non-human cells, which are then grown in cell culture. The clotting factor produced by these cells is harvested from the fluid in which the cell culture is suspended. Although the risk of contamination cannot be completely ruled out, recombinant products are considered to be safer than their plasma derived counterparts.

Most of the recombinant products that are currently commercially available, however, are first- and second-generation products, and the cell cultures in which they are grown contain small amounts of human or animal plasma proteins. In addition, in first-generation recombinants human albumin is used as the stabiliser in the final product. Third-generation recombinants, which have no human or animal cell content (meaning that the risk of contamination is even lower), are now becoming commercially available.

While recombinants are largely supplanting plasma derived Factors VII, VIII and IX, in Australia there is a continuing residual level of demand for the plasma derived factors.

A brief history of plasma fractionation and of arrangements in Australia

The effective use of blood transfusions in clinical care dates from the early twentieth century, following the publication in 1901 of Dr Karl Landsteiner's identification of the main blood groups. Prior to that time, there were no efficacious treatments available for people with blood disorders such as haemophilia, a condition whose prevalence within the royal families of Europe has been well documented (see story on next page).

3 The term 'coagulation factors' encompasses products that either promote clotting or extend clotting times.

Queen Victoria's haemophilia: The Australian connection

Queen Victoria was a carrier of haemophilia. Her youngest son, Prince Leopold (1853–1884), had a severe form of the condition, while two of the Queen's daughters were also carriers of the haemophilia gene.*

Prince Alfred in the full dress uniform of an admiral in the Royal Navy

It has been suggested that Prince Leopold had aspirations to be the governor of the colony of Victoria. Some historians have proposed that it was the British prime minister, Benjamin Disraeli, who recommended to the Queen that she send the Prince to Australia on a royal visit in 1867–68, on the grounds that the warmer climate would be beneficial for his health. The Queen, however, did not wish to be parted from Prince Leopold. Instead she chose to send her second son, Prince Alfred, on what would prove to be an incident-filled visit to Australia.

As a 24-year-old captain in the Royal Navy, Prince Alfred sailed for Australia in command of the wooden steam frigate HMS Galatea, arriving in Adelaide on 31 October 1867. Several months later in Sydney, on the afternoon of 12 March 1868, he attended a picnic with many of the city's dignitaries, including the Governor of New South Wales and the Chancellor of the University of Sydney. During the course of this picnic, to the horror of the assembled crowd, Prince Alfred was fired upon and was wounded in the chest. The would-be assassin, Henry James O'Farrell, a Fenian sympathiser, was immediately arrested, and some six weeks later was found guilty of attempted murder and hanged at Darlinghurst Gaol. The Prince eventually made a full recovery.

The people of Sydney were so appalled by the attack that, following a public meeting at Sydney Town Hall, they collected £30 000 in an effort to make some reparation to the Queen. It was the Prince's wish that these moneys be used to create a hospital. With the approval of the Senate of the University of Sydney, a new teaching hospital was founded on university land. Prince Alfred Hospital (later Royal Prince Alfred Hospital) would open on 25 September 1882.

In Melbourne there was also a strong public reaction to the shooting of the Prince. Moneys were again collected from the public and these donations, combined with a Victorian government grant, were used to establish the Alfred Hospital in Prahran. Prince Alfred laid the foundation stone of the new hospital on 6 March 1869. He eventually sailed from Australia the following month.

Had Prince Leopold been involved in an incident similar to that suffered by his brother during the royal visit to Australia, the wound might well have been fatal, because of the amount of bleeding that would have ensued. At the time, there were no plasma products available, and blood transfusions would not become a viable clinical option until after the discovery of blood groups in 1901.

* Through Princess Alice and Princess Beatrice, haemophilia was transmitted to the family of the Tsar of Russia and to the Spanish royal family. It could even be argued that the condition played a role in the origins of the Russian Revolution of 1917 and the Spanish Civil War of 1936–39. The influence of Rasputin on the Romanovs in Russia was directly related to haemophilia: that of the Tsar and Tsarina's only son, Prince Alexei. There has been speculation that the illness led to severe strain within the Russian royal family, enabling Rasputin to gain influence over them and thus ultimately contributing to the downfall of the once-powerful Romanov dynasty. The abdication of King Alfonso XIII in Spain was also related to haemophilia. In both cases the repercussions were profound and far-reaching.

As transfusion science developed, groups of blood donors were recruited and blood banks were established in many countries during the 1920s and 1930s.

The need for albumin for the treatment of battlefield casualties in World War II provided the impetus for the large-scale separation of plasma proteins, as fractionated products are concentrated into a small volume and can be better preserved and more readily transported than fresh plasma.

In the early 1940s a team at Harvard Medical School, led by Dr Edwin Cohn and with support from the United States National Research Council, pioneered the fractionation of human plasma using cold-ethanol techniques. Once full-scale production for the war effort commenced, several US companies became involved in fractionation. A similar project to develop fractionation techniques was initiated in Britain during the war years; after the war, fractionation plants commenced operations in many countries in the developed world.

In Australia, the Red Cross and the then Commonwealth Serum Laboratories (now CSL Limited) took a keen interest in these advances. The Red Cross found that CSL had the basic equipment and expertise to develop a fractionation plant. Following representations to the federal government by the Red Cross, seeking funding for CSL to enable it to establish fractionation facilities, Cabinet gave approval in 1949. CSL commenced production of fractionated products in 1953.[4]

The Commonwealth Serum Laboratories were founded in 1916. Originally a federal government entity, CSL has undergone a number of organisational changes during its history, culminating in its privatisation as a listed public company in 1994. Since then it has built up considerable overseas interests, and the CSL Group of companies together operate as a major global fractionator.

The organisation's original function was to produce vaccines for treating illnesses such as diphtheria, tetanus, typhoid fever, cholera, whooping cough and influenza. While CSL continues to develop and produce vaccines, plasma fractionation has become a major component of its Australian operations.

Since fractionation commenced in Australia, the Australian Red Cross has collected plasma and supplied it to CSL for fractionation. Collections are today made by the Australian Red Cross Blood Service, which is an operating division of the Australian Red Cross Society.

Australia's first organised blood transfusion service was established by the Red Cross in Victoria in 1929, with similar services subsequently being established in the other states and territories. These Red Cross Blood Transfusion Services were largely autonomous and were funded predominantly by state and territory governments. In 1995, the Commonwealth Review of the Australian Blood and Blood Product System (the McKay Wells Review) identified the need for a single, integrated blood supply agency in Australia, in the interests of enhancing the safety, efficiency and adequacy of supply of blood and blood products. In 1996, the separate state and territory blood services combined to form the ARCBS.

The Review of the Australian Blood Banking and Plasma Product Sector (the Stephen Review), which was completed in 2001, recommended the establishment of an authority to provide national management and oversight of Australia's blood system. As part of the

4 See Alfred Brogan, *Committed to Saving Lives: A History of the Commonwealth Serum Laboratories*, Hyland House, South Yarra, Vic., 1990, chapter 10.

introduction of national blood arrangements following the Stephen Review, the National Blood Authority (NBA) came into operation in 2003.[5] Until this time, fractionation services in Australia had been funded entirely by the Commonwealth.

The formation of the NBA saw funding and service delivery arrangements with suppliers consolidated into a unified approach. The NBA manages funding arrangements in relation to the ARCBS, as well as CSL Limited and other blood product suppliers, and coordinates the supply of blood and plasma products on behalf of Australia's federal, state and territory governments. Under the national blood arrangements, funding for the provision of plasma products to meet Australia's needs is now cost shared, on a 63%/37% basis, between the Commonwealth and the state and territory governments respectively.

In Australia, the safety, quality and efficacy of plasma products throughout the collection, manufacturing and supply chain are regulated by the Therapeutic Goods Administration. There is an inherent risk that infectious agents will be transmitted through plasma products, due to the biological origin of the material used in their manufacture. The TGA has stringent regulations in place to minimise this risk. The regulations govern donor selection policies; the testing of donations; procedures to inactivate or remove pathogens during the manufacturing of plasma products; processes and procedures for maintaining the integrity of plasma and finished plasma products throughout all transportation, distribution and storage phases; and the auditing of the manufacturing process.

The key drivers of demand for fractionation services have changed over time as new plasma products have become commercially available and alternative therapies have emerged for some conditions. The product in most demand initially was albumin, but the pattern of demand began to change in the late 1960s, after researchers in the United States pioneered a concentrated form of Factor VIII – which had a clotting power one hundred times greater than that of plasma – for the treatment of haemophilia A. Demand for intravenous immunoglobulin (IVIg) increased rapidly during the 1990s and 2000s, and now accounts for the bulk of worldwide demand for plasma products (see Chapter 2).

Plasma products available in Australia

Table 1.1 lists the plasma derived products currently provided to Australian consumers under Australia's national blood arrangements. It should be noted that a number of other plasma products (including alternatives to the products identified in this table) have been approved by the Therapeutic Goods Administration for use in Australia but are not provided under the national blood arrangements.

All of the products that CSL Limited manufactures in Australia, through its CSL Bioplasma business unit, are fractionated using plasma collected by the Australian Red Cross Blood Service from voluntary, non-remunerated donors.

The ARCBS retains some plasma for use in acute care settings and in the preparation of fresh frozen plasma (FFP) and cryoprecipitate. FFP is used to treat patients who develop clotting problems after trauma or liver transplantation. Cryoprecipitate is prepared from FFP and contains the blood clotting substances fibrinogen, Factor XIII, von Willebrand factor, fibronectin and Factor VIII. The product is used in surgery, for patients with

5 Australia's national blood arrangements are discussed in detail in Chapter 5.

Table 1.1 Plasma products currently available in Australia

Product group	Produced by CSL in Australia	Imported plasma products
Albumin	• Albumex® 4 • Albumex® 20	
Immunoglobulins	• Intragam® P (intravenous immunoglobulin (IVIg)) • Normal Immunoglobulin (intramuscular immunoglobulin (IMIg))	• Octagam® • Sandoglobulin®
Hyperimmunes (specific immunoglobulins)	• CMV Immunoglobulin • Hepatitis B Immunoglobulin • Rh(D) Immunoglobulin • Tetanus Immunoglobulin IM • Tetanus Immunoglobulin IV • Zoster Immunoglobulin	• WinRho SDF™★
Coagulation factors	• Biostate® • MonoFIX®-VF (Factor IX concentrate) • Prothrombinex™-HT (Factor IX complex concentrate) • Thrombotrol®-VF (antithrombin III concentrate)	• Ceprotin®(protein C concentrate) • Factor VII concentrate • Factor XI concentrates • FEIBA VH® Inhibitor Treatment • Fibrogammin P® (Factor XIII concentrate)

★ WinRho SDF™, an alternative product to Rh(D) Immunoglobulin, is manufactured in Canada by Cangene; Baxter is the Australian distributor. The regular importation of WinRho to Australia is no longer necessary, because a shortage of Australian Rh(D) hyperimmune plasma was overcome in early 2006. WinRho remains listed, however, on the National Supply Plan for blood products, and a small level of demand in Australia remains because the product can be administered intravenously when clinically appropriate, unlike the domestically produced Rh(D) Immunoglobulin.

particular clotting factor deficiencies; in cardiac surgery where there is persistent post-operative bleeding; in the intensive care setting when there is massive blood loss, or overwhelming infections with persistent bleeding; and in liver transplants. However, cryoprecipitate, a single-donor product, is not virally inactivated.

The National Blood Authority, acting on behalf of all Australian governments, has a contract with CSL Limited for the manufacture of products from Australian plasma. This contract, the Plasma Products Agreement (PPA), is a five-year agreement (from 1 January 2005 to 31 December 2009).

As far as is practicable, Australia uses products fractionated from plasma collected in this country. It is also necessary, however, to import quantities of a number of products, either because they are not manufactured in Australia, or to supplement domestically sourced supplies. The NBA has contractual arrangements with suppliers of these imported blood products (referred to as Defined Blood Products), which

include the plasma derivatives listed in the right-hand column of table 1.1, together with the following recombinant products, which are also manufactured overseas:

- Novoseven® (second-generation recombinant Factor VIIa, produced by Novo Nordisk)
- Recombinate® (first-generation recombinant Factor VIII, produced by Baxter)
- Advate® (third-generation recombinant Factor VIII, produced by Baxter)
- ReFacto® (second-generation recombinant Factor VIII, produced by Wyeth)
- Benefix® (second-generation recombinant Factor IX, produced by Wyeth)

All products – local and imported – that are provided to Australian consumers under Australia's national blood arrangements are provided free of charge to recipients.[6]

Recent developments in plasma products

A number of plasma derivatives are currently not provided under Australia's national blood arrangements. Generally these products have become commercially available relatively recently. They include subcutaneous immunoglobulin (SCIg), alpha-1 antitrypsin, C1 esterase inhibitor, and fibrin sealants.

Immunoglobulins, as noted above, are generally used by people suffering from immunodeficiency syndromes and autoimmune disorders. Traditionally there have been two forms of immunoglobulin: intravenous immunoglobulin (IVIg) and intramuscular (normal) immunoglobulin (IMIg). IVIg infusions are delivered directly into the vein, usually in a hospital clinic but sometimes in the patient's home. This process takes approximately two to four hours and it is usual for an individual with chronic immune deficiency to receive a dose of IVIg once every month.

Although some existing immunoglobulin products have been used subcutaneously, there is now a move towards products specifically formulated for subcutaneous injection. These involve slowly infusing the antibody preparation directly under the skin, and the injections can be self-administered using a special pump. Infusions are usually required at least once a week, as only 10–15 millilitres can be infused into any one site at a given time; a 10 millilitre SCIg infusion can be delivered in half an hour.[7]

While there is growing demand for IVIg in Australia, SCIg has not yet become a significant driver of demand for plasma products, although it is increasingly being used in Europe as an alternative to IVIg. A specific SCIg preparation is not currently available in Australia.

Alpha-1 antitrypsin is used for chronic replacement therapy for patients with congenital alpha-1 antitrypsin deficiency together with clinically demonstrable panacinar emphysema, which is a chronic lung condition ('panacinar' refers to the involvement of all the lobes of the lung in a uniform manner). Alpha-1 antitrypsin deficiency is a rare disorder, affecting about 200 patients in Australia. Alpha-1 antitrypsin is available in Australia through the Special Access Scheme. This program,

6 Any potential additions to the plasma products listed on the National Supply Plan would need to undergo an evidence-based evaluation process (as specified in Schedule 4 of the National Blood Agreement), prior to consideration of their inclusion.

7 See Australasian Society of Clinical Immunology and Allergy, *About Immunoglobulin Replacement Therapy*, Information Bulletins, Australasian Society of Clinical Immunology and Allergy, Balgowlah, NSW, 2006, <http://www.medeserv.com.au/ascia/aer/infobulletins/immuno_replacement.html>.

operating under the auspices of the Therapeutic Goods Administration, allows individual patients to access therapeutic goods that have not been approved for and included on the Australian Register of Therapeutic Goods (ARTG). Applications are assessed on a case-by-case basis.[8]

C1 esterase inhibitor, used to treat C1 esterase inhibitor deficiency (also known as hereditary angioneurotic oedema (HANE)), is also available in Australia via the Special Access Scheme. HANE is caused by low levels of the plasma protein C1 inhibitor (C1-INH). Acute episodes can result in respiratory difficulties, with severe and even fatal consequences.

Fibrin sealants, used primarily in surgery – to control bleeding, seal wounds and promote healing – are being utilised increasingly, particularly in neurosurgery and vascular surgery. Fibrin sealants are particularly advantageous for patients with abnormal haemostasis. Prepared from a combination of fibrinogen (from human plasma) and thrombin (from bovine sources or human plasma), these products also contain Factor XIII (fibrin-stabilising factor), which cross-links the fibrin strands so as to promote wound healing.

In Australia, the fibrin sealant Tisseel®, manufactured by Baxter, is included on the ARTG. Hospitals are required to purchase Tisseel out of their operating budgets. Tisseel is also on the Prostheses List, administered by the Department of Health and Ageing. This register lists the prostheses and human tissue products that attract private health fund benefits, and the amount of benefit to be paid.

Hospitals sometimes constitute fibrin sealants from cryoprecipitate (supplied by the Australian Red Cross Blood Service), which contains fibrinogen: pharmaceutical-grade thrombin is appropriately added to the cryoprecipitate, generally in the context of emergency or major surgical procedures. The blood components used for constituting fibrin sealants in hospitals are subject to regulation by the TGA.

As alternatives to fibrin sealants and platelet gels, synthetic surgical glues provide a new therapy in the field of haemostatic sealants used in surgery to control microvascular bleeding.

Clinical indications for plasma products

Outlined below are the therapeutic uses for each of the plasma derived products currently provided under Australia's national blood arrangements. These products are manufactured in Australia by CSL unless otherwise stated.

Albumin products

Albumex® 4

The function of Albumex 4 (4% albumin solution) is to increase plasma volume.

Albumex 4 may be used when blood volume is low (hypovolaemia), during heart–lung bypass surgery, and in plasma exchange. Hypovolaemia can also occur during shock, after heart–lung bypass surgery, and in patients with multiple organ failure or leaky small blood vessels.

8 For further information on the Special Access Scheme, see Therapeutic Goods Administration, *Access to Unapproved Therapeutic Goods via the Special Access Scheme*, Therapeutic Goods Administration, Canberra, 2004; also available online at <http://www.tga.gov.au/docs/pdf/unapproved/sas.pdf>.

Albumex® 20

The main function of Albumex 20 (20% albumin solution) is to retain fluid in the bloodstream and to carry biochemical products to the appropriate sites in the body so that they can perform their specific functions.[9]

Albumex 20 may be used when the quantity of protein in the blood is low in an acutely ill patient; for resuscitation of patients in shock due to acute loss of blood or plasma; in the treatment of extensive burns or respiratory distress syndrome; in haemodialysis (for renal failure); in plasma exchange; and for patients with venoocclusive disease resulting from complications of bone marrow transplantation.

Immunoglobulins

Intravenous Immunoglobulin (IVIg)

In general terms, IVIg is a successful clinical strategy for the replacement of immunoglobulins in patients with congenital or acquired immunodeficiency syndromes who are subject to frequent and/or severe infections. IVIg is also used in other situations where there is an increased risk of infection, for example following solid organ or bone marrow transplantation, in surgery, or in the treatment of trauma or burns.

The other major use of IVIg is for immunomodulation in patients with autoimmune disorders of neurological, haematological, dermatological or immunological origin. IVIg is also used as an immunomodulant in solid organ (e.g. kidney) transplants when there is a high risk of rejection of the donor organ, or if acute rejection occurs.

Three IVIg products are provided under Australia's national blood arrangements:

Intragam® P

Intragam P is CSL Limited's Australian-sourced liquid-form IVIg product.

Octagam®

Octagam is an overseas-sourced IVIg product in liquid form, imported in order to supplement supplies of IVIg sourced from Australian-collected plasma. Octagam is manufactured and supplied by Octapharma.

Sandoglobulin®

Sandoglobulin is an overseas-sourced IVIg product in powder form, which CSL Limited supplies, under an arrangement separate to the Plasma Products Agreement, in order to supplement Australia's IVIg stocks. Sandoglobulin is manufactured by CSL Behring, a business unit of CSL Limited.

Normal Immunoglobulin (IMIg)

Normal Immunoglobulin (intramuscular immunoglobulin (IMIg)) is used to prevent infection by viruses such as poliomyelitis, hepatitis A and measles, in those coming into contact with a source of infection (e.g. family members), or where there is an outbreak of the disease.

9 Various natural products of metabolism (e.g. bilirubin) circulate as a complex of metabolite and albumin. Many drugs used for the treatment of disease circulate in the same way – as a complex of the drug and albumin.

CMV Immunoglobulin

CMV Immunoglobulin is used to provide protection against cytomegalovirus (CMV) infection in specific transplant patients and may also help in the treatment of CMV infection. CMV Immunoglobulin donors are selected on the basis that their plasma contains high levels of antibody specific to this virus.

Hepatitis B Immunoglobulin

Hepatitis B Immunoglobulin is used to prevent hepatitis B infection in persons who come into contact with blood or other material suspected of being infected with this disease. This product is also routinely given at birth, 2, 4 and 6 months of age and can be given at other ages for people who have not previously been vaccinated.

Rh(D) Immunoglobulin

Rh(D) Immunoglobulin is given to women who have an Rh(D) negative blood group, in the following circumstances: the product is administered to all Rh(D) negative women during pregnancy, and again after the birth of an Rh(D) positive baby, to prevent a mother generating antibodies to the Rh(D) on the red blood cells of a baby in a future pregnancy. Rh(D) Immunoglobulin is also used when an Rh(D) negative woman of child-bearing age is exposed to Rh(D) positive blood, and in particular is routinely used after termination of pregnancy in Rh(D) negative women.

If a pregnant woman is Rh(D) negative and her baby is Rh(D) positive, the baby's blood is incompatible with that of the mother, and this could cause rhesus haemolytic disease in the baby. This condition is known as Haemolytic Disease of the Newborn (HDN), a form of anaemia requiring exchange transfusions in order to lower levels of bilirubin, which is a breakdown product of haemoglobin. Bilirubin has the potential to cause deafness and mental retardation in an affected infant. In severe cases, HDN can cause severe anaemia, leading to death *in utero* (hydrops fetalis). The antibodies in Rh(D) Immunoglobulin can prevent HDN due to Rh incompatibility.

Tetanus Immunoglobulin IM

Tetanus Immunoglobulin IM, a preparation for intramuscular administration, is used for the prevention of tetanus in persons who have not been immunised within the recommended period and who have suffered an injury that could expose them to the tetanus bacteria.

Tetanus Immunoglobulin IV

Tetanus Immunoglobulin IV is a preparation used in the treatment of tetanus infection and administered intravenously.

Zoster Immunoglobulin

Zoster Immunoglobulin is used for the prevention of chickenpox and shingles in people who are susceptible to virus infection and who come into contact with an infected person. This product is administered in particular to those whose ability to fight infection is weakened, such as people with leukaemia and patients who have had bone marrow transplantation.

Plasma derived coagulant products

Biostate®

Biostate is a dried preparation that contains purified and concentrated human Factor VIII, a protein that is essential for normal blood clotting and that circulates in a bound form in plasma, with von Willebrand factor. Factor VIII deficiency is the cause of haemophilia A. Biostate, which contains von Willebrand factor as well as Factor VIII, is administered to people with haemophilia A and to people with the bleeding disorder known as von Willebrand's disease (vWD). It is important to note that Biostate is the only blood product currently available in Australia for the treatment of vWD, which is estimated to affect up to 1% of the population, although mild forms of the condition are by far the most common. Only a minority of people diagnosed with vWD will therefore require treatment with Biostate, but those with the disorder may be administered this product when undergoing surgical or dental procedures.

Monofix®-VF

MonoFIX-VF is a dried preparation containing purified and concentrated Factor IX, a protein essential for normal blood clotting. MonoFIX is used to treat people with haemophilia B (Christmas disease), a bleeding disorder resulting from reduced levels of Factor IX. This product has now been largely replaced by recombinant Factor IX.

Prothrombinex™-HT

Prothrombinex-HT is a dried preparation of proteins essential for normal blood clotting. The product mainly contains concentrated Factor IX, together with Factor II and Factor X – proteins that belong to a grouping referred to as human prothrombin complex.

Prothrombinex-HT is used for the prevention and treatment of bleeding in patients with low levels of Factor IX, Factor II or Factor X and is now the recommended clinical strategy when reversal of oral anticoagulant therapy is required as a matter of some urgency.[10]

Thrombotrol®-VF

Thrombotrol-VF is a dried preparation that contains the protein antithrombin III in a concentrated form. Antithrombin III, normally present in the blood, prevents the extension of blood clots beyond sites of injury.

Thrombotrol-VF may be administered, as a preventive measure, when persons with an inherited deficiency of antithrombin III are pregnant or are about to undergo childbirth or surgery. Such patients may be at risk of a spontaneous thrombosis (blood clot) or a pulmonary embolism (a blood clot that stops blood circulating through the lungs). The risk of these conditions increases with age, and in association with surgery, pregnancy and childbirth.

Ceprotin®

Ceprotin (protein C concentrate) is used to treat congenital deficiency of protein C, a substance that regulates coagulation and prevents abnormal clot formation (thrombosis). Severe congenital protein C deficiency causes life-threatening blood clotting complications. Ceprotin, which is manufactured and supplied by Baxter, may also have an important role in the treatment of meningococcal septicaemia, where protein C concentrate may be limb- and life-saving.

10 See R. Baker, P. Coughlin, A. Gallus, P. Harper, H. Salem & E. Wood, 'Warfarin Reversal: Consensus Guidelines, on Behalf of the Australasian Society of Thrombosis and Haemostasis', *Medical Journal of Australia*, vol. 181, no. 9, 1 November 2004, pp. 492-7.

Factor VII Concentrate

Factor VII Concentrate is administered to treat Factor VII deficiency, a rare congenital bleeding disorder characterised by spontaneous bleeding episodes in severely affected individuals, and by bleeding following trauma or surgery in mildly affected patients. Factor VII Concentrate is manufactured and supplied by Baxter. This product has been largely replaced by recombinant Factor VIIa (Novoseven®). Novoseven has proved very effective in treating people with haemophilia who have inhibitors and is also a valuable haemostatic agent for use in managing extensive surgical or obstetric bleeding.

Factor XI Concentrates

Factor XI deficiency, also known as haemophilia C, affects about one in 100 000 people and, unlike haemophilia A and B, affects both males and females. CSL Limited supplies BPL Factor XI and Hemoleven®.

Feiba VH® Inhibitor Treatment

FEIBA (Factor Eight Inhibitor Bypass Agent) VH is used in the treatment of bleeding episodes (including those occurring as a result of surgical interventions) experienced by people with haemophilia A or B who have Factor VIII or Factor IX inhibitors respectively.[11] Patients with these serious complications of haemophilia can now also be treated quite effectively with recombinant Factor VIIa (Novoseven®). FEIBA VH is manufactured and supplied by Baxter.

Fibrogammin P®

Fibrogammin P (Factor XIII concentrate) is used to treat inherited Factor XIII deficiency. Factor XIII deficiency is a very rare bleeding disorder with an incidence of one case per 2–5 million population, and affecting both males and females. Severe forms of this disorder may cause bleeding from the umbilical stump or cerebral haemorrhage in the newborn, as well as other forms of bleeding. Fibrogammin P is supplied to the Australian market by CSL Limited.

Blood product usage in Australia

While some plasma products are administered only to people with specific conditions, such as severe bleeding disorders, there are other products – for example, albumin and some of the immunoglobulin products associated with the treatment or prevention of particular diseases – that are extensively used in hospitals (e.g. in surgery, childbirth or intensive care). It can therefore be said that everyone is a potential recipient of plasma products.

It has been estimated that in this country there are approximately 5000 people with chronic or inherited conditions who are long-term users of plasma derived products. Some 125 000 Australians use plasma products each year (see table 1.2), and nearly one in three Australians will use a plasma product in his or her lifetime. In addition, as many as 300 000 people receive fresh blood products in Australia each year. As noted earlier, all blood products provided under Australia's national blood arrangements are issued free of charge to recipients.

11 Inhibitors are antibodies that recognise clotting factors administered in factor replacement therapy as 'foreign', and attack and neutralise the Factor VIII or Factor IX that has been introduced to the body. The procedure of administering high doses of clotting factors to 'swamp' these inhibitors is known as tolerisation.

Table 1.2 Plasma product use in Australia, 2005–06

Plasma derived product	Use	Est. number of patients*
Rh(D) immunoglobulin	Rh negative pregnancy	74 722
IMIg	Prevention of infections	18 200
Albumin	Burns, shock	13 476
Hyperimmune immunoglobulins	Prophylaxis for specific diseases	11 330
IVIg	Immunodeficiency	5 937
Prothrombin complex concentrate	Multiple factor deficiency	2 143
Factor VIII	Haemophilia A; von Willebrand's disease	320
Factor IX	Haemophilia B	25
Antithrombin III	Antithrombin III deficiency	21
Total		126 174

Source: Estimates of patient numbers provided by the Australian Red Cross Blood Service.

* The estimates relate to CSL Limited products produced in Australia. In addition, a number of patients receive imported IVIg, either exclusively or in combination with Intragam® P, and a very small number receive other imported plasma derived products.

Expenditure in Australia in 2005–06 under the national blood arrangements, for all blood products, including plasma derivatives, is detailed in table 1.3.

Table 1.3 Purchase of blood and blood-related products in 2005–06, by supplier

Supplier	Products purchased	Amounts (A$ millions)
CSL Limited	Plasma products • albumin products • immunoglobulin products (including IVIg and hyperimmune products) • plasma derived clotting factors Diagnostic reagent products • blood grouping sera • reagent red cell products Defined Blood Products • Rh(D) immunoglobulin • Factors XI and XIII • IVIg Standing Offer Management of National Reserve	136.77

Table 1.3 Purchase of blood and blood-related products in 2005–06, by supplier (cont.)

Supplier	Products purchased	Amounts (A$ millions)
Australian Red Cross Blood Service	Fresh blood products • whole blood • red blood cells • platelets • clinical fresh frozen plasma • cryoprecipitate • buffy coat (white cells) • plasma for fractionation	297.7
Baxter Healthcare Pty Ltd	Defined Blood Products • recombinant Factor VIII • protein C • Factor VII concentrate • Factor Eight Inhibitor Bypass Agent (FEIBA)	68.47
Wyeth Australia Pty Ltd	Defined Blood Products • recombinant Factor IX	15.87
Novo Nordisk Pharmaceuticals Pty Ltd	Defined Blood Products • recombinant Factor VIIa	23.57
Octapharma Pty Ltd	Defined Blood Products • IVIg Standing Offer	21.98
DiaMed Australia Pty Ltd	Diagnostic reagent products • blood grouping sera • reagent red cell products	0.84
Ortho-Clinical Diagnostics (a Johnson & Johnson Company)	Diagnostic reagent products • blood grouping sera • reagent red cell products	0.17
Australian Laboratory Services Pty Ltd	Diagnostic reagent products • blood grouping sera • reagent red cell products	0.03
Total purchases of blood and blood products		**565.40**

Source: National Blood Authority, *Annual Report 2005–06*, National Blood Authority, Canberra, 2006, pp. 29–30.

Note: All amounts exclude GST.

Table 1.4 lists the unit prices of the preparations supplied by CSL Limited under the Plasma Products Agreement; in terms of volume and expenditure, these account for the bulk of plasma products available in Australia. The role of the Australian Red Cross Blood Service as Australia's collector of plasma for fractionation is funded separately, under the arrangements between the NBA and the ARCBS, and the plasma product prices recorded in table 1.4 therefore do not reflect the costs associated with plasma collection and delivery to the fractionator.

Table 1.4 Prices of plasma products supplied by CSL Limited, 2005

Product	Unit size	Final price (A$, excl. GST)	Final price (A$, incl. GST)
Albumex® 20	10 mL	12.17	13.39
Albumex® 20	100 mL	44.30	48.73
Albumex® 4	50 mL	12.17	13.39
Albumex® 4	500 mL	44.30	48.73
Intragam® P	50 mL	171.60	188.76
Intragam® P	200 mL	686.40	755.04
Biostate®	250 IU	137.80	151.58
MonoFIX®-VF	500 IU	353.60	388.96
Prothrombinex™-HT	500 IU	404.04	444.44
Thrombotrol®-VF	1000 IU	1154.40	1269.84
CMV Immunoglobulin	30 mL	1029.11	1132.02
Hepatitis B Immunoglobulin	100 IU	37.61	41.37
Hepatitis B Immunoglobulin	400 IU	86.11	94.72
Normal Immunoglobulin	2 mL	27.09	29.80
Normal Immunoglobulin	5 mL	44.40	48.84
Rh(D) Immunoglobulin	250 IU	25.48	28.03
Rh(D) Immunoglobulin	625 IU	63.70	70.07
Tetanus Immunoglobulin IM	250 IU	37.18	40.90
Tetanus Immunoglobulin IV	4000 IU	594.88	654.37
Zoster Immunoglobulin	200 IU	235.87	259.46

Source: *Plasma Products Agreement* [edited version for publication on NBA website], National Blood Authority, Canberra, 2004, p. 92, <http://www.nba.gov.au/PDF/PPA%20for%20web.pdf>.

Note: Prices specified are subject to indexation at the rate of 1.75% per annum, with indexation taking effect on 1 July 2006 and on the first day of each financial year thereafter for the duration of the Agreement.

Australia's total annual consumption of and expenditure on plasma products under the national blood arrangements is monitored at the jurisdictional level and, as indicated in table 1.2, numbers of recipients can be estimated. Yet, it is difficult – because of the degree of variation on a case-by-case basis – to derive a meaningful 'average' or 'typical' quantity, or cost, with respect to a product used to treat individual patients with a specific medical condition. Furthermore, while some patients with chronic or inherited disorders require ongoing treatment with a plasma product, certain hyperimmune products may be administered on a single occasion in a person's lifetime.

Table 1.5 Estimated use of and expenditure by Governments on CSL Limited plasma products in Australia, 2005–06

Plasma derived product	Use	Est. number of patients*	% of total plasma product recipients	Est. cost to govts for fractionated products supplied by CSL (A$)†	Amount per product as % of total expenditure	Average est. cost per patient per annum (A$)††
Rh(D) immunoglobulin	Rh negative pregnancy	74 722	59.22	5 474 123	4.51	73
IMIg	Prevention of infections	18 200	14.42	752 921	0.62	41
Albumin	Burns, shock	13 476	10.68	10 504 698	8.66	780
Hyperimmune immunoglobulins	Prophylaxis for specific diseases	11 330	8.98	3 971 502	3.27	351
IVIg	Immunodeficiency	5 937	4.71	81 959 763	67.55	13 805
Prothrombin complex concentrate	Multiple factor deficiency	2 143	1.70	5 380 601	4.43	2 511
Factor VIII	Haemophilia A; von Willebrand's disease	320	0.25	8 748 922	7.21	27 340
Factor IX	Haemophilia B	25	0.02	3 462 098	2.85	138 484
Antithrombin III	Antithrombin III deficiency	21	0.02	1 070 129	0.88	50 959
Totals		126 174	100.00	121 324 757	100.00	962

* Estimates of patient numbers provided by the Australian Red Cross Blood Service.

† Adapted from data on expenditure held by the Department of Health and Ageing. These figures for expenditure by Australian governments on the supply of fractionated products do not represent the overall amount of funding provided to CSL Limited in 2005–06, as the cost of managing reserve products is not included.

†† These are per capita averages only and *do not* reflect actual clinical usage and costs. The case studies later in this chapter provide more information on the variables associated with clinical use of plasma products.

It is possible to generate in the first instance an extremely general figure for average overall expenditure on plasma products per patient per annum: a figure in the order of A$1000 is derived from the ratio of annual expenditure on products supplied under the PPA (approximately A$120 million), to the number of recipients of plasma products (approximately 125 000).

In considering these figures, it is again important to note that actual clinical use is very specific to the physical and medical circumstances of individual patients. For example, the treatment regime for a person with a clotting factor deficiency is dependent on several variables, including:

- dosage – corresponding either to the person's age and weight (for patients who have not reached physical maturity) or to the person's plasma volume (for adults)
- severity of condition (severe, moderate or mild)
- severity and nature of bleeding
- any surgical procedures that the patient undergoes
- frequency of treatment (whether on a regular basis, for prophylaxis, or intermittent – prophylactic treatment for haemophilia A and B typically requires about three times the amount of product as is used in treatment on demand, and can cost in the order of A$100 000–$150 000 per patient per annum; there are long-term savings, however, in regard to joint sequelae).

Attempts to obtain an average cost per person per annum are further complicated in the case of IVIg by the many clinical indications for which a product may be a beneficial therapy. There are varying regimes for IVIg, in terms of frequency and strength of dosage, as well as duration of treatment, with these factors also depending on individual patient circumstances and variations in clinical practice (see Case Studies below).

The price of a product, moreover, does not give the complete picture of expenditure on treatment, particularly when hospitalisation is required. While some preparations are self-administered, others are provided in hospital or in same-day clinical care settings, with resulting implications for the costs of an episode of care. (These costs, aside from the costs of plasma products, are outside the scope of the national blood arrangements.) Co-morbidities (medical conditions requiring simultaneous treatment) must also be considered: for example, albumin tends to be administered in conjunction with other therapies and medical procedures. For these reasons, an attempt to assess the full cost of treatments in which plasma products are used becomes problematic.

It is likely that these difficulties are the reason that assessments of per capita consumption of products (assessments that often include comparisons between Australia's health systems and comparable systems overseas), and not of the cost of individual treatment episodes, tend to be used in planning and forecasting exercises with respect to the provision of blood and plasma products.

Case studies

Estimated costs associated with the following case scenarios reflect only the price of the plasma product prescribed (excluding costs of plasma collection by the Australian Red Cross Blood Service) and do not account for other costs, such as the full cost of hospitalisation, the financial impact of time away from work, impact on family, and costs arising from adverse outcomes (e.g. central venous line infections).

Indirect cost savings ensuing from treatment are difficult to quantify but can include savings associated with a reduction in acute hospital admissions and a reduction in disease-related side effects. Increased quality of life, as a result of treatment, can mean social benefits both for patients and for their families.

Case study 1

Immunomodulatory therapy: Adult Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

IVIg is used for many conditions where the aim of therapy is to prevent the immune system from damaging important parts of the body in patients with the so-called autoimmune conditions. People tend to consider autoimmune conditions in terms of the area of the body most affected, but the underlying problem lies with the balance of the immune system, so that the most sensible treatments are those directed at the immune system itself. This is why IVIg, which is an immunomodulator (an agent that augments or diminishes immune responses), is used to treat a collection of diverse conditions that do not appear at first glance to be related to one another.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is one of the key autoimmune conditions. In this disorder, there is a sustained autoimmune attack on the myelin sheath surrounding the nerves, resulting in abnormal sensation and in motor weakness. The outcome for the patient may be great disability but the manifestations can vary greatly from one person to another, and for any particular individual may fluctuate with time. Neurologists caring for CIDP patients need to design their therapies according to patients' individual needs.

IVIg may be very effective at blocking an autoimmune attack on nerves, but therapy may have to be sustained for many months or even for years.

Clinical scenario

Janet is a 42-year-old lawyer and the mother of two children. Four weeks after a moderate viral infection of the upper respiratory tract, she develops numbness, burning in the limbs and difficulty walking, but she recovers without treatment.

Several weeks later a further attack occurs. Janet's symptoms become so severe that she is unable to walk and requires assistance with showering. She is referred to a neurologist, who carries out nerve conduction and cerebral spinal fluid studies, takes X-rays and performs a nerve biopsy. Findings are suggestive of CIDP.

The neurologist prescribes IVIg (Intragam® P), to commence at 0.4 g/kg for five consecutive days, followed by an initial maintenance strategy of one infusion at 0.4 g/kg per month for three months. Janet weighs 65 kilograms.

Janet experiences prompt improvement in her symptoms and she is able to return to work. In the week before her second IVIg treatment, however, her symptoms worsen

Dose requirements and cost

	Initial treatment	Current maintenance	Proposed maintenance
Dose	0.4 g/kg x 65 kg = 26 g per dose for 5 consecutive days	0.4 g/kg x 65 kg = 26 g per dose – 12 doses per year	0.4 g/kg x 65 kg = 26 g per dose – 17 doses per year
Volume	Treatment dose: 2 x 12 g bottle and 1 x 3 g bottle = 27 g	Treatment dose: 2 x 12 g bottle and 1 x 3 g bottle = 27 g	Treatment dose: 2 x 12 g bottle and 1 x 3 g bottle = 27 g
Cost	2 x $755.04 plus 1 x $188.76 = $1698.84 per daily dose Total (5 doses) = $8494.20★	2 x $755.04 plus 1 x $188.76 = $1698.84 per monthly dose Total (12 doses) = $20 386.08★	2 x $755.04 plus 1 x $188.76 = $1698.84 per three-weekly dose Total (17 doses) = $28 880.28★
Initial treatment plus current maintenance treatment = $28 880.28 per annum			
Initial treatment plus proposed maintenance treatment = $37 374.48 per annum			

★ Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

once again. Her neurologist recommends continuation of the maintenance infusions, but at a frequency of once every three weeks.

Qualifier: The individual dosage for IVIg depends on a patient's responsiveness to the therapy, and the dose could potentially be increased during the course of treatment.

Case study 2

Replacement therapy

Primary immune deficiency (PID)

Common variable immunodeficiency (CVID)

There are more than 150 different types of primary immunodeficiencies. These are disorders where an individual is born with defects in the immune system that prevent normal defence against infection. Primary immunodeficiencies range in severity from rare, fatal diseases in childhood to relatively common disorders of adulthood, all of which are characterised by the failure of normal antibody responses. Typically, adult patients develop severe and recurrent bacterial infections of the lungs and sinuses, which over time lead to chronic lung damage and bronchiectasis.

Immunoglobulins function as antibodies. Therefore IVIg gives doctors the opportunity to prevent infections and long-term damage in these patients. The disease termed 'common variable immunodeficiency' (CVID) is the single largest user of IVIg in Australia. Treatment, which is continued monthly and is lifelong, is impressively effective, returning many patients to normal lives.

Dose requirements and cost

	Current maintenance
Dose	0.4 g/kg x 80 kg = 32 g per dose – 12 doses per year
Volume	Treatment dose: 3 x 12 g bottle = 36 g
Cost	3 x $755.04 = $2265.12 per monthly dose*
Maintenance treatment = $27 181.44 per annum	

* Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

Clinical scenario

Clyde is a 37-year-old bus driver. From the age of nine he experienced recurrent episodes of middle ear infection, requiring grommets. Throughout his high school years he was, in his own words, 'constantly' on antibiotics for ear, and sinus, infections, and he has had two operations to clear his sinuses. At age 17 he developed severe pneumonia, requiring admission to intensive care, but he recovered with the aid of antibiotics. By age 21 he was coughing up infected phlegm every day, and by his early thirties was experiencing shortness of breath when climbing stairs. He has started to have long absences from work.

A respiratory physician detects early bronchiectasis via a CT scan of Clyde's chest, and measures antibody levels in his blood. When these are found to be low, Clyde is referred to an immunologist, who is able to confirm a profound defect in antibody production, consistent with CVID. IVIg (Intragam P) is commenced immediately. Within two months of beginning this therapy, Clyde is free of infections for the first time he can remember. More gradually, his breathing returns to normal, although he remains at risk of pneumonia, due to the chronic scarring in his lungs.

Clyde, who weighs 80 kilograms, begins treatment with an IVIg dose of 0.4 g/kg, or 32 g, per month by infusion.

Case study 3

Immunomodulatory therapy: Paediatric Kawasaki disease

Kawasaki disease is an uncommon illness that occurs mainly in preschool-aged children. The incidence of the disease is 15 per 100 000 children (US figures). It occurs more frequently in the Japanese population. Although rare, Kawasaki disease tends to occur with seasonal peaks.[12] Its cause is currently not known but it is thought to be a severe abnormal immune response to infection. The result is inflammation of blood vessels (vasculitis), all over the body. When vasculitis affects important organs such as the heart, severe complications and death may follow. There is no simple diagnostic test for this condition, but the clinical challenge is to identify patients early (as Kawasaki disease may easily be confused with other illnesses, including simple viral infections), and to intervene quickly with IVIg to prevent

12 The 2004–05 and 2005–06 annual reports of the Australian Institute of Health and Welfare did not report on the incidence of Kawasaki disease in Australia, and it is therefore difficult to determine incidence with any accuracy.

Dose requirements and cost

	Current maintenance
Dose	2 g/kg x 20 kg = 40 g
Volume	3 x 12 g bottle and 1 x 3 g bottle = 39 g
Cost	3 x $755.04 plus 1 x $188.76 = $2453.88*
Total IVIg treatment cost = $2453.88	

* Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

cardiovascular and other complications. The timely use of IVIg can also reduce the length of hospitalisation required.

IVIg therapy is particularly useful in the paediatric age group, for two main reasons: first, with the body size of the patient so much smaller, the doses required are much less than those needed in order to achieve the same effect in adults; and second, alternative immunosuppressive therapies may have very undesirable long-term side effects in young people. The treatment of Kawasaki disease provides an excellent example of how IVIg is used in paediatrics.

Clinical scenario

Jonathon is a four-year-old boy who presents to hospital with high fever, rash, swollen lymph glands, cherry-red lips and eyes, and redness and swelling of the hands. A diagnosis of Kawasaki disease is made and Jonathon, who weighs 20 kilograms, is prescribed aspirin and IVIg 2 g/kg (Intragam P) as a single dose over 12 hours.

Case study 4

Clotting factor deficiency

Von Willebrand's disease (vWD)

Von Willebrand's disease (vWD) is an inherited autosomal dominant disorder characterised by a deficiency of von Willebrand factor, a highly complex plasma protein. The functions of von Willebrand factor are to enable the adherence of platelets to areas of blood vessel wall damage and to carry the anti-haemophilic clotting factor Factor VIII.

Von Willebrand's disease may affect as many as 1% of the population, but in the great majority of cases is very mild, and is frequently diagnosed only after severe trauma or major surgery. There are three types of vWD: types I, II and III. Type III is the rarest but most severe form of the condition. The disease affects both sexes, and in contrast to haemophilia has more clinical consequences in females than in males.

The fractionated plasma product Biostate® contains both von Willebrand factor and Factor VIII, and is used for the treatment of bleeding episodes in severe cases of vWD. It is to be noted that recombinant Factor VIII is not effective in treating vWD as the recombinant form does not contain von Willebrand factor.

Dose requirements and cost

	Current maintenance
Dose	30 units Factor VIII/kg x 50 kg = 1500 units per dose for first 3 days of monthly menstrual period
Volume	Treatment dose: 6 x 250 unit vial = 1500 units
Cost	6 x $151.58 = $909.48 per daily dose* 3 x $909.48 = $2728.44 per monthly dose*
Maintenance treatment = $32 741.28 per annum	

* Treatment cost is inclusive of GST but exclusive of administration and hospital costs.

Clinical scenario

A 12-year-old girl, Sarah, is referred by her general practitioner to a gynaecologist because of heavy and irregular menstruation. There is a family history of menorrhagia, and of hysterectomy for menorrhagia in young relatives. Sarah has had frequent nosebleeds and bruises easily. Her gynaecologist suspects a congenital bleeding disorder, and orders blood investigations, which establish the diagnosis of severe vWD, type I.

Sarah and her parents are given the choice of hormone replacement therapy to suppress her periods, or infusions of Biostate at the beginning of and during menstruation. The family are very concerned about the side effects of hormone replacement therapy and choose treatment with Biostate.

Sarah is referred to a clinical haematologist, who is to decide on the frequency and dose of Biostate. The haematologist finds that in addition to vWD she has iron deficiency anaemia, due to her severe blood losses, and prescribes treatment with oral iron tablets to correct the iron deficiency. At the visit to the haematologist, Sarah weighs 50 kilograms.

The haematologist arranges for infusions of Biostate, in a dose of 30 units of Factor VIII/kg (a total dose of 1500 units of Factor VIII) each day for the first three days of the patient's menstrual period. The dose calculation is based on the Factor VIII content of Biostate, since it is known that the amount of von Willebrand factor closely parallels that of Factor VIII in the product. (The ratio of von Willebrand factor to ristocetin co-factor is 2:1.)[13] In addition, the haematologist prescribes an antifibrinolytic oral medication, to enhance the bleeding control effect of Biostate.

There are a variety of ways of measuring responses to Biostate therapy. Perhaps the most common is to measure a patient's levels of Factor VIII after therapy. Clinical response may also be used as a measure of success of therapy. If, in the present case, abnormal bleeding were to persist, the dose of Biostate could be increased incrementally, to as much as 60 units of Factor VIII/kg.

13 Biostate product information.

The patient will continue her treatment with Biostate into early adult life or until she becomes sexually active, at which time her treatment could change to hormone replacement therapy, boosted, if required, by occasional Biostate infusions.

In conclusion, under Australia's national blood arrangements three main types of plasma products – albumin, immunoglobulins and clotting factors – are provided to Australian patients. These products are used to treat or prevent a diverse spectrum of conditions, with varying levels of incidence. Administration of plasma products takes place in various clinical care settings.

Intravenous immunoglobulin (IVIg), in particular, is notable for its association with a very broad range of clinical indicators, across immunological, neurological, haematological and transplant situations. IVIg is by far the main driver of demand for plasma products in Australia and worldwide. On the other hand, there are a number of products that are used solely for the treatment of single, specific conditions. In terms of the treatment of individual recipients with a given product, there are considerable variations in usage patterns, dosage and frequency of dosage administration.

These issues present challenges from the point of view of managing plasma product supply and predicting demand. Demand and supply trends will be addressed at length in subsequent chapters.