2. About bleeding disorders

Inherited bleeding disorders are genetic conditions and occur in families.

2.1 Types of bleeding disorders

2.1.1 HAEMOPHILIA

Haemophilia is caused by a mutation or alteration in the gene making factor VIII (8) or IX (9).

- Haemophilia A is the most common form of haemophilia and is due to reduced levels of clotting factor VIII.
- Haemophilia B is due to reduced levels of clotting factor IX.

The reduced levels of clotting factor produce bleeding episodes, or 'bleeds', largely internally into joints, muscles or organs. These bleeding episodes may have no obvious cause or may occur as a result of trauma or injury, including medical procedures and surgery and menstruation and childbirth in women.

If internal bleeding is not managed quickly with treatment to increase clotting, it will result in pain and swelling. It can be life-threatening, particularly when bleeding is into organs. Over time, repeated bleeding into joints and muscles will cause joint and tissue destruction which leads to permanent damage such as arthritis, chronic pain and joint damage requiring surgery.

- **Severe haemophilia:** people with severe haemophilia bleed frequently into their muscles and joints, sometimes once or twice a week and often from no apparent cause. They use replacement factor therapy often throughout their life. Severe haemophilia is rare in females.
- **Moderate haemophilia:** People with moderate haemophilia bleed less frequently. They may have bleeding problems after minor injuries, such as sporting injuries, as well as after medical and dental procedures, surgery or major injury.
- **Mild haemophilia:** People with mild haemophilia usually only have serious bleeding episodes as a result of surgery, dental extractions or injury. If females have haemophilia, they are most likely to have mild haemophilia. Females may also have significant bleeding problems with menstruation or after childbirth.

2.1.2 VON WILLEBRAND DISEASE (VWD)

VWD is the most common inherited bleeding disorder and occurs in women and men equally. It is caused by reduced levels of a blood clotting protein called von Willebrand factor or where the protein does not work properly. Like haemophilia, it results from a genetic alteration.

In VWD bleeding usually involves the mucous membranes, the delicate tissues that line body passages such as the nose, mouth, uterus, vagina, stomach and intestines. Nose and gum bleeds and easy bruising are common. Some women experience heavy and prolonged menstrual bleeding and postpartum haemorrhage after childbirth. There can be excessive bleeding after injury, surgery, or medical and dental procedures. In severe VWD, there can also be bleeding into joints and muscles. VWD can often be undiagnosed. Although more recently people with VWD have been encouraged to go to a Haemophilia Treatment Centre for treatment, it has usually been managed by other health professionals in the community, such as general practitioners.

- **Severe VWD:** People with severe VWD may have frequent bleeding episodes, and sometimes joint and muscle bleeds. Severe VWD is rare.
- **Mild VWD:** Most people with VWD have a mild form and do not need treatment unless they have surgery, medical or dental procedures or an injury; or may also have bleeding problems with menstruation or childbirth if they are female.

2.1.3 OTHER RARE BLEEDING DISORDERS

Apart from haemophilia and VWD, there are also other rare bleeding disorders.

Rare clotting factor deficiencies are caused when the body does not produce enough of a specific certain clotting factor, or when the factor does not work properly. They include factor I (1), II (2), V (5), VII (7), X (10), XI (11), or XIII (13) deficiencies and combined factor V (5) and factor VIII (8) deficiency.

In **platelet function disorders**, the platelet plug does not form properly, leading to a tendency to bleed for longer than normal or bruise easily. Since platelets have many roles in blood clotting, platelet function disorders can range from mild to severe. Examples include Glanzmann thrombasthenia and Bernard-Soulier syndrome.

These bleeding disorders are very uncommon.[3,4]

2.1.4 ACQUIRED HAEMOPHILIA AND VWD

In very rare cases a person can develop a different type of haemophilia or VWD over their lifetime, usually as an adult, which is not genetic or inherited. It is known as an acquired bleeding disorder.

Acquired haemophilia can occur when a person's immune system produces antibodies that mistakenly target their own factor VIII. It is very rare but can sometimes occur in older people and young women who are in the later stages of pregnancy or have recently given birth. The bleeding pattern is different to inherited haemophilia and it is usually curable with treatment.

Acquired von Willebrand disease can also occur but is extremely rare.[4,5]

Acquired bleeding disorders are not inherited or passed on to children. Men and women are equally likely to be affected by an acquired bleeding disorder.

2.2 Age distribution of people with bleeding disorders in Australia

Data for this section was sourced from the Australian Bleeding Disorders Registry (ABDR). The data was released to HFA by the National Blood Authority (NBA) following an HFA request to the ABDR Steering Committee for approval.

By June 2019 there were more than 6300 people diagnosed with bleeding disorders in Australia. Bleeding disorders are rare, but some occur more commonly than others and some are diagnosed more often than others.

Table 1 shows the age distribution in haemophilia, VWD, factor XI deficiency and platelet disorders, which was collated from the June 2019 data from the Australian Bleeding Disorders Registry (ABDR). These were the more commonly diagnosed bleeding disorders.

Mild disorders are likely to be under-represented in the ABDR as many people may not be diagnosed until they have a major bleeding episode or may be managed by a general practitioner or a clinician that is not associated with an HTC and their data not contributed to the ABDR. VWD, for example, is the most common bleeding disorder but if they have mild symptoms, many people may not be aware they have the disorder.[4] Table 2 shows that, although VWD is more prevalent in the population than haemophilia, fewer people with VWD have been diagnosed and their diagnosis recorded in the ABDR than those with haemophilia. Mild bleeding disorders may be challenging to diagnose, especially if there is no recognised family history.[6] Consultation for the HFA women's project found that some women with mild disorders had experienced years of misdiagnosis or lack of diagnosis before their bleeding disorder was identified.[7]

Many bleeding disorders are very rare. This is demonstrated in table 2: the numbers of these other rare bleeding disorders were too small to aggregate by age group and have been collated in total by gender.

Table 1: Age distribution of haemophilia, VWD, factor XI deficiency and inherited platelet disorders in Australia 2019

	0-19 yrs	20-34 yrs	35-49 yrs	50-64 yrs	65-79 yrs	80-94 yrs	95 yrs plus	TOTAL
Haemophilia - Female	79	118	167	83	53	7	-	507
Haemophilia - Male	704	557	494	353	245	62	8	2423
Haemophilia - total	**783**	**675**	**661**	**436**	**298**	**69**	**8**	**2930**
VWD - Female	165	400	392	247	165	36	<5	1408
VWD - Male	222	204	149	131	81	25	<5	813
VWD - total	**387**	**604**	**541**	**378**	**246**	**61**	**<5**	**2221**
Factor XI deficiency - Female	21	47	61	26	30	13	<5	199
Factor XI deficiency - Male	21	22	18	14	16	7	<5	99
Factor XI deficiency - total	**42**	**69**	**79**	**40**	**46**	**20**	**<5**	**298**
Inherited platelet disorders - female	35	47	48	34	29	7	-	200
Inherited platelet disorders - male	29	41	20	22	10	<5	-	123
Inherited platelet disorders - total	**64**	**88**	**68**	**56**	**39**	**8**	**-**	**323**

Table 2: Other bleeding disorders in Australia 2019

	Female	Male	Total
Other inherited bleeding disorders			
Factor V deficiency	9	9	18
Factor VII deficiency	44	43	87
Factor X deficiency	9	9	18
Factor XII deficiency	9	6	15
Factor XIII deficiency	11	17	28
Fibrinogen disorders	70	43	113
Other bleeding disorders	130	63	193
Acquired bleeding disorders			
Acquired haemophilia	33	46	79
Acquired VWD	14	18	32

2.2.1 VWD SEVERITY

VWD diagnostic categories are currently being revised internationally and the ABDR data reflects this changing picture of how severity in VWD is understood. However, table 3 shows at a broad level the smaller proportion of males and females in Australia diagnosed as having the severe form in comparison to the larger numbers with other milder forms of VWD. While the severe form is likely to be diagnosed in childhood due to the frequency of bleeding episodes, mild forms may not be diagnosed until the person is an adult and it is thought that a large proportion in Australia remain undiagnosed.

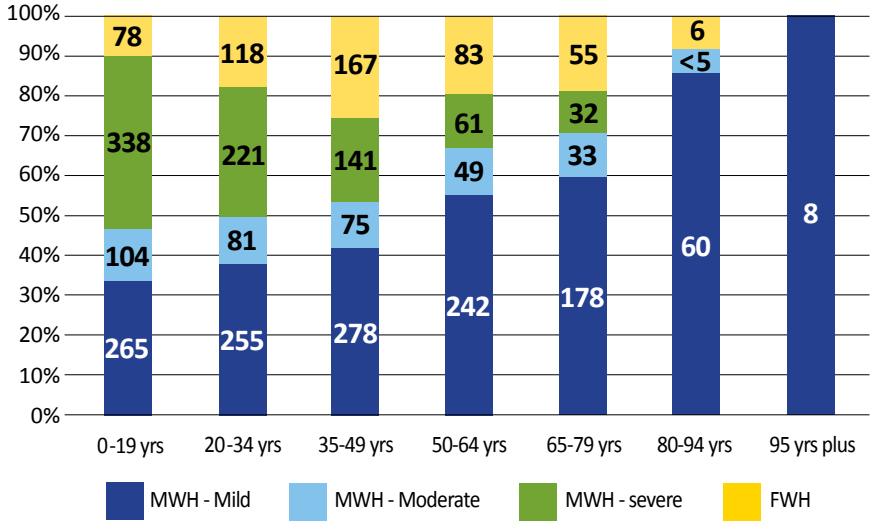
Table 3: VWD in Australia 2019 by gender and severity

	Mild	Moderate	Not applicable	Severe	Unknown	Total
VWD - female	813	148	320	72	55	1408
VWD - male	376	112	221	71	33	813
VWD - total	**1189**	**260**	**541**	**143**	**88**	**2221**

2.2.2 HAEMOPHILIA SEVERITY AND SURVIVAL

Figure 1 shows the age distribution of haemophilia by severity. This analysis highlights the very low numbers of people with moderate or severe haemophilia who have survived into their senior years and what a new phenomenon this is; and that the larger proportion have mild haemophilia. In June 2019 there were, for example, only 69 men with moderate or severe haemophilia listed in the ABDR nationally who were 65 years or over.

Figure 1: Age distribution of haemophilia in Australia 2019: males with haemophilia (MWH) by severityand females affected by haemophilia (FWH)*



* Females affected by haemophilia (FWH) includes females with factor levels below normal and females classified in the ABDR as haemophilia 'carriers'.

The complications causing lower survival rates in people with moderate and severe bleeding disorders, including both haemophilia and VWD, are discussed in the literature review, under **Older people with bleeding disorders population** (section 3.4).

2.3 Treatment

Treatment for bleeding disorders may be **preventive ('prophylaxis')** or **'on demand'**, to treat bleeds as they occur.

There is a variety of treatment products used to treat bleeding disorders.

Clotting factor concentrates are infused (injected) into a vein. The intention of treating with a clotting factor concentrate is to replace the specific clotting factor that is missing or does not work properly to help blood to clot and prevent or control bleeding episodes.

Plasma-derived factor concentrate is manufactured from pooled donations of human plasma, the pale yellow fluid part in blood. In the past people with bleeding disorders acquired bloodborne viruses from plasma-derived products, but with improved safety measures the infection risk is now considered to be extremely low.

Recombinant factor concentrate is a clotting factor made by genetic engineering, containing little or no human product. There have been no reports that viruses have been transmitted by recombinant products.

In some rare bleeding disorders a clotting factor concentrate specific to the factor deficiency may not yet have been developed or be suitable.

In this case **fresh frozen plasma** may be used. This is prepared from human plasma donations and contains the range of proteins or factors required to help blood to clot. It is stored frozen and thawed for treatment, when it is infused into a vein.

Platelet transfusion may be required for more severe inherited platelet function disorders and on occasion for other bleeding disorders. To avoid reactions to platelets, the transfusions are often matched to the individual. This requires specialised testing which can take some weeks.

Desmopressin (DDAVP) is a synthetic hormone that boosts levels of factor VIII and von Willebrand factor. It may be injected under the skin or infused into a vein.

Tranexamic acid is an antifibrinolytic agent that slows blood clots from breaking down after they have been formed. While it does not prevent bleeds, it can help to control bleeding from skin and the mucous membranes and is often used to treat mouth or nosebleeds, gut bleeding, bleeding after dental work and heavy menstrual bleeding. Most commonly it is taken as tablets, syrup or in a mouthwash and it can be used as an addition to a clotting factor concentrate.

Women may also be prescribed hormonal contraceptives such as the oral contraceptive pill or the Mirena intra-uterine device to manage heavy menstrual bleeding.[4,8,9,10]

2.4 Comprehensive care

International best practice for treatment and care of a person with a bleeding disorder is through co-ordinated delivery of **comprehensive care**. This is provided by a multidisciplinary team with specialised expertise in bleeding disorders, who address the wide-ranging physical and psychosocial needs of the person with a bleeding disorder and their family:

- a haematologist
- a nurse co-ordinator
- a psychosocial expert, preferably a social worker or psychologist
- musculoskeletal experts including a physiotherapist and orthopaedics or rheumatology specialists
- and access to a specialised laboratory.

To provide integrated care to their patients, the team will also co-ordinate their care with other relevant specialities, which should include at least pain management, a geneticist, infectious diseases, immunology and hepatology, gynaecology and obstetrics, dentistry and vocational counselling.[11]

In Australia comprehensive care is provided by specialist **Haemophilia Treatment Centres (HTCs)**. There is at least one HTC in each Australian state or territory. These are usually located in tertiary public hospitals and provide a collaborative and educational role statewide, with outreach services to isolated patients and the capacity to undertake research.[4]

An important tool in comprehensive care is the **Australian Bleeding Disorders Registry (ABDR)**. This system is used by HTCs for the clinical care of their patients. The ABDR collects data on people with bleeding disorders, their bleeding episodes and related problems, treatments and care. Statistical data from the system can be used to better understand the impact of the bleeding disorder, outcomes of various treatments and for treatment product supply and planning. People with a bleeding disorder and parents of a child with a bleeding disorder can contribute data about their bleeds and home treatments through the **MyABDR** app and website. MyABDR links directly to the ABDR system.[4]

National groups of the specialist health professionals at HTCs have been established to promote clinical excellence and research in each discipline:

- Australian Haemophilia Centre Directors' Organisation (AHCDO)
- Australian Haemophilia Nurses Group (AHNG)
- Australia/New Zealand Haemophilia Psychosocial Group (ANZHPG)
- Australian And New Zealand Physiotherapy Haemophilia Group (ANZPHG).