Advances in the treatment and care of haemophilia have transformed this rare bleeding disorder from a fatal disease into a long-term condition, with which people are increasingly living into old age. However, the legacy of the contaminated blood scandal – in which around 5,000 people with haemophilia and other blood disorders in the UK were infected with contaminated blood products in the 1970s and 1980s – is still being felt, highlighted by the revelations of an ongoing public inquiry (infectedbloodinquiry.org.uk). Described as “the worst treatment disaster in NHS history” (Reed, 2021), it led to more than 3,000 deaths from hepatitis and HIV in people with blood disorders. The UK began using recombinant (manufactured) clotting therapies in the late 1990s, guaranteeing such a tragedy will never happen again, but it took over 30 years to launch an independent public inquiry into the scandal (Bit.ly/THSMHSupport).

What is haemophilia?
Haemophilia is a rare bleeding disorder in which the body does not produce enough of a protein that helps the blood to clot. There are two main types:
- Haemophilia A – caused by deficiency of the functional plasma clotting factor VIII;
- Haemophilia B (also known as Christmas disease, after the first patient diagnosed) – caused by deficiency of the functional plasma clotting factor IX.

Advances in the treatment and care of haemophilia have transformed this rare bleeding disorder from a fatal disease into a long-term condition, with which people are increasingly living into old age. Haemophilia is a rare bleeding disorder associated with a lack of coagulation factor VIII (type A) or IX (type B). Haemophilia A is the most common, affecting 1 in 5,000 male births. The hallmark of severe haemophilia is recurrent and spontaneous joint bleeds, which can cause permanent joint damage and bleeding in other locations, such as the skull; they can be life threatening. However, recombinant clotting factor and non-factor replacement therapies are transforming the outlook for people with haemophilia, and more people are living with the disorder into old age. This article describes haemophilia and its management.
**Clinical Practice**

**Review**

**Congenital haemophilia**

Most haemophilia is congenital, caused by an inherited X chromosome genetic mutation that mainly occurs in males, although female carriers may have mild, or rarely severe, bleeding symptoms (Bit.ly/NORD-HemophiliaA). People with haemophilia usually have a family history of the disorder, but around a third of males diagnosed have no family history due to a spontaneous mutation in the female line that has not been inherited by a male family member before (Srivastava et al, 2020; Khair, 2019).

Who is affected by congenital haemophilia?

There are an estimated 10,000 people with haemophilia in the UK (Khair, 2019). Haemophilia A is the most common type, affecting around 1 in 5,000 male births, with around 60% experiencing a severe form; haemophilia B is less common, affecting around 1 in 25,000 male births (Khair, 2019; Bit.ly/NORDHemophiliaA). Around 20% of people with mild haemophilia are women; moderate-to-severe forms in women are rare (Bit.ly/HaemophiliaFemale).

**Acquired haemophilia**

Haemophilia can also be an acquired condition that is not caused by a genetic defect. This is a rarer and lesser-known condition in which people with previously normal haemostasis (clotting) develop autoantibodies (inhibitors) against clotting factors, most frequently factor VIII (Kruse-Jarres et al, 2017). It occurs mostly in frail, older people but can occasionally be associated with pregnancy, particularly occurring post partum, and with autoimmune disease in younger people. In around half of all cases, it has no known cause; in others, it is associated with malignancy, autoimmune disorders and other conditions (Kruse-Jarres et al, 2017; Bit.ly/NORD-HemophiliaA).

People with acquired haemophilia develop potentially life-threatening complications associated with abnormal, uncontrolled bleeding that is often spontaneous and severe (Kruse-Jarres et al, 2017). This includes bleeding into the muscles, skin and soft tissue, as well as during surgery or after trauma. Symptoms of acquired haemophilia include nosebleeds, bruising, haematomas (solid swellings of congealed blood), blood in the urine and gastrointestinal or urogenital bleeding (Bit.ly/NORDHemophiliaA).

Acquired haemophilia in frail, older people can be challenging to manage and percentage of circulating factor in the blood compared with normal levels:

- Severe (less than 1%) – this causes frequent bleeding, often for no apparent reason, most commonly in the joints or muscles;
- Moderate (1% to 5%) – this is associated with less-frequent bleeding, which is usually not spontaneous but can be prolonged after injury, surgery or a dental procedure;
- Mild (6% to 40%) – this causes bleeding that is usually only prolonged after injury or surgery and may never be spontaneous (Srivastava et al, 2020; Makris et al, 2018; The Haemophilia Society, 2017).

Haemorrhage is a main cause of morbidity and death in people with haemophilia, although infectious diseases from contaminated blood products have featured prominently in recent decades, particularly in people treated with clotting factors before 1985 (Darby et al, 1995). Without treatment, the prognosis is poor; however, the development of recombinant clotting-factor replacement therapies and non-factor replacement therapy has recently improved the outlook for patients (Khair, 2019).

**Clinical features**

Haemophilia A and B have the same clinical features, although treatment depends on which clotting factor is missing and the severity of symptoms (The Haemophilia Society, 2017). There are three levels of severity (phenotypes), defined by the

Legs of an 18-year-old with haemophilia and bleeding in the knee joint after surgery

Bleeding in the knee joint can occur spontaneously in patients with haemophilia is associated with a high mortality risk due to underlying comorbidities, bleeding or treatment. The main treatment is haemostatic management and eradicating inhibitors; recommendations for management are provided in Kruse-Jarres et al’s (2017) consensus paper. Although acquired haemophilia is estimated to account for at least a third of all haemophilia cases, it is likely that it is underdiagnosed and misdiagnosed in real-world clinical practice (Kruse-Jarres et al, 2017).

**Diagnosis**

When there is a family history of haemophilia, the disorder will be suspected and diagnosed before, at, or soon after birth. If there is no family history or the family is unaware of it (for example, if recent generations have only included female carriers), diagnosis will only be made when bleeding...
Prophylactically – replacement therapy is given regularly to prevent bleeding and long-term damage caused by bleeding into joints and muscles, and bleeding from minor injuries. This is mainly used for children and some adults with severe haemophilia and some with moderate haemophilia who have frequent bleeding problems;

On demand – replacement therapy is given to stop bleeding when it occurs. This is generally used for people with mild-to-moderate haemophilia, very young children and some adults with severe haemophilia who choose not to take prophylaxis (The Haemophilia Society, 2017).

International guidelines from the WFH (2013) recommend prophylaxis for severe haemophilia, although patients who dislike regular infusions may prefer treatment on demand (Bit.ly/haemophiliaTreat). Prophylaxis is especially important in children, because their articular cartilage is more vulnerable to permanent damage; it is usually started at around the age of one, after the first or second joint bleed (Khair, 2019). Infusions are usually three times a week for haemophilia A, and twice a week for haemophilia B; patients and carers learn to administer them at home. For very young children, or children whose veins are difficult to access, this can often necessitate a central venous access device (Khair, 2019).

Minor bleeds can often be treated at home, but acute bleeds need to be managed in hospital; the treatment for acute bleeds is outlined in Box 2. More than one infusion may be needed, depending on the site and severity of the bleed (The Haemophilia Society, 2017). People with mild-to-moderate haemophilia can sometimes bleed as much as those with severe haemophilia, who usually have their bleeding controlled by prophylaxis. However, patients having prophylaxis may still have bleeds that require extra factor infusions, particularly after injuries.

People with haemophilia who are about to undergo a surgical or dental procedure may need extra treatment, including factor infusions or other haemostatic agents.

Extended half-life treatments
A newer type of factor replacement therapy uses extended half-life factors, in which the factor molecule has been modified by the addition of stabilising molecules, which extend the half-life of the infused factor. These can last longer in the bloodstream than standard factor, so
prophylactic infusions can be given less frequently:
- Twice a week for haemophilia A;
- Weekly or fortnightly for haemophilia B.

The reduced frequency of infusions and increased levels of factor can decrease the treatment burden (Khair et al, 2019). Bleeds can also be controlled more quickly, often requiring only a single infusion.

Emicizumab
Emicizumab is a non-factor replacement therapy used for haemophilia A. It is injected subcutaneously to prevent or reduce bleeding episodes, but is not used to treat bleeding (Bit.ly/HaemophiliaNonFactor). The first commercially available product in a new generation of bypassing agents, it is a monoclonal antibody that works by bridging activated factor IX and X to restore the function of the missing activated factor VIII needed for effective blood clotting (Bit.ly/NICEemicizumab).

Emicizumab is available in the UK for people with severe haemophilia A with and without antibodies. It can revolutionise care: treatment is a subcutaneous injection, given once weekly for the first four weeks, and then weekly, fortnightly or every four weeks in the maintenance phase (Khair, 2019). As more people with haemophilia survive into old age, emicizumab is also useful for treating people who struggle with repeated venous access or who are no longer able to self-infuse, such as those in residential care homes who have congenital haemophilia.

In the UK, only a haemophilia comprehensive care centre can prescribe emicizumab and care is needed when co-infusing it with other treatments because of potential thrombotic side-effects (Khair, 2019).

Desmopressin
Desmopressin stimulates the release of von Willebrand factor from endothelial cells by acting on the V2 receptor; it is used to:
- Control minor bleeding episodes in people with milder forms of haemophilia;
- Help prevent bleeding associated with minor operations, including dentistry (Haemophilia Society, 2017).

It is injected subcutaneously but can also be delivered intravenously or as a nasal spray. Side-effects include hyponatraemia (low sodium levels) and seizures; fluid retention can also occur, and patients are asked to restrict fluids after treatment. Its use is not recommended for children aged under two years (Khair, 2019).

Transaxamic acid
This drug helps hold a clot in place once it has formed, and is helpful for mouth bleeds, nosebleeds and heavy menstruation (The Haemophilia Society, 2017). Given as a liquid, tablet or mouthwash, it is often used with clotting factor or desmopressin.

**“In] the contaminated blood scandal around 5,000 people with haemophilia and other blood disorders in the UK were injected with contaminated blood products”**

Complications
Haemophilia can have many short- and long-term complications; the main ones are discussed below.

**Inhibitors**
The development of antibodies (inhibitors) to clotting factor replacement therapy is the main complication of contemporary care; it occurs in around 14% of people with haemophilia A and 2% of those with haemophilia B (Khair, 2019). Inhibitors prevent clotting factor from working, mainly affecting people with severe haemophilia A.

When they arise, inhibitors commonly develop during the first 30 treatment days, and usually in the first 20 days. This means that, in people with severe haemophilia A, inhibitors generally appear in childhood, while in those with mild-to-moderate forms they tend to develop later in life (Bit.ly/HaemophiliaBleeding). Periodic screening for inhibitors should be part of haemophilia care; patients also need screening before any surgical procedure, including dental work.

Treatment of inhibitors includes:
- Attempting to eradicate the underlying antibody by building up immune tolerance through regular exposure to high doses of coagulation factor (immune tolerance induction);
- Treating bleeding episodes with infusions of bypassing agents factor VIIIa or activated prothrombin complex concentrate (Khair, 2019);
- Prophylaxis with emicizumab.

**Joint and muscle damage**
Damage to muscles and joints caused by serious or repeated bleeding is a main cause of morbidity in severe haemophilia, and can result in chronic joint disease, functional impairment and disability (Khair, 2019). Bleeding into joints is a particular problem, as it can damage the synovium (joint lining), cartilage and surrounding tendons and tissues, leading to arthritic pain and reduced joint movement and strength (Nacca et al, 2017).

Older people with haemophilia are likely to have joint damage, due to limited access to treatment when they were young, and often require orthopaedic surgery. Prophylaxis and prompt treatment of bleeds means children often now reach skeletal maturity with well-preserved joint function, although most people with severe haemophilia still experience joint problems at some stage. Hanley et al’s (2017) best-practice guidance for managing acute joint bleeds and chronic synovitis was published by the United Kingdom Haemophilia Centre Doctors’ Organisation.

Infection-related complications
Improved blood donor screening in manufacturing plasma-derived products and the switch to recombinant clotting factors has virtually eliminated the risk of transfusion-transmitted infections in the UK. However, there are still patients living with the long-term health effects of transfusion-transmitted viruses and their treatments, and the psychological effect on the families involved is only just being acknowledged (Bit.ly/THSMHSupport).

**Life-threatening complications**
The most critical life-threatening complications of haemophilia are:
- Bleeding in the skull;
- Haemorrhages in the soft tissue around airways or other internal organs.

Spontaneous ICH occurs in up to 8% of people with haemophilia, and around 30% of those will die from it (Hegde et al, 2016).

**Patient care**
All UK patients diagnosed with haemophilia should be registered with a haemophilia comprehensive care centre that provides core multidisciplinary care from doctors, nurses, physiotherapists, psychosocial carers and coagulation laboratory staff, who liaise with non-haemophilia specialists – including dentists and surgeons – when necessary. People with haemophilia carry a bleeding disorder information card and have all aspects of their care coordinated by their specialist haemophilia team, even when care is delivered in other settings (Srivastava et al, 2020).
Clinical Practice Review

The nurse’s role
Clinical nurse specialists in haemophilia practice at advanced levels have a pivotal role in comprehensive care as part of the multidisciplinary team, including promoting evidence-based care, advocacy and self-management skills for people with haemophilia (Khair et al, 2014). The changing role of the specialist nurse is discussed in detail by Khair (2021).

Nurses and other health professionals should liaise with the specialist haemophilia team about all aspects of care for patients with haemophilia, regardless of the care setting or how patients present. The increase in modified factor products and alternative treatments means not all patients are treated with standard clotting factors (VIII and IX), and the patient’s specialist haemophilia team can advise.

In haemophilia, bleeding is often internal, and nurses need to be able to recognise the signs. In addition, it is important to be aware that older people with mild-to-moderate haemophilia may not bleed often enough to develop the skills to self-treat at home, or may be reluctant to learn; this means they might present more often at hospital with bleeds than people who have severe haemophilia.

Patients with haemophilia who are on surgical wards will need infusions to prevent potentially life-threatening bleeds. Pain management is also more complex – non-steroid anti-inflammatory drugs cannot be used because they make bleeding worse. Nurses caring for patients with haemophilia must refer to the specialist haemophilia team.

Toddlers and young children presenting with problems in weight-bearing joints can be in severe pain; if a child is distressed, screaming and unwilling to use the affected limb, nurses should not attempt to pull it straight to demonstrate mobility. Any child with haemophilia presenting at the emergency department with a head injury should be fast-tracked and not go through the usual triage.

Children who have severe haemophilia may need a central venous access device for prophylactic infusions; this can pose an infection risk and care may fall under that of the community paediatric team. A history of bruising and bleeds in children who have not been diagnosed with haemophilia – particularly when there is no family history – can raise safeguarding issues; this is a main source of stress for parents when their child is first diagnosed (The Haemophilia Society, 2018). However, it is also important to be aware that a diagnosis of haemophilia does not exclude the possibility of non-accidental injury and, if there is concern, usual child-protection procedures should be followed.

“All UK patients diagnosed with haemophilia should be registered with a haemophilia comprehensive care centre that provides core multidisciplinary care”

Moving forward
Current treatment with prophylactic factor replacement in severe haemophilia reduces the frequency of bleeding and improves patients’ quality of life. Use of modified factor products and alternative treatment options is reducing the burden of treatment for some patients with haemophilia, and has the potential to improve patient adherence and outcomes, although some challenges remain (Nogami and Shima, 2019).

Like emicizumab, which disrupts coagulation, there are other molecules in early clinical trials that may impact on future haemophilia care. Although these are, so far, only in trials in adults, they show some promise for other subcutaneous treatment.

Gene therapy may provide another alternative. This works by delivering the gene to make the missing factor, although the person will still be a carrier of the mutated gene (Bit.ly/HaemophiliaGene). Clinical trials for gene therapy in severe haemophilia have been extremely successful, and one company has applied to the European Medicines Agency and US Food and Drug Administration for licence for routine clinical use. All this adds up to a brighter outlook for people with haemophilia; however, those who live for longer with the disease will present with new and different challenges and it will be important to understand how to manage haemophilia in frail, older people with significant comorbidities. NT

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