

Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management

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Abstract

Mild haemophilia is defined by factor levels between 0.05 and 0.40 IU/mL and is characterised by traumatic bleeds. Major issues associated with mild haemophilia are that it may not present for many years after birth, and that awareness, even within families, may be low. Methodological problems exist in diagnosis, such as inconsistencies in results obtained from different assays used to measure factor levels in mild haemophilia. Advances in genetic testing provide insight into diagnosis as well as the likelihood of inhibitor development, which is not uncommon in patients with mild or moderate haemophilia and can increase morbidity. The management of patients with mild haemophilia is a challenge. This review includes suggestions around formulating treatment plans for these patients, encompassing the full spectrum from clinical care of the newly diagnosed neonate to that of the ageing patient with multiple comorbidities. Management strategies consider not only the vast differences in these patients' needs, but also risks of inhibitor development and approaches to optimally engage patients.

Keywords: mild haemophilia, factor VIII, factor IX, inhibitors, practical recommendations.

An introduction to mild haemophilia

Haemophilia is an inherited bleeding disorder most commonly caused by deficiencies of the coagulation factors VIII (FVIII; haemophilia A) and IX (FIX; haemophilia B)¹. As an X-linked recessive disorder, haemophilia predominantly affects men (who have only one X chromosome), but women (with two X chromosomes) can also be affected². Women are more commonly heterozygote carriers with no, or mild, bleeding symptoms. In rare cases, women can have

haemophilia; for example, as a result of X-chromosome inactivation (lyonisation phenomenon), partly or completely lacking an X chromosome (Turner's syndrome), or if both parents carry the abnormal gene^{2,3}.

FVIII and FIX plasma concentrations determine bleeding tendency, which is classified as mild, moderate, or severe¹. The definition of mild haemophilia (factor levels >0.05-0.40 IU/mL; 5-40% of normal) is broad compared with that of the moderate (0.01-0.05 IU/mL; 1-5% of normal) and severe (<0.01 IU/mL; <1% of normal) forms⁴.

Generally, mild haemophilia is only diagnosed when an injury or medical intervention results in prolonged bleeding. Thereafter, management of a patient may be relatively neglected as they do not usually experience spontaneous bleeds and, therefore, it may be perceived that they need little in the way of regular medical care. There is a paucity of literature devoted to mild haemophilia; clinical evidence and guidance are largely extrapolated from data derived from severe haemophilia, in part because patients with mild haemophilia are ineligible for many clinical trials. Although there can be complacency around treating mild haemophilia, recent data show that inhibitor development in patients with mild or moderate haemophilia is not uncommon and can increase the severity of bleeding episodes⁵. Mild haemophilia can also negatively affect health-related quality of life, particularly when it is associated with bleed-related joint damage.

The life expectancy of patients with mild haemophilia is close to that of the normal population⁶. For example, in a Swedish cohort followed from 1960 to 1980, individuals with mild haemophilia had a life expectancy of 72.0 years, compared with 75.5

years for the normal population⁷. In addition, data from the Netherlands show a life expectancy of 73 years for subjects with mild haemophilia and 76 years for the normal population⁸. The life expectancy of patients with mild haemophilia leads to considerations regarding their management, such as comorbidities and polypharmacy, as they age.

In this article we review the symptomatology, epidemiology, and genetics of mild haemophilia and discuss diagnostic and management challenges, from the neonate to the elderly patient. The latest information on inhibitor prevalence in this disease and mutations that predispose to inhibitor development is summarised, and we provide practical recommendations for the management of mild haemophilia (Table I).

Table I - Ten principles of care for the patient with mild haemophilia.

1)	Diagnosis Measure factor levels to detect more mild haemophilia cases - both chromogenic and one-stage assays should be used.
2)	Diagnosis Genotype all patients, if possible, to confirm the diagnosis of haemophilia and to differentiate from other disorders associated with low factor levels.
3)	Genetics Mutation screening should ideally be performed for all new cases and some context to the findings should be provided to the physician; for example, has the mutation been recorded previously? Is it likely to be causative? Is it associated with an increased incidence of inhibitor development, discrepancy between one-/two- stage assays or response to DDAVP?
4)	Monitoring Factor levels should be monitored before and within 6 weeks of factor replacement for surgery.
5)	Monitoring Keep records of patient's lifetime exposure to FVIII, as this will influence their risk of inhibitor development as well as guide diagnosis and treatment should inhibitors develop later in life.
6)	Management in neonates Diagnosis is challenging; investigate all instances of unusual bleeding in the neonate.
7)	Management in adults In adult patients with mild haemophilia A, minor bleeds can be treated with DDAVP; in haemophilia B, bleeds can be treated with anti-fibrinolytic therapy or by factor replacement. Use DDAVP where possible to avoid factor exposure. Factor replacement should be used to treat major bleeding episodes during major surgical procedures.
8)	Management in older patients Recommendations to combat increasing orthopaedic issues in older patients with mild haemophilia include greater training for self-infusion prior to joint surgery, more domiciliary care, and a broader scope for joint orthopaedic clinics.
9)	Management in older patients Given the increased risk of hypertension (although the risk is greater with more severe disease), blood pressure monitoring should be routine in patients with mild haemophilia aged ≥ 30 years.
10)	Management in symptomatic carriers Many haemophilia carriers with normal factor levels have bleeding symptoms; treat them as you would someone with mild haemophilia.

DDAVP: desmopressin acetate; FVIII: factor VIII.

Clinical presentation

Frequent spontaneous bleeding, common in severe haemophilia, is rare in mild haemophilia. Indeed, patients may not bleed excessively unless they experience trauma or undergo a surgical intervention^{1,4,9}. Consequently, one of the dangers of mild haemophilia is that patients may delay seeking treatment following injuries because bleeding occurs rarely and is not always recognised. It is therefore important for people with mild haemophilia to be able to identify the symptoms and clinical presentation, and to clearly understand when to seek medical assistance.

Mild haemophilia may be diagnosed because of a family medical history of haemophilia (which is absent in a third of people with haemophilia) or following a bleeding episode^{1,10}. A diagnosis of mild haemophilia is frequently made later in life than that of more severe forms of the disease^{9,10}. In a French cohort of 599 individuals born with haemophilia between 1980 and 1994, the median age at diagnosis of mild haemophilia was 28.6 months compared with 5.8 months for severe haemophilia and 9.0 months for the moderate form¹¹. Later data (1990-1999) from 100 Swedish patients showed a significantly older age at first bleed for patients with mild haemophilia (median 6.5 years, range 3.8-18.2 years) compared with that for patients with moderate (median 4.0 years, range 1.6-7.0 years) or severe (median 1.0 years, range 0.5-2.0 years) haemophilia¹².

Accurate assessment of the global epidemiology of mild haemophilia is challenging. Proportions of patients with mild haemophilia vary widely between countries, mostly related to under-diagnosis in countries with more limited resources due, in part, to inadequate medical infrastructures and the fact that this disease is not a government priority^{1,10}. According to the World Federation of Hemophilia (WFH) 2014 Annual Report, in middle-income countries (gross national income per capita [GNI] in US dollars, \$ 4,126-\$ 12,735), 23% of male haemophilia A patients have mild disease; however, this figure is 37% in high-income countries (GNI $\geq$ \$ 12,736) and 9% in low-income countries (GNI $<$ \$ 4,125)¹³. For women, this trend is even more marked, with 88% of cases of haemophilia A being diagnosed as mild in the highest-income countries compared to 9% in the lowest-income countries; the trend for haemophilia B is similar¹³. In a survey of all known people with haemophilia in Sweden, a country considered to have a well-characterised haemophilia population, 54% of patients had mild disease⁷.

Diagnostic challenges

Mild haemophilia is often under-diagnosed; patients who are unaware that they have haemophilia may ignore

symptoms until they become severe or complications have developed, leading to a more challenging clinical scenario. In the case of familial haemophilia, screening the members of affected families can help address this challenge, as there can be clusters of patients with mild haemophilia within these families.

The initial laboratory investigation of a patient suspected of having a bleeding disorder includes coagulation tests such as the activated partial thromboplastin time (aPTT) and prothrombin time (PT)^{4,14}. Most aPTT screening tests should be prolonged at factor levels <0.3 IU/mL, thereby indicating underlying haemophilia A or B⁴. However, the aPTT may not reveal underlying haemophilia because of different sensitivities of reagents to FVIII/FIX levels¹⁵. Therefore, if there is a suspicion of haemophilia, a factor assay should be performed, even if the aPTT is normal. However, neither the one-stage nor the chromogenic assay always accurately reflects FVIII activity in individuals with mild haemophilia¹⁶.

The one-stage assay is predominant worldwide, due largely to its simplicity and low cost; however, it is prone to substantial variability because of differences in the reagents and instrumentation used across centres¹⁷. Strategies to improve the reliability of the one-stage assay have been explored, including the use of a recombinant FVIII reference standard to try and counteract underestimation of FVIII levels, which is often observed with a plasma standard¹⁸. The chromogenic assay was developed from the two-stage assay and has now largely superseded it¹⁹. Despite the greater expense of the chromogenic assay vs the one-stage assay, there is increasing recognition of the former's advantages. For example, the chromogenic assay is often more sensitive at low FVIII levels than the one-stage assay, and largely unaffected by modifications to the recombinant FVIII molecule or the presence of interferences such as heparin and lipids^{16,20}. Uptake of the chromogenic assay is therefore increasing¹⁶.

In the case of mild haemophilia A, in approximately 30% of patients the level of measured FVIII varies according to which of the three assays is used, leading to misdiagnosis or even lack of diagnosis^{4,21-23}. Such assay discrepancies in haemophilia A occur in two ways²³: lower two-stage discrepancy (in which reduced factor levels are observed with the two-stage or chromogenic assay vs the one-stage assay), and lower one-stage discrepancy (in which reduced factor levels are observed with the one-stage assay vs the two-stage or chromogenic assay). In general, in mild haemophilia A lower two-stage discrepancy is more common than lower one-stage discrepancy^{19,22}. Recently, lower one-stage discrepancy was reported in mild haemophilia B, which was observed for 24% of patients analysed²⁴. Assay discrepancy can be

associated with certain *F8* and *F9* gene mutations^{19,23,24}; this is discussed in detail in the next section. There is no universal consensus as to whether the one-stage or chromogenic assay should be used to diagnose patients with mild haemophilia A, but in light of the discrepancies between the assays, the WFH and others recommend that both assays are used^{4,21,22,25}.

Other challenges include lack of diagnostic experience or variable access to the laboratory equipment or services required for accurate identification¹⁴. Furthermore, there can be large inter-laboratory variability between the findings of the tests, differences in factor levels due to physiological changes (examples include stress, acute phase reaction, and blood group), overlap with the normal range of FVIII/FIX levels, and increasing levels of FVIII in the elderly and during pregnancy.

It is important to assess bleeds in addition to measuring factor levels; for example, residual FVIII concentration does not always correlate with joint bleeding in patients with mild or moderate haemophilia A²⁶. Scoring systems are available to help estimate bleeding risk²⁷.

Genetics

Haemophilias are caused by *F8* or *F9* gene mutations; the type of mutation can predict disease severity^{16,28-30}. Molecular genotyping can therefore confirm the diagnosis of haemophilia as well as help to differentiate haemophilia from bleeding disorders that may have a similar phenotype, such as von Willebrand's disease Normandy. Genetic testing can also trace family history and inheritance patterns of the disease, and help inform particular aspects such as assay disparity in mild haemophilia A or likelihood of inhibitor development^{28,29}.

Mutations, including point mutations, deletions, and insertions, can cause haemophilia^{28,29}. Given the advances in molecular genetic methodologies, approximately 97% of mutations in these diseases can now be identified^{28,29}. Missense point mutations are the most common type of mutation occurring in mild haemophilia A and B^{29,31-33}. Not all mutations are necessarily causative; they can be harmless polymorphisms²⁸. Several options are available to determine whether a detected point mutation in *F8* or *F9* is causal: (i) consultation of an international database to see whether the mutation has been previously reported to cause haemophilia; options include the FVIII Variant Database (www.factorviii-db.org), CDC Hemophilia A Mutation Project (CHAMP, www.cdc.gov/ncbddd/hemophilia/champs.html), or Factor IX Variant Database (www.factorix.org/); (ii) use a mutation model, such as SIFT (<http://sift.jcvi.org/>) or PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2/>), to predict whether the point mutation may affect protein function; and (iii) produce the recombinant FVIII or recombinant FIX protein and conduct *in vitro* tests.

Factor assay discrepancies observed in this disease (discussed previously) appear to be related to certain *F8* and *F9* gene mutations^{19,23,24}. The *F8* mutation p.Arg1985Gln has been tentatively linked to lower two-stage discrepancy while p.Tyr365Cys appears to be linked to lower one-stage discrepancy²³. The *F9* mutation p.Arg191His is also reported to be linked to lower one-stage discrepancy²⁴. FVIII circulates bound to von Willebrand factor, an interaction that is crucial for the stability of FVIII. Consequently, FVIII C1-domain mutations that result in reduced binding to von Willebrand factor are another cause of mild/moderate haemophilia A³⁴. Some mutations are associated with an increase in inhibitor incidence, discussed further below³⁵.

It is important to perform mutation screening for all new cases of haemophilia, if possible. When screening results are received from the genetic testing centre, additional information that can place the genetic findings into context should be provided (and requested if not provided). This may include whether the mutation has been recorded previously, the probability that it is causative, whether the mutation has been reported to be associated with an increased incidence of inhibitor development, whether the mutation is known to cause discrepancies in one- or two-stage assays, or the possible impact of the mutation on the response to desmopressin acetate (DDAVP).

Management considerations in mild haemophilia

DDAVP raises FVIII levels by three to six times baseline levels and can be used to treat minor bleeding episodes in most patients with mild haemophilia A^{4,36-38}. Genetic mutation analysis may assist with predicting DDAVP responsiveness. DDAVP has no effect on FIX levels, and so is ineffective as a therapy for haemophilia B. Antifibrinolytic therapy, such as tranexamic acid, is effective alone or combined with DDAVP for the treatment of mucosal bleeds or oral/dental procedures in haemophilia A and B^{4,37}.

For haemophilia B, and for more severe bleeds in haemophilia A or in those patients unresponsive to DDAVP, replacement therapy with plasma-derived or recombinant FVIII or FIX is the treatment of choice^{4,37,39}. Factor replacement should also be used to treat major bleeding episodes during major surgical procedures³⁷. The WFH guidelines recommend using viral-inactivated plasma-derived or recombinant concentrates to treat haemophilia, in preference to cryoprecipitate or fresh frozen plasma⁴. Prophylaxis is an important part of haemophilia management, but is generally not required by patients with mild disease⁴.

It is important to be aware that certain analgesics affect haemostasis and may, therefore, need to be avoided⁴. These include acetylsalicylic acid and

non-steroidal anti-inflammatory drugs; paracetamol/acetaminophen is an appropriate alternative for pain relief. Future therapeutic options for haemophilia are in development. Gene therapy research has been ongoing for many years and a 2014 study reported the successful conversion of severe haemophilia B to mild or moderate disease in ten adult males⁴⁰. As one of the outcomes of this research is to achieve a mild haemophilia phenotype, this approach may not be practical in patients with mild disease.

Management of symptomatic carriers

Females are predominantly carriers of haemophilia². Carriers are detected by DNA analysis, commonly mutation analysis². Indeed, in the 1980s and 1990s, genetic analysis of *F8* was primarily focussed on carrier detection²⁸. Most carriers are asymptomatic, having sufficient clotting factor (>60% of normal) to control bleeding². Some carriers will demonstrate haemophilia symptoms; haemophilia A carriers may have reduced joint range of motion compared with those with no haemophilia⁴¹ and report reduced health-related quality of life, particularly for the components of pain and general health⁴².

A large study by Plug *et al.* reported that in women who had been tested for carriership of haemophilia, the median clotting factor level was 0.60 IU/mL (range, 0.05-2.19 IU/mL) for carriers and 1.02 IU/mL (range, 0.45-3.28 IU/mL) for non-carriers⁴³. Plug *et al.* found an increased bleeding risk in women with clotting factor levels between 0.41 and 0.60 IU/mL⁴³. Other studies have also shown an increased bleeding tendency in carriers with average factor levels of 0.48-0.82 IU/mL⁴⁴⁻⁴⁶. As demonstrated in the study by Plug *et al.*, carriers of haemophilia exhibit a wide range of clotting factor levels, from very low, resembling affected males, to the upper limit of normal⁴³. This may be due to lyonisation, a process whereby expression of one of the two X chromosomes is randomly suppressed^{2,4}. However, the X-inactivation pattern in peripheral blood cells does not always explain the ranges in factor levels⁴⁷. Although factor levels are reduced in carriers, many blood parameters and coagulation tests are in the normal range, and studies show that neither clotting factor level nor thrombin generation is a good predictor of bleeding in carriers of haemophilia A and B^{44,48}. An association between phenotype and genotype was, however, reported among 46 carriers of haemophilia A in a single centre: severity of bleeding tendency correlated with the type of *F8* gene mutation ($p < 0.05$) and with the severity of haemophilia in affected male relatives ($p < 0.0005$)⁴⁹. For detection of carriers, we recommend molecular analysis alongside a haemophilia carrier testing algorithm published by the Mayo Clinic⁵⁰.

Bleeding in carriers can be treated with DDAVP, tranexamic acid, factor concentrates, or oral contraceptive, and depends upon the factor levels and type of bleed. In carriers planning a family, pre-conception counselling and confirmation of haemophilia carrier status prior to conception are recommended. Pregnancy causes changes in factor levels (correction of FVIII levels in haemophilia A carriers but little change in FIX levels in haemophilia B); therefore factor levels should be checked at 28 and 34 weeks of gestation⁵¹. The risk of bleeding from invasive procedures and the risk of serious post-partum bleeding complications are both increased with factor levels <0.5 IU/mL and prophylaxis should be arranged⁵¹. Carriers with low FVIII or FIX levels (in the region of 0.05–0.3 IU/mL) are symptomatic and should be treated in the same way as those with mild haemophilia⁵¹. As with most arbitrary thresholds, there are overlaps among the definitions of those with mild haemophilia, symptomatic carriers, and asymptomatic carriers. The thresholds mentioned herein should, therefore, be considered as guidelines and all patients with bleeding symptoms should be treated as having mild haemophilia, even if their factor levels are outside the prescribed ranges.

Pregnancy and the diagnosis and management of the neonate

A female carrier's decision to start a family is a time when medical advice should be sought, both for managing the pregnancy itself and for care of the neonate.

In the absence of a family history, the diagnosis of haemophilia during the neonatal period is a particular challenge, with the disorder often only being identified upon investigation of bleeding events. A serious event such as intracranial haemorrhage may be the first indication of coagulation factor deficiency and haemophilia⁵². In general, the diagnosis is difficult because factor levels are often within normal ranges and bleeding events related to the neonate during delivery may not be considered abnormal⁵². Babies who should be tested after delivery are those with a family history of haemophilia, those with carrier mothers, and those with bleeding symptoms at birth. If a child is not diagnosed with haemophilia during the neonatal period, the family might notice unusual bruising once the child begins standing or crawling. As FVIII and FIX do not cross the placenta, factor levels can be determined using umbilical cord blood⁵³. Haemophilia A can be diagnosed at birth, but mild haemophilia B cannot be diagnosed at this time as FIX levels do not reach adult values until day 90⁵³. As the partial thromboplastin time and aPTT can be within normal ranges in mild haemophilia, genetic testing should be performed. However, genetic testing is not performed for carrier females in many countries

before 18 years of age, when the patient can make the decision to undergo testing. The potential for parental revelations must also be kept in mind.

Neonates with mild haemophilia A should not be treated with DDAVP because of the risk of dilutional hyponatraemia with consequent seizures⁵⁴. Possible treatments for neonates are factor concentrates, fibrinolysis inhibitors, and tranexamic acid, depending on the particular circumstance; neonatal haemostasis is complex, being strongly influenced by age⁵⁵, and treatment decisions are not straightforward. Along with routine vaccinations, babies with haemophilia should also receive vaccinations against hepatitis A and B, as the risk of contamination during routine blood transfusions still exists. While inhibitors can occur in mild haemophilia, they do not normally develop in the neonate and, in children with haemophilia A, they usually occur only after intensive exposure to factor concentrates⁵⁶. It is of the utmost importance to educate patients about their child's mild haemophilia, to keep them informed and updated on their condition through regular visits, and to implement appropriate diagnostic tools and treatment modalities.

Management of the ageing patient

As mentioned earlier, patients with mild haemophilia have a good life expectancy⁶. The ageing patient with mild haemophilia is thus important, considering the global ageing of the population. In patients aged >60 years, mild haemophilia will tend to predominate over moderate or severe haemophilia and yet it remains under-diagnosed. Even if diagnosed, many patients will encounter no haemophilia-related issues until they experience comorbidities; their first exposure to medical care can often be in the Accident and Emergency department. These older patients may have little knowledge of their mild haemophilia and may not even mention it to the healthcare professionals treating them. The WFH guidelines emphasise the importance of appropriate management of comorbidities in ageing patients with haemophilia because the comorbidities may accentuate problems associated with haemophilia and affect quality of life⁴.

Orthopaedic care will be an important issue for the older population, as the number of hip and knee replacements is expected to increase markedly in the general population over the next 15 years⁵⁷. While patients with mild disease suffer less from haemophilic arthropathy⁵⁸, it may complicate degenerative joint disease and the use of non-steroidal anti-inflammatory drugs may be problematic. Recommendations to combat increasing orthopaedic issues in older patients with mild haemophilia include greater training for self-infusion of factor concentrates prior to joint surgery and more

domiciliary care. Moreover, the management of falls in the elderly should not be overlooked: 30% of those aged >65 years fall annually, and falls are the leading cause of hip fractures⁵⁹. The impact of mild haemophilia on bleeding from falls will depend upon baseline factor levels and bleeding phenotype. Greater proactivity from patients and physicians may be required to prevent the most common causes of secondary osteoarthritis, such as obesity, trauma, gout, and diabetes.

Cardiovascular disease is very common in the elderly. In the past, it was assumed that haemophilia provided protection against thrombotic events⁶⁰, but in older patients it is important to consider comorbidities such as atherosclerosis, acute coronary syndrome and atrial fibrillation, and whether the patient has undergone stenting. Currently there is little guidance on how patients with haemophilia with cardiovascular disease should be managed. Mannucci *et al.* offered advice on managing acute coronary syndrome and non-valvular atrial fibrillation in patients with haemophilia⁶¹. They suggested prophylactic FVIII or FIX during dual antiplatelet therapy to maintain a factor level of >30%⁶¹. For individuals with mild bleeds who have non-valvular atrial fibrillation, vitamin K antagonists or low-dose aspirin were proposed, depending on the patient's stroke risk⁶¹.

There is also a growing risk of intracranial haemorrhage with increasing age⁶², and mortality is high⁶³. The first choice for investigating a potential bleed is normally via a computed tomography scan, but the management of intracranial haemorrhage is not well defined. Chronic hypertension, which is common in the elderly, is an important risk factor for primary intracranial haemorrhage and prevention of such haemorrhages in older patients with haemophilia may involve blood pressure control and management of cardiovascular risk factors⁶⁴. Given the increased risk of hypertension (although the risk is greater in patients with more severe haemophilia disease), blood pressure monitoring should be routine in patients with mild haemophilia aged over 30 years⁶⁵. The risk of chronic subdural haematoma increases with age and falls, and it is likely that patients with mild haemophilia are at greater risk than the normal population. In a study of patients with severe-moderate (n=31) and mild (n=18) haemophilia A, cognitive dysfunction and cerebral micro-bleeds were common⁶⁶.

Considerations about the management of mild haemophilia in ageing patients include increased interaction with the haemophilia team to improve awareness and teach required skills, such as self-injection techniques for those patients requiring factor replacement. In this regard, telephone clinics may be a valuable option in some settings. In addition, regular monitoring of factor levels - while understanding that levels will increase with age - should also be encouraged.

Inhibitor development in mild haemophilia

Antibodies that neutralise the haemostatic effects of clotting factors occur in mild haemophilia⁴, and generally manifest as a worsening bleeding pattern that is akin to that observed in severe or acquired haemophilia⁵. Inhibitors are more common in haemophilia A than haemophilia B; in patients with mild to moderate haemophilia A, the lifetime risk of developing inhibitors is 5-10%, whereas inhibitors to FIX develop in 1.5-3.0% of patients with all severities of haemophilia B^{4,67}. Therefore, fewer data are available in the literature for haemophilia B and the examples that follow relate to inhibitors of FVIII⁶⁷.

Inhibitor development can occur later in life and is less common in mild haemophilia A than in severe haemophilia⁵. In a 1998 study, the annual incidence of inhibitor formation in a small UK population was calculated at 0.84 per 1,000 patients with mild haemophilia A, compared with 3.5 per 1,000 patients with severe haemophilia A⁶⁸. A more recent study, published in 2003, calculated the incidence of inhibitors in a population with mild haemophilia A at 7.4% overall, but at 14% in those previously treated with replacement therapy⁵⁶. It has been speculated that improved diagnosis and increased use of FVIII products have increased the reported incidence of inhibitor formation in mild haemophilia A⁵. Along with age, intensive exposure to FVIII is also a risk factor for inhibitor development in patients with mild haemophilia^{69,70}. It is therefore useful to keep records of a patient's exposure to FVIII throughout their life.

In addition to treatment-related factors, other genetic and non-genetic risk factors influence the development of inhibitors^{31,56,71}. These include familial predisposition, mutation type, human leucocyte antigen class II polymorphism, immunological factors, and environmental factors such as surgery and trauma. Certain *F8* gene missense mutations contribute to the incidence of inhibitors in patients with mild/moderate haemophilia, sometimes up to the level observed in patients with severe disease^{31,72}. This association with *F8* mutations was demonstrated in a cohort study of 128 patients with mild haemophilia A, and ten patients with moderate haemophilia A⁷¹. Genotyping revealed the Arg593Cys missense mutation in 52 patients (38%); of ten patients who developed inhibitors, eight carried the Arg593Cys mutation⁷¹. The INSIGHT study, a registry involving 34 haemophilia treatment centres across 11 countries, from 1980 to 2010, investigated this link with missense mutations further³⁵. Among 1,112 patients with non-severe haemophilia A, 59 developed an inhibitor with a cumulative incidence of 5.3% after a median of 28 exposure days³⁵. Inhibitor risk at 50 exposure days was 6.7% and at 100 exposure days was 13.3%³⁵. Among

a total of 214 different *F8* missense mutations, 19 were associated with inhibitor development³⁵; information on these mutations should be available for the genetic centres to ensure that appropriate action is taken when the mutations are detected.

Inhibitor development has a considerable impact on the incidence of bleeding episodes in patients with mild haemophilia. This was shown in a study of 100 patients with mild to moderate haemophilia A (FVIII level 0.02-0.4 IU/mL) who developed inhibitors; during the inhibitor period a 10-fold increase in the incidence of bleeding episodes was observed, resulting in a median annual bleeding rate of 1.1 episodes per year⁷³.

Immune tolerance induction is a common approach to the elimination of inhibitors that develop in people with haemophilia A after exposure to FVIII therapy. Although data in mild and moderate haemophilia are scarce, this strategy seems to be more effective in severe haemophilia⁵. Treatment options for managing bleeds in patients with mild/moderate haemophilia who have developed inhibitors are recombinant activated factor VII (FVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) or, if antibodies are directed against exogenous FVIII only, DDAVP. An advantage of recombinant FVIIa and DDAVP is that they do not induce an anamnestic rise in inhibitor titre⁵. Alternatively, tranexamic acid can be used. Plasma-derived activated prothrombin complex concentrate should be avoided if possible, as it contains FVIII and therefore carries the risk of causing an anamnestic response. It is possible that with no intervention, the inhibitor will clear spontaneously, and therefore a "wait and see" approach is an option⁷⁴. Nevertheless, it is important to recognise that true tolerance occurs only when no anamnestic response arises after re-challenge with FVIII concentrate⁵.

Overall, as data on therapeutic options for inhibitor eradication in patients with mild haemophilia are particularly scarce¹⁰, bleeding management in these patients must be conducted in consultation with an experienced haemophilia treatment centre⁴. Some important points for the prevention of inhibitor development in mild haemophilia are to never neglect a prolonged aPTT, genotype all patients, conduct annual reviews and increase awareness of mild haemophilia, use DDAVP where available to avoid exposure to replacement factors, and avoid continuous infusion of FVIII.

Strategies to improve patients' engagement

At the patient level, the challenges of mild haemophilia include potentially limited knowledge of haemophilia and its management (such as the ability to self-infuse factor), a tendency to be less engaged with the healthcare team, and complacency around the disease. Symptomatic carriers should have regular

clinical visits as their increased bleeding risk should not be overlooked. In families that are used to living with haemophilia, the increased occurrence of bleeding can be considered normal, and this should be challenged. Factor levels should be monitored before surgery or medical interventions and within 6 weeks of factor replacement for surgery.

Although many haemophilia carriers or patients with mild haemophilia may have few symptoms and little need of healthcare services, it is important that they understand their condition and its potential consequences, and know where they can get help when required. Haemophilia societies have an important role to play in this regard. The potential link between haemophilia team interventions and clinical outcome was examined in a Canadian study⁷⁵, which revealed activities that facilitated shared decision-making by the patient and care team, and patient autonomy. Within this framework, there was a shift away from focussing on adherence towards a more patient-led management plan, resulting in reduced bleeding episodes. New technology may become increasingly used by patients with haemophilia. The Hemophilia Injury Recognition Tool (HIRT) is a newly developed mobile application that describes bleeding symptoms and helps patients with mild haemophilia determine their need for first-aid management or healthcare assistance⁷⁶.

Conclusions

Compared with severe or moderate haemophilia, mild haemophilia is under-diagnosed and tends to be neglected by the patient and in the scientific literature. There are many areas that would benefit from improvements; a few of those recommended by the authors are listed in Table II. To improve diagnosis, the authors encourage all individuals with a family history of haemophilia to undergo genotyping and, for those with suspected disease, factor levels should be measured using the chromogenic assay. Ideally all patients with mild haemophilia should be genotyped as this provides a wealth of valuable information, not least in determining susceptibility to inhibitor development.

Table II - Recommended areas for improvement.

Improved diagnosis of mild haemophilia, including routine laboratory measurements and genetic screening.
Development of new treatment models, such as monoclonal antibodies that target anticoagulation (these include the anti-tissue factor pathway inhibitor concizumab).
Research to define predictors of inhibitor development in mild haemophilia.
Establishment of improved immune tolerance induction therapy regimens for patients with mild haemophilia.

Many patients with mild disease avoid interactions with their healthcare team, as they have no symptoms. It is important that patients have access to the latest information on clinical advances in haemophilia and a full understanding of their condition. For physicians, having a complete and updated clinical history will be invaluable in the eventuality of the patient presenting with a trauma-induced bleed. Improving patients' engagement is, therefore, key.

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