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CLINICAL REVIEW

Diagnosis and management of haemophilia

Karin Fijnvandraat *paediatric haematologist*[1 2], Marjon H Cnossen *paediatric haematologist*[3], Frank W G Leebeek *haematologist*[4], Marjolein Peters *paediatric haematologist*[1 2]

[1]Amsterdam Haemophilia Treatment Centre, Academic Medical Center, 1100 DD Amsterdam, Netherlands ; [2]Department of Paediatric Haematology, Emma Children's Hospital, Academic Medical Center, Amsterdam, Netherlands; [3]Department of Paediatric Haematology and Oncology, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, Netherlands; [4]Department of Haematology, Erasmus Medical Center, Rotterdam, Netherlands

Haemophilia, which means love ("philia") of blood ("haemo"), is associated with prolonged and excessive bleeding. It is a hereditary disorder of haemostasis that occurs in one in 5000 men (prevalence of 10 in 100 000 people) and is caused by a deficiency of clotting factor VIII (in haemophilia A) or factor IX (in haemophilia B) as a result of defects in the *F8* and *F9* genes. Basic knowledge of the inheritance and management of haemophilia is essential for a broad group of healthcare workers, because severe or even life threatening bleeding can be prevented if the condition is adequately diagnosed and promptly treated. Furthermore, in women carriers who have an affected fetus, special precautions are needed to prevent perinatal bleeding in both the mother and the newborn baby. This review presents current recommendations for the diagnosis and management of haemophilia, which are generally based on observational studies and case series because few randomised clinical trials have been published in this relatively rare disease.

What causes haemophilia?

When the body is injured, the haemostatic process is immediately initiated to protect the body's integrity and to prevent further bleeding. Activation of platelets at the site of injury is followed by sequential activation of clotting factors and fibrin formation. Factor VIII and factor IX are essential for enhancement of thrombin generation and propagation of fibrin formation. Circulating factor VIII is bound to von Willebrand factor (VWF) to protect it from proteolytic degradation.[1] Both factor VIII and factor IX are encoded by genes located on the long arm of the X chromosome. When the *F8* or *F9* gene sequence is disrupted, the synthesis of factor VIII or factor IX is reduced or absent, or a less functionally active form is produced (http://hadb.org.uk/).[2 3]

How can patients with haemophilia be identified?

The severity of bleeding symptoms in patients with haemophilia depends on the residual plasma concentration of the deficient coagulation factor. Coagulation factor concentration is expressed in international units (IU); 1 IU is defined as the concentration of coagulation factor in 1 mL of normal pooled plasma. Healthy people have a factor VIII or factor IX plasma concentration of 0.50-1.50 IU/mL. Factor VIII or factor IX concentrations can also be expressed as percentages of normal pooled plasma (defined as 100%), with normal levels between 50% and 150%. Patients with haemophilia are classified into three severity groups: severe, moderate, and mild.[4] Patients with severe haemophilia have no measurable factor VIII or factor IX (<0.01 IU/mL or <1%) and may bleed spontaneously without preceding trauma. In patients with moderate and mild haemophilia, the plasma factor VIII or factor IX concentration is 0.02-0.05 IU/mL (or 2-5%) or 0.06-0.40 IU/mL (or 6-40%), respectively. Excessive bleeding usually occurs after minor trauma, dental procedures, or surgery.

The diagnosis of haemophilia can be established shortly after birth of an affected son when the mother is a known carrier. When this is not the case, the diagnosis is established when bleeding symptoms occur, either spontaneously or after mild trauma. Characteristic bleeding symptoms are intracranial bleeding in full term infants after delivery, painful swelling of the joints caused by haemarthroses, unexplained bruising when the baby starts to crawl or walk, postoperative bleeding, extensive subcutaneous bleeding after venepuncture, and muscle bleeding—either spontaneously or after intramuscular vaccination.

How is the diagnosis of haemophilia established?

Haemorrhagic manifestations that cannot be explained by trauma and prolonged or excessive bleeding after surgical or dental procedures require a thorough haemostatic laboratory evaluation, including activated partial thromboplastin time and analysis of factor VIII and factor IX. Patients with haemophilia usually have a prolonged activated partial thromboplastin time, although a normal result cannot rule out a mild form of haemophilia. Before a definite diagnosis of mild haemophilia A is established, a defect in the binding of factor VIII and VWF, which can also

Correspondence to: K Fijnvandraat c.j.fijnvandraat@amc.nl

Summary points

- In patients with major (head) trauma or major spontaneous bleeding, always give coagulation factor concentrates without delay, before diagnostic imaging or other interventions
- Prophylactic administration of factor VIII or factor IX concentrate is the standard of care for patients with severe haemophilia in countries where this is economically feasible
- Avoid drugs that affect haemostasis, such as platelet inhibitors and anticoagulants because they aggravate bleeding symptoms
- A safety amulet that makes patients with haemophilia easily recognisable may be life saving and is recommended for all patients
- Advise female relatives of patients with haemophilia to seek genetic counselling because they may be carriers
- Female carriers may have reduced plasma concentrations of factor VIII or factor IX, similar to those seen in patients with mild haemophilia and may also have bleeding symptoms

Sources and selection criteria

We searched Medline and the Cochrane Database of Systematic Reviews for "haemophilia" and "hemophilia", and we consulted the TRIP database for national guidelines on the management of haemophilia. Finally, we also used our personal reference libraries, giving preference to the highest level of evidence available.

cause reduced concentrations of factor VIII, needs to be ruled out. This defect characterises type 2N or "Normandy type" von Willebrand disease, which can also affect female patients because unlike haemophilia it is inherited in an autosomal pattern. The diagnosis of type 2N von Willebrand disease can be established by special binding assays or by molecular genetic testing.[5] Bleeding in patients with type 2N von Willebrand disease is treated by administration of VWF concentrate.

Use of clotting factor concentrates to treat haemorrhages

Bleeding in patients with haemophilia is treated by administration of the deficient clotting factor. The first clotting factor concentrates were derived from plasma and became available around 1970. Recombinant factor VIII and factor IX concentrates were developed in the 1990s. As stated in a recent UK guideline, these are currently the preferred treatment for children in the developed world, and for adult patients in some countries, such as the United Kingdom and Sweden.[6]

The dose and duration of clotting factor administration depends on the severity and type of bleeding. An important treatment principle in case of major (head) trauma or bleeding is: factor first. Coagulation factor concentrates should always be administered without delay before performing diagnostic imaging or other interventions. This strategy can be life saving because clotting factors are a prerequisite for the immediate arrest of haemorrhage in patients with haemophilia. Unfortunately, this need is not always recognised, and preventable morbidity or death does still occur.

When aiming for specific factor VIII or factor IX plasma concentrations, the following rules of thumb apply: 1.0 IU/kg body weight of factor VIII concentrate increases the plasma concentration by about 0.02 IU/mL and 1.0 IU/kg body weight of factor IX concentrate increases the plasma concentration by about 0.01 IU/mL. In case of a life threatening bleed, aim for a plasma concentration of 1.00 IU/mL for either factor. This can be achieved by infusion of 50 IU/kg of factor VIII concentrate or 100 IU/kg of factor IX concentrate. The short half lives of these factors—six to 12 hours for factor VIII and about 24 hours for factor IX—require repeated administration of clotting factor concentrates to maintain plasma concentrations above the haemostatic threshold of 0.40-0.50 IU/mL. For joint bleeds one or two infusions are often enough, whereas intracranial bleeds may need treatment for up to two weeks.

Are there alternative treatments to clotting factor concentrates?

In patients with mild haemophilia A, minor bleeding may be managed by infusion of desmopressin, which can be given intravenously (0.3 µg/kg body weight) or intranasally (150 µg in children or 300 µg in adults). A robust experimental study showed that desmopressin increases factor VIII plasma concentrations threefold to fivefold by inducing the release of VWF.[7] Because large differences are seen in the response to this drug, it is important to measure the effect of a test dose of desmopressin in each individual patient. The effect of the drug decreases after consecutive administrations as stored VWF is depleted. Desmopressin cannot be used in the treatment of haemophilia B.

For mucocutaneous bleeding in haemophilia A and B (supplementary) treatment with tranexamic acid is effective (25-50 mg/kg/day; maximum dose of 4 g in three to four oral or intravenous doses).

Whenever possible avoid drugs that impair haemostasis, such as platelet inhibitors and anticoagulant drugs, because these will aggravate bleeding symptoms.

Use of prophylaxis to prevent joint damage

Repetitive joint bleeding may cause extensive damage to the synovia by deposition of iron and subsequent chronic inflammation. This causes pain, swelling, and instability of the joint, predisposing it to further bleeding and ultimate development of arthropathy: painful joint deformation with limited function.

To prevent haemarthrosis, a recent UK guideline recommended prophylactic administration of factor VIII or factor IX concentrate two to three times a week as the standard of care for patients with severe haemophilia A or B who live in countries where this is economically feasible.[8] Patients with moderate or mild haemophilia are generally treated "on demand"—only when bleeding occurs. A well conducted randomised clinical trial in 65 boys with severe haemophilia A recently established the benefits of prophylaxis. The relative risk of joint damage detected by magnetic resonance imaging at the age of 6 years with on demand treatment versus prophylaxis was 6.1 (95% confidence interval 1.5 to 24.4).[9] This beneficial effect was confirmed in another randomised trial of 45 children.[10] A well designed case-control study established

that prophylaxis also protects against intracranial haemorrhage (odds ratio 0.50, 0.32 to 0.77).[11] Current guidelines on the use of prophylaxis in patients with severe haemophilia A deal with several aspects of care.[8 12] Most patients with severe haemophilia infuse themselves with clotting factors at home. A national survey found that this has greatly improved their health related quality of life and reduced medical costs.[13 14]

In developing countries the availability of clotting factor concentrates is limited, owing to restricted financial resources. About 70% of the patients with haemophilia worldwide are estimated not to receive adequate treatment. This is associated with an enormous burden of musculoskeletal morbidity and decreased life expectancy.[15]

How should surgery be managed?

To prevent haemorrhage during surgical or dental procedures it is important to establish a perioperative management plan in advance of the procedure. Factor VIII or factor IX concentrations should be raised to 0.80-1.00 IU/mL immediately before surgery and kept above 0.50 IU/mL for five to 14 days after the operation, depending on the type and site of surgery. Guidelines for perioperative care, based on a thorough review of the current literature, are available.[16]

What are the complications of treatment with clotting factor concentrates?

The most challenging complication is the formation of inhibiting antibodies (inhibitors) directed against active parts of the factor VIII or factor IX protein, which decrease its coagulant activity.[17 18] Inhibitors usually occur in young children within the first 50 days of treatment and increase the tendency to bleed. Inhibitors often occur in haemophilia A (cumulative incidence 25% in patients with severe haemophilia A) but are rare in haemophilia B. Bleeding episodes in patients with these inhibitors can be prevented or treated with agents that bypass the coagulant factors, such as recombinant factor VIIa (Novoseven) or activated prothrombin complex (FEIBA). A recent well conducted randomised crossover trial in 26 patients with inhibitors showed that prophylactic treatment with activated prothrombin complex reduced haemarthrosis by 61% compared with on demand treatment.[19] To eradicate the inhibitors, frequent administration (twice a week to daily) of high doses of factor VIII or factor IX is needed, a regimen called immune tolerance induction, which may be continued for months or even years.[20]

Allergic reactions to clotting factor concentrates are extremely rare because current concentrates are very pure. However, severe anaphylactic reactions are possible after administration of factor IX concentrates in patients with factor IX inhibitors.

In the 1980s, all clotting factor concentrates were derived from plasma pooled from large numbers of blood donors. This facilitated transmission of blood borne viruses such as hepatitis B and C and HIV when untested blood from unscreened donors was used, with devastating consequences. Currently, plasma clotting factor concentrates are considered safe with regard to transmission of these viruses because donors are tested extensively before blood donation and viral inactivating procedures are performed.

Carriers of haemophilia can have bleeding symptoms too

Haemophilia is an X linked hereditary disease that affects men. Women are carriers of the disease. However, female carriers may also have reduced concentrations of coagulant factors owing to inactivation of one X chromosome per somatic cell. A cross sectional observational study of 223 female carriers found that 23% of these women had plasma factor VIII or factor IX concentrations below 0.40 IU/mL—within the mild haemophilia range. These reduced concentrations of coagulant factors were associated with bleeding symptoms.[21]

Plasma concentrations of factor VIII or factor IX should be measured in all potential carriers, preferably at a young age before surgical procedures take place. Carriers with factor concentrations below 0.50 IU/mL should receive regular care from a haemophilia treatment centre. Oral contraceptives and antifibrinolytics (such as tranexamic acid) are effective in reducing blood loss in women with menorrhagia.[22] Haemostasis should be optimised before any invasive procedure, as it is for patients with mild haemophilia.

A normal factor concentration does not rule out carrier status, which can be excluded only by molecular genetic analysis.

How are pregnancy and delivery managed in carriers of haemophilia?

All daughters of a patient with haemophilia are obligate carriers. Daughters of a carrier or other female relatives of a person with haemophilia have a 0-50% chance of being a carrier. A recent UK guideline has based the following recommendations on a thorough review of the literature. Carriers of haemophilia should be identified by genetic counselling, which should be offered from around the age of 16 years and should provide information, education, and active counselling on the different reproductive options—accepting the risk, undergoing prenatal diagnosis, opting for preimplantation genetic diagnosis, adopting a child, or remaining childless.[23] Prenatal diagnosis by chorion villus sampling at 11-14 weeks' gestation is a widely used invasive procedure that has a small but not negligible rate (0.5-1%) of pregnancy loss.[23] Preimplantation genetic diagnosis combines assisted reproductive technology with molecular genetics and cytogenetics to allow affected embryos to be identified before implantation.[24]

The recent evidence based UK guideline recommends that pregnancy and childbirth be managed in a haemophilia treatment centre by a multidisciplinary team including a (paediatric) haematologist, obstetrician, and anaesthesiologist.[25] The sex of the fetus can be identified by Y chromosome polymerase chain reaction in maternal blood at around 10 weeks' gestation or by ultrasound scan at 18-20 weeks' gestation.[26] Haemostasis should be corrected during delivery in carriers with factor VIII or factor IX plasma concentrations below 0.50 IU/mL. In the third trimester of pregnancy, factor VIII values may rise temporarily, but values drop quickly after delivery, placing the mother at risk of postpartum haemorrhage. Thus, prophylactic administration of clotting factor concentrates, desmopressin, or antifibrinolytics should be considered in the postpartum period. A systematic review found that desmopressin is effective in reducing bleeding complications associated with pregnancy and childbirth in selected cases.[27] However, at the time of childbirth, desmopressin must be used with extreme caution because it can cause severe hypotension, fluid retention, hyponatraemia, and seizures in both mother and child.

Two observational cohort studies from the Netherlands and Sweden showed that instrumental delivery (ventouse and forceps) poses a significant risk (relative risk 17.8, 4.0 to 78.4 and 12.9, 5.4 to 32.6) for the respective studies in newborns with haemophilia compared with spontaneous deliveries or

caesarean sections.[28 29] This was confirmed in a large European cohort study.[30] Ventouse extraction and forceps are to be avoided in newborns with suspected haemophilia. There is considerable debate on the indication for elective caesarean section.[25] The option of elective caesarean section in an attempt to reduce the risk of neonatal intracranial haemorrhage should be considered on an individual basis, taking the fetal haemophilia status and potential maternal morbidity into account.[25] Haemophilia carrier status itself is not a contraindication to a vaginal delivery. A caesarean section should be performed early if the vaginal delivery does not proceed normally. There is no evidence for the benefit of routine neonatal ultrasound screening or postnatal prophylactic administration of clotting factors to reduce or prevent intracranial haemorrhage in the newborn.

Future of haemophilia treatment

Several new developments in haemophilia care have emerged in the past few years. Long acting factor VIII and factor IX concentrates that enable less frequent prophylactic dosing are currently being tested in clinical trials.[31] These proteins have been engineered by site directed glycopegylation or the fusion of albumin or IgG to the clotting factors. Several research groups have made great progress with gene therapy in the past few years.[32] Recently, six patients with haemophilia B were infused with a single dose of adenovirus associated virus vector expressing a human factor IX transgene. They showed sustained low level expression of human factor IX for six to 16 months without side effects and minor immune responses against the vector.[33] Four of the six patients could discontinue their prophylaxis without the occurrence of spontaneous bleeding. Long term efficacy data are crucial for the future of this approach.

Conclusion

Haemophilia can be treated safely and effectively by infusion of clotting factor concentrates that are currently available. Joint impairment may be prevented by regular administration of such concentrates. In emergency trauma situations immediate administration of clotting factor concentrates is necessary. All potential carriers should be identified to optimise genetic counselling and haemostasis at the time of delivery. This may prevent excessive bleeding in the mother and any newborns with haemophilia. Because haemophilia is a rare disease that needs a multidisciplinary approach, patients should be cared for in comprehensive care haemophilia treatment centres.[34]

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Ongoing and future research questions

- Will gene therapy be the ultimate answer to haemophilia?
- Will oral treatment of haemophilia ever be possible?
- How can we prevent the development of inhibitors?
- How can joint bleeding best be prevented in patients with inhibitors?
- How can the eradication of inhibitors be improved?
- Can we make treatment available for all patients with haemophilia around the globe?

Additional educational resources

Resources for patients

- World Federation of Hemophilia (www.wfh.org)—A global network of healthcare providers, national haemophilia associations, people with haemophilia, and their families
- Centers for Disease Control and Prevention (www.cdc.gov/ncbddd/hemophilia/people.html)—Information for patients and their families

Resources for healthcare professionals

- International Society on Thrombosis and Haemostasis (www.isth.org)—Society with more than 3000 members (doctors and researchers) from more than 80 countries
- American Society of Hematology (www.hematology.org/)—The world's largest professional society concerned with the causes and treatment of blood disorders
- European Association of Haemophilia and Allied Disorders (www.eahad.org)—A multidisciplinary association of healthcare professionals who provide care for patients with haemophilia and other bleeding disorders
- Haemophilia A Mutation, Structure, Test and Resource Site (http://hadb.org.uk) and CDC Hemophilia A Mutation Project (www.cdc.gov/ncbddd/hemophilia/champs.html)—Databases with mutations of factor VIII associated with haemophilia
- Haemophilia B Mutation Database (www.kcl.ac.uk/ip/petergreen/haemBdatabase.html)—Database with mutations of factor IX associated with haemophilia

A parent's perspective

Daniel and Sep are 7 year old twin brothers with haemophilia A. They have a 14 year old brother and two sisters, aged 17 and 19 years, who are healthy. I discovered that I was a haemophilia carrier when the twins started to have bleeding symptoms at 6 months of age. Daniel started to have strange big bruises, first in his upper arm—did we grab him too firmly? We were summoned to the healthy baby clinic and directly referred to the general practitioner, who concluded that child abuse must have occurred. After that, my husband hardly dared to touch the babies. At some time later Daniel's cheek became very hard. We immediately visited the emergency department of the local hospital, where his blood was tested. The next day we were referred to the haemophilia treatment centre in Amsterdam. The centre confirmed that Daniel had haemophilia and tested Sep, who did not yet have any symptoms, as well. Both boys had severe haemophilia A. At the age of 14 months they were started on prophylaxis. We knew nothing about the disease at the time of diagnosis, but the team at the haemophilia treatment centre has shown us the way, coached us, and guided us.

Tips for non-specialists

- Unexplained excessive bleeding at any age, especially intracranial haemorrhage in term baby boys, justifies a haemostatic investigation, including coagulation screening tests and determination of factor VIII and factor IX plasma concentrations
- No surgical or dental procedure should be performed in patients with haemophilia without consultation with the patient's haemophilia treatment centre. An authorised treatment regimen will ensure adequate haemostasis during the intervention
- Desmopressin is useful in the treatment of mild haemophilia A, but test the individual patient's response to the drug before administration to assess whether it is sufficient to ensure haemostasis during haemorrhage and procedures
- Major trauma and head trauma in patients with haemophilia can be life threatening and require immediate administration of clotting factor concentrates, before performing diagnostic imaging and other interventions
- The development and increased availability of safe clotting factor concentrates as well as the enrolment of patients in comprehensive care programmes has greatly improved the clinical outcome and quality of life of these patients

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