TREATMENT OF HEMOPHILIA

December 2008 · No. 46

SYMPTOMATIC CARRIERS OF HEMOPHILIA

Eveline P. Mauser-Bunschoten
Van Creveldkliniek and Haematology
University Medical Centre, Utrecht
Utrecht, The Netherlands

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Published by the World Federation of Hemophilia (WFH), 2008

© Copyright World Federation of Hemophilia, 2008

The WFH encourages redistribution of its publications for educational purposes by not-for-profit hemophilia organizations. In order to obtain permission to reprint, redistribute, or translate this publication, please contact the Programs and Education Department at the address below.

This publication is accessible from the World Federation of Hemophilia's eLearning Platform at **eLearning.wfh.org**
Additional copies are also available from the WFH at:

World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel. : (514) 875-7944
Fax : (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

The *Treatment of Hemophilia* series is intended to provide general information on the treatment and management of hemophilia. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimes are continually revised and new side-effects recognized. WFH makes no representation, express or implied, that drug doses or other treatment recommendations in this publication are correct. For these reasons it is strongly recommended that individuals seek the advice of a medical adviser and/or to consult printed instructions provided by the pharmaceutical company before administering any of the drugs referred to in this monograph.

Statements and opinions expressed here do not necessarily represent the opinions, policies, or recommendations of the World Federation of Hemophilia, its Executive Committee, or its staff.

Treatment of Hemophilia Monographs
Series Editor
Dr. Sam Schulman

Acknowledgement

The author would like to thank Dr. Garrett Bergman and Dr. Alison Street for their critical review.

Table of Contents

Symptomatic Carriers of Hemophilia

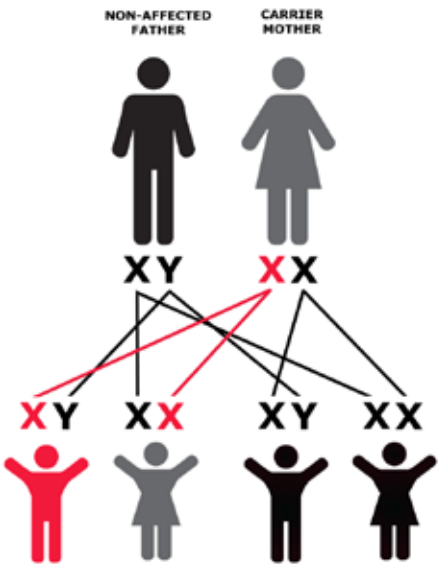
Eveline P. Mauser-Bunschoten

Introduction

Hemophilia occurs in one out of every 5,000 male births. Hemophilia A, a deficiency in factor VIII (FVIII), and hemophilia B, a deficiency in factor IX (FIX) are most often inherited as sex-linked (X-linked) recessive disorders. About 30% of mild and moderate cases of hemophilia, and 50% of severe cases, however, are so-called "sporadic" or "isolated" cases [1]. The abnormal mutation occurs in the developing fetus and these patients are the first known cases of hemophilia in their family.

Males have only one X chromosome, which they inherit from their mother. If the mother has the abnormal gene and passes it on to her son, he will have hemophilia (Figure 1). Women, who have two X chromosomes, can only have hemophilia if they inherit two abnormal copies of the gene, which is extremely rare. They are most often heterozygote carriers of the disease (i.e. they have one abnormal copy and one normal copy of the gene) and are usually unaffected or only mildly affected with bleeding symptoms. Carriers generally have adequate levels (> 60%) of clotting FVIII or FIX to control bleeding. However, clotting factor levels vary from one carrier to another due to lyonization [2], in which the expression of one of the two X chromosomes is randomly suppressed. The average clotting factor level in carriers of hemophilia is 50% of normal, consistent with exactly 50% suppression of each X chromosome (one affected, the other one normal).

Figure 1: Inheritance of hemophilia



Carriers have one normal and one abnormal gene. They have a 50% chance of passing the hemophilia gene on to each child. Boys who inherit the abnormal gene will have hemophilia; girls who inherit it will become carriers. A girl can only have hemophilia if her father has hemophilia and her mother is a carrier, which is very uncommon.

Carrier Detection

Only females can be carriers; males always have hemophilia if they have the affected X chromosome. There are two types of carriers: (1) obligatory carriers, who necessarily carry the affected X chromosome; and (2) possible carriers.

Obligatory carriers are:

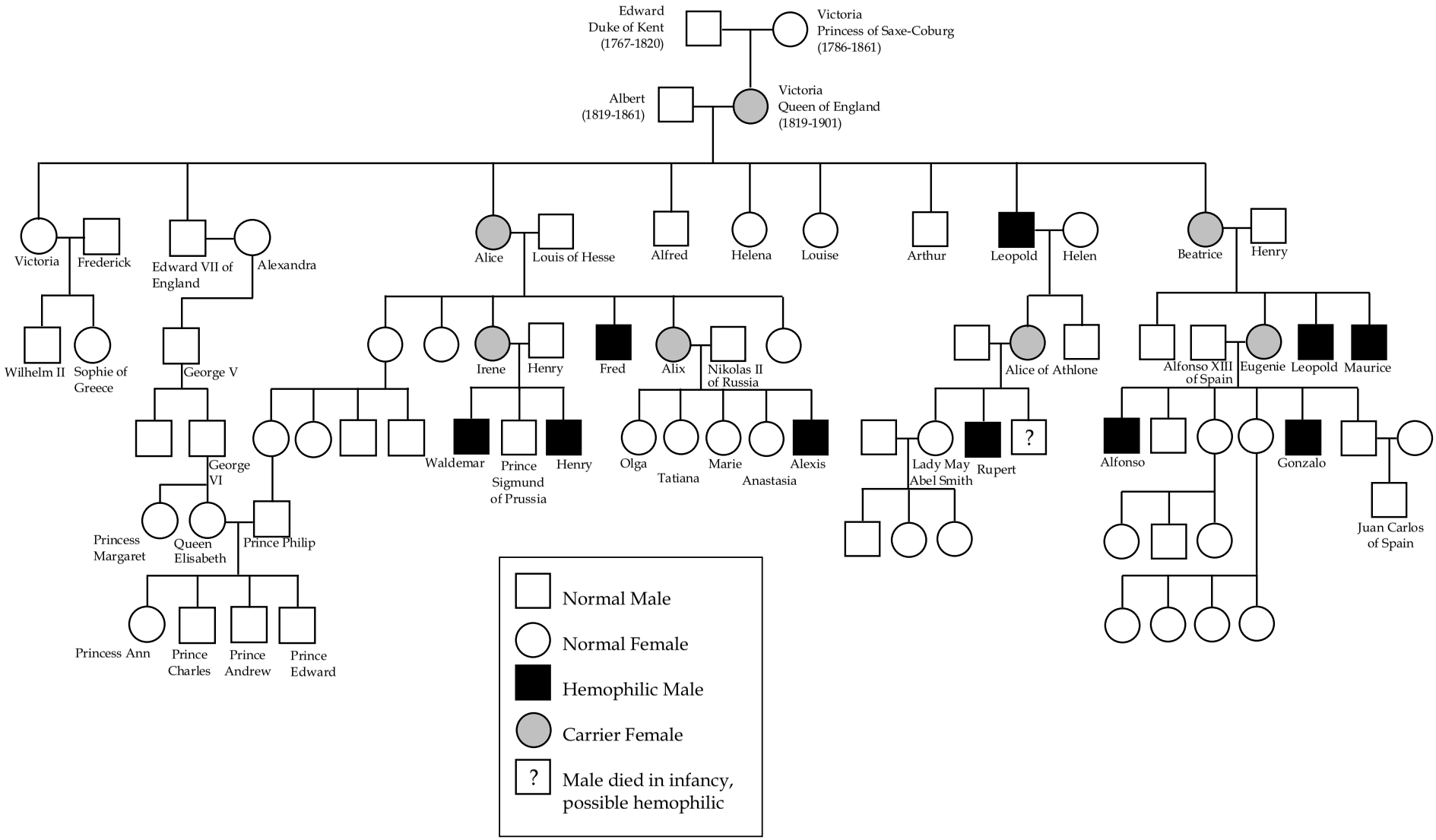
- All daughters of a man with hemophilia
- Mothers of one son with hemophilia and at least one other family member with hemophilia (brother, maternal grandfather, uncle, nephew, or cousin)
- Mothers of one son with hemophilia and a family member who is a carrier of the hemophilia gene (mother, sister, maternal grandmother, aunt, niece, or cousin)
- Mothers of two or more sons with hemophilia

Possible carriers are:

- All daughters of a carrier
- Mothers of one son with hemophilia who have no other family members who either have or are carriers of hemophilia
- Sisters, mothers, maternal grandmothers, aunts, nieces, and female cousins of carriers

Pedigree analysis is important to detect obligatory carriers. The family tree of Queen Victoria of England, for example, illustrates how hemophilia was transmitted through the royal families of Europe (Figure 2).

Figure 2: The family tree of Queen Victoria of England, in which obligatory and possible carriers are clearly shown



Previously, FVIII and FIX clotting factor levels were measured to detect carriers of hemophilia [3]. In the 1980s, it became possible to detect carriers by means of DNA analysis. First conducted with haplotyping, for which linkage markers were used, today diagnosis is most often made by mutation analysis, which offers 100% certainty of carrier status [4, 5].

Clotting Factor Levels in Carriers of Hemophilia

The expected mean clotting factor levels in carriers of hemophilia is 50% of the concentration found in the healthy population. However due to lyonization, a wide range in clotting factor levels is found in carriers of hemophilia A and B, from <1 % to >150%. Lyonization (or X chromosome inactivation) takes place in an early phase of embryonic development [2]. When a female embryo consists of only a few cells, one of the two X chromosomes inside each cell is inactivated. This is a completely random process. Normally, about half of each of the X chromosomes will be inactivated, but in some cases more X chromosomes carrying the hemophilia mutation are inactivated. In other females, the majority of "healthy" X chromosomes may be inactivated. Therefore, females typically have a mosaic of affected and unaffected X chromosomes being expressed.

Other factors such as ABO blood group, pregnancy, and stress may also influence levels of clotting FVIII [6, 7] and liver function may influence FIX levels. Since some carriers may have low levels of FVIII or FIX, one may expect some to have a bleeding tendency [8, 9].

Bleeding Symptoms in Carriers of Hemophilia

Carriers with clotting factor levels of less than 60% of normal may have an increased bleeding tendency. The occurrence of symptoms correlates very closely with the carrier's plasma concentration of FVIII or FIX; the lower a patient's levels of factor, the greater the likelihood that they will experience bleeding symptoms. In most cases, clinical symptoms are comparable to those in mild hemophilia, except the carrier may also have increased bleeding during menstruation and after delivery. Carriers with normal clotting factor levels do not have an increased bleeding risk.

Besides casuistic papers, two surveys on bleeding tendency in carriers of hemophilia have been published [8, 9]. In these studies, a detailed bleeding history in identified carriers was compared with bleeding history in non-carriers. Both studies showed an increased bleeding risk in carriers, which was related to their clotting factor levels.

In the first study, bleeding tendency in 135 carriers was compared to bleeding tendency in 25 non-carriers and in an age-matched group of 60 women (Table 1). Compared to the other two groups, the carrier group had a significantly higher tendency to bruise,

Table 1: Bleeding tendency in carriers, non-carriers, and an age matched group

	Carriers	Non-carriers	Reference
Number analysed	135	25	60
Mean age in years	37.0	23.9	37.4
Range of age in years	7-76	12-65	11-66
Tendency to bruise	37%	24%	17%
Long bleeding from small wounds	20%	0%	2%
Nose bleeding	8%	12%	5%
Prolonged bleeding after tooth extraction	43%	45%	13%
Prolonged bleeding after tonsillectomy	45%	11%	11%
Prolonged bleeding after operation	30%	11%	6%
Prolonged bleeding after delivery	22%	0%	6%
Menorrhagia	31%	10%	23%

Reproduced with permission from: Mauser-Bunschoten EP et. al. Thromb Haemost *1988, 59: 349-352.*

showed prolonged bleeding from small wounds, and demonstrated a prolonged bleeding tendency after tonsillectomy, tooth extraction, operation, and delivery. The tendency to bleed was directly correlated with the pre-existing plasma levels of FVIII and FIX. When FVIII or FIX levels were less than 20% of normal, carriers showed a 50% bleeding risk after surgery, tooth extraction, or tonsillectomy.

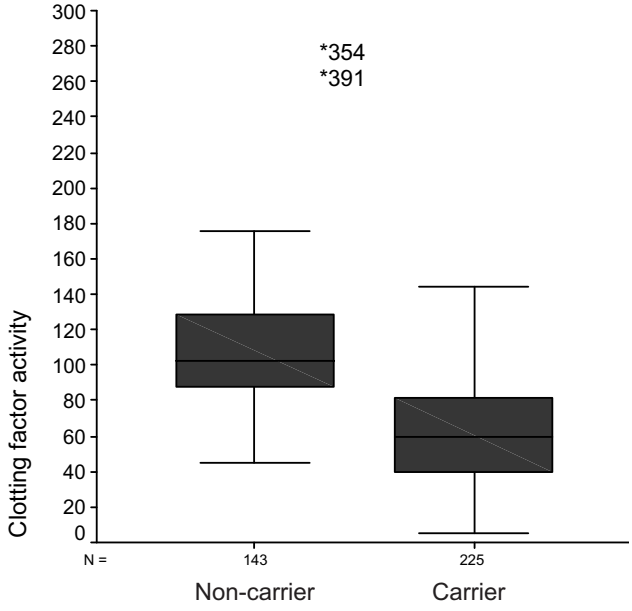
In the second study, bleeding tendency was evaluated in 274 carriers and 272 proven non-carriers. Clotting factor levels were missing for 18% (49/274) of carriers and 43% (103/245) of non-carriers. The median age of the carriers and non-carriers was similar, at 39 (range 18-77) and 40 (range 20-90) years, respectively. The median clotting factor level in carriers was 60% (range 5%-219%) and in non-carriers 102% (range 45-328%) (Figure 3). In the range of 5-60% of normal, lower clotting factor levels were increasingly associated with prolonged bleeding from small wounds.

Bleeding after medical intervention

Plug et. al. compared the risk of bleeding between carriers and non-carriers after several medical interventions known to cause bleeding in the hemophilia population (Table 2).

Figure 3: Clotting factor level in relation to carrier status

This box-whisker plot shows the median and the interquartile range of clotting factor activity levels in carriers and non-carriers for whom clotting factor level is known. The box is marked by the first and the third quartile; the whiskers extend to the range.



Reproduced with permission from Plug I et. al., Blood 2006; 108:52-56.

Tooth extractions were performed in 228 carriers and 219 non-carriers. The risk of bleeding for more than three hours after extraction was two times higher in carriers compared to non-carriers. In 24 of 228 carriers, additional treatment was needed, compared to one of 219 non-carriers. In some cases, clotting factor correction with desmopressin (Minirin®, Octostim®, Stimate®) was required. Clotting factor levels below 60% were associated with prolonged bleeding after tooth extraction.

Decreasing clotting factor levels were also associated with prolonged bleeding after (adeno-) tonsillectomy. Women with a clotting factor level of 40% or below had a 2.1-fold increased risk of bleeding compared to women with a clotting factor level above 60%. Bleeding for more than three hours following tonsillectomy was reported by 24% of carriers and 13% of non-carriers. In eight carriers (3%), a blood transfusion was required after (adeno-) tonsillectomy, compared to none of the non-carriers.

Prolonged bleeding after one or more operations was reported by 52 of 170 carriers and by 19 of 146 non-carriers. Women with a clotting factor level of 40% or below were three times more likely to report prolonged bleeding after operations than were women with a clotting factor level of above 40%. Additional treatment during or after surgery due to bleeding problems was necessary for 12% of the carriers and 5% of the non-carriers. In some cases, infusion of clotting factor concentrate or a second operation was required to control bleeding. One or more blood transfusions were given for 11% of operations in carriers, compared to 7% in non-carriers.

Menorrhagia

Plug et. al. also examined the effect of clotting factor levels on menstruation (Table 3). Women with lower clotting factor levels reported excessive blood loss during the menstrual period (menorrhagia) more often. Women with a clotting factor level of 40% or lower needed iron supplementation 80% more often than did women with a clotting factor level of 60% or more. Twenty-three percent of carriers visited the general practitioner with complaints of menorrhagia, compared to 20% of non-carriers. Fifty-eight women (31 carriers [11%] and 21 non-carriers [9%]) consulted a gynecologist, and in another 18 women a hysterectomy was performed

Table 2: Risk of bleeding after medical interventions

	Carriers	Non-carriers	Relative risk (CI)*
Tooth extraction			
Prolonged bleeding (> 3 hours)	61/228 (27)	26/219 (12)	2.3 (1.5-3.4)
Treatment after intervention	24/228 (11)	1/219 (0.5)	23.1 (3.1-169)
Tonsillectomy or adenotomy †			
Prolonged bleeding (> 3 hours)	29/123 (24)	16/122 (13)	1.8 (1.0-3.1)
Treatment after intervention	10/123 (8)	1/122 (0.8)	9.9 (1.3-76.3)
Operations †			
Prolonged bleeding (> 3 hours)	52/170 (31)	19/146 (13)	2.4 (1.5-3.8)
Treatment (ever)	16/174 (9)	6/149 (4)	2.3 (0.9-5.7)
Blood transfusion	29/174 (17)	18/149 (12)	1.4 (0.8-2.4)

Data presented are frequencies (percentage)
*CI = 95% confidence interval
†Participants who had been treated prior to the clinical intervention with clotting factor preparations, tranexamic acid, or desmopressin were excluded from the analysis.

Reproduced with permission from Plug I et al. Blood *2006, 108:52-56*

for uncontrolled menorrhagia. Mild to severe restrictions in the activities of daily life due to menorrhagia were reported by 18% of women with a low clotting factor level, compared to 9% of the women with a clotting factor level above 60%.

Bleeding after delivery

Carriers had a higher risk of post-partum bleeding after their first delivery compared to non-carriers, irrespective of clotting factor levels. The same was observed for the need of blood transfusions during or after delivery. Carriers needed blood transfusions more often when they had a cesarean section than when they had a vaginal delivery.

Prevention of Bleeding in Carriers

Since 50% of carriers may have decreased clotting factor levels, and thus are at risk for bleeding, it is important to measure clotting factor levels in all carriers, whether obligatory, proven, or possible carriers. As medical interventions and trauma may happen at any age, clotting factor levels should be measured early in life. Carriers or possible carriers with clotting factor levels of 60% or less should be referred to a hemophilia centre for counselling and education and, if required, for clotting factor replacement.

Carriers with clotting factor levels of 30% or less have, in fact, mild hemophilia, and must be treated accordingly. Clotting factor level correction is indicated to control bleeding prior to medical intervention and after trauma. These patients should be seen regularly by a physician specialized in hemophilia treatment. In those rare women with extremely low clotting factor levels of ≤ 1%, spontaneous joint bleeding may occur, and prophylaxis with clotting factor replacement is indicated, just as in severe hemophilia.

Prevention of bleeding during pregnancy

FVIII levels increase by more than 100% in the third trimester of pregnancy [7,10]. Data on FIX levels are conflicting. Briët et. al. found FIX levels remained the same, where as Chi found a significant rise of FIX levels in the third trimester of pregnancy [10, 11]. Therefore, women with pre-existing FVIII or FIX levels of 60% or less should be re-tested during the last trimester of pregnancy.

At term, FVIII levels in a normal pregnant woman are physiologically very elevated. Therefore, previously low levels in a pregnant carrier should be normal. Chi found that 8% (2/24) of carriers of hemophilia A, and 50% (4/8) of carriers of hemophilia B had FVIII or FIX levels < 50% [10] at the time of delivery. If a pregnant carrier's FVIII or FIX level is less than 60% at term, clotting factor correction is indicated and delivery should take place in a hospital specialized in the treatment of hemophilia [10].

After delivery, FVIII levels decrease to, or often below, pre-pregnancy levels. This physiologic drop in FVIII level can be severe enough to cause bleeding

Table 3: Characteristics of the menstrual period in relation to clotting factor levels

	Clotting factor level			
	>0.60 IU/mL	**0.40-0.60 IU/mL**	**0-0.40 IU/mL**	**p for trend**
Excessive blood loss				
Frequency (%)	93/195 (48)	31/54 (57)	31/51 (61)	
Relative risk	1	1.2	1.3	0.07
Anemia				
Frequency (%)	16/195 (8)	9/54 (17)	8/51 (16)	
Relative risk	1	2.0	1.9	0.07
Iron supplementation				
Frequency (%)	15/195 (8)	11/54 (20)	7/51 (14)	
Relative risk	1	2.6	1.8	0.07
Hysterectomy*				
Frequency (%)	7/44 (16)	2/10 (20)	2/11 (18)	
Relative risk	1	1.3	1.1	0.9
Restrictions in daily life (%)‡	17/189 (9.0)	9/53 (17)	9/49 (18)	
Relative risk	1	2.0	2.3	0.04

***** Reported by postmenopausal women due to excessive blood loss.
‡ Moderate to severe restrictions in daily life due to excessive blood loss during the menstrual period
Reproduced with permission from Plug I et al. Blood *2006, 108:52-56*

in women who had low FVIII levels before pregnancy, but normal FVIII levels at the end of pregnancy.

Treatment of Bleeding in Carriers

Most carriers will be asymptomatic in day-to-day life activities. However, if subjected to trauma or medical intervention, they may show prolonged bleeding. In these instances, carriers must be treated in the same way as patients with hemophilia. Dosage and duration of treatment depend on the pre-existing clotting factor level and the cause and severity of the bleed (Table 4). Desired plasma FVIII and FIX levels are shown in Appendix 1 [12].

Treatment products

Desmopressin
Desmopressin is a synthetic analogue of the antidiuretic hormone vasopressin used in the treatment of mild hemophilia A. Due to variable individual responses, hemophilia A carriers with clotting factor levels of 10% or more should have their response to desmopressin tested prior to use. Desmopressin is not effective in carriers of hemophilia B as it does not raise levels of FIX.

The dosage of desmopressin is 0.3 micrograms (μg) per kg of body weight given subcutaneously, or diluted in 50-100 mL NaCl solution given intravenously over 30 minutes or subcutaneously. Intranasal desmopressin is also available in a concentration of 1.5 mg/mL. For patients weighing less than 30 kg, the dosage is 1 intranasal puff, and for those weighing above 30 kg, 2 intranasal puffs. Desmopressin is contraindicated in the presence of head trauma, hematuria, cardiac dysfunction, hypertension, or convulsions, as well as in children younger than four years of age. Many physicians do not give desmopressin during pregnancy, as it may precipitate premature delivery, hyponatremia, hypotension, and intrauterine growth retardation [14-15]. Clinicians considering the use of desmopressin should be familiar with the albeit scant literature before prescribing it.

In the presence of severe trauma or severe bleeding, and after major surgery, FVIII levels should be monitored regularly. Desmopressin should not be

Table 4: Guidelines for clotting factor correction in carriers of hemophilia A and B with clotting factor levels of less than 60%*

	Hemophilia A			Hemophilia B	
	FVIII < 5%	5-30%	>30%	FIX < 30%	> 30%
Menorrhagia	TA** OC† FVIII 20 U/kg	TA OC DDAVP‡	TA OC DDAVP	TA OC FIX 40 U/kg	TA OC FIX 20 U/kg
Delivery	FVIII 50 U/kg	FVIII 40 U/kg	FVIII 30 U/kg	FIX 80 U/kg	FIX 50 U/kg
Bleeding post-partum	TA FVIII 25 U/kg	TA DDAVP	TA DDAVP	TA FIX 50 U/kg	TA FIX 15 U/kg
Surgery	FVIII 50 U/kg	FVIII 40 U/kg	DDAVP	FIX 80 U/kg	FIX 50 U/kg
Dental extraction	TA plus FVIII 20 U/kg	TA plus DDAVP	TA DDAVP	TA plus FIX 40 U/kg	TA
Medical intervention (scope, puncture, biopsy)	FVIII 50 U/kg	FVIII 40 U/kg	DDAVP	FIX 80 U/kg	FIX 50 U/kg
Severe trauma	FVIII 50 U/kg	FVIII 40 U/kg	DDAVP	FIX 80 U/kg	FIX 50 U/kg
Bleeding	FVIII 20 U/kg	DDAVP	DDAVP	FIX 40 U/kg	FIX 20 U/kg
Severe bleeding	FVIII 25 U/kg	DDAVP	DDAVP	FIX 50 U/kg	FIX 15 U/kg

* Duration of treatment, dose and intervals depend on clinical situation, effectiveness and laboratory test results

** TA = tranexamic acid

† OC = Oral contraceptive drugs

‡ DDAVP = desmopressin; dosage 0.3 μg/kg

administered more than once daily and for no more than two or three days, because its efficacy is reduced with continuous use (tachyphylaxis) and because of the risk of water intoxication.

Clotting factor concentrates

In carriers in whom desmopressin is either ineffective or contraindicated, or when the risk of severe bleeding is high (such as prior to or during surgery or delivery), treatment with clotting factor concentrates is indicated (see Table 4 and Appendix 1 for dosages and target factor levels).

Antifibrinolytic agents

The antifibrinolytic agents tranexamic acid and epsilon aminocaproic acid promote blood clot stability. They may be used as adjunctive therapy for minor surgical and dental procedures, and to treat menorrhagia.

Management of specific bleeding problems

Menorraghia

In most cases, menorrhagia can be treated with tranexamic acid during the first days of menstruation [16, 17]. Treatment will decrease blood loss. When the response to tranexamic acid is insufficient, or when the medication is not available, oral contraceptive drugs (OC) with an estrogen component may be of use. In fact, OCs may have an advantage in that menstrual blood loss will decrease, and menstrual periods can be postponed with continuous use. Another option is continuous treatment with prostaglandins or a prostaglandin containing intrauterine device (IUD). When all these therapies have failed, clotting factor replacement may be required, or, in carriers of hemophilia A, desmopressin might be effectively used. When factor levels are less than 10%, correction with FVIII concentrates (15 U/kg)

or FIX concentrates (30 U/kg) are indicated. Initially one should aim to achieve clotting factor levels of 30-40%, but when clinical effect is poor, higher levels may be required.

Pregnancy and delivery
Therapy during delivery is dependent on the need to prevent bleeding due to low FVIII or FIX levels. FVIII levels may increase two to three times during pregnancy. In carriers of hemophilia A with pre-existing FVIII levels of less than 50%, FVIII levels should be checked in the third trimester of pregnancy [14]. FIX levels will increase only minimally during pregnancy [10, 11]. When FVIII or FIX levels are higher than 50%, routine clotting factor correction during delivery is not indicated [10].

Clotting factor replacement may be necessary to treat complications like uterine rupture, episiotomy, or manual removal of the placenta, or if a cesarean section is performed. Desmopressin should be avoided until the umbilical cord has been ligated. It is also contraindicated in pre-eclampsia and eclampsia, because of the risk of inducing hyponatremia and seizures from water retention.

Complete clotting factor correction is indicated in the case of cesarean section, dosing to achieve levels of 100% for several days. FVIII or FIX levels should be checked daily to calculate the exact dosage and intervals of clotting factor concentrate replacement.

Desmopressin is not excreted in breast milk, and need not be withheld from a nursing mother, although the prescriber's information may state lactation as a contraindication to its use.

Post-partum period
As FVIII levels decrease to or below pre-pregnancy levels in the first days after delivery, bleeding may occur. Most bleeding events will be seen in carriers with low pre-pregnancy clotting factor levels. In these patients, clotting factor levels should be measured daily if a cesarean section has been performed, if prolonged bleeding occurs, and before removal of an epidural catheter. When intermittent blood loss occurs, tranexamic acid is indicated.

If this is not effective or not available, desmopressin or clotting factor concentrates may be used.

Other types of bleeds
Joint and muscle bleeds and all other bleeding events in carriers with low FVIII or FIX levels are treated in the same way as in patients with hemophilia. Treatment schedules depend on the severity and type of bleeding.

When baseline FVIII levels are >10%, desmopressin will be sufficient in most cases. Desmopressin is relatively contraindicated in the presence of hematuria: hematuria patients have to increase fluid intake, and when desmopressin is given fluid intake has to be restricted. Carriers with FVIII levels of <10% and hemophilia B carriers must be treated with clotting factor concentrates.

Trauma
Carriers (as well as doctors) should be aware that carriers with low baseline FVIII or FIX levels are at risk for developing severe bleeding after trauma. Therefore, a specialist in hemophilia should be contacted in any case of trauma, traffic accident, cerebral contusion, joint contusion, or abdominal trauma. Depending on the severity and type of trauma, complete clotting factor correction may be required to prevent the development of severe bleeding. In minor trauma, often a single dose may be sufficient; however in severe trauma or head injury, complete clotting factor correction for one week or longer is indicated. In these cases, FVIII and FIX levels should be regularly monitored to calculate the optimal dose and dosing intervals.

Surgery
In preparation for surgery, complete clotting factor correction is required, and should aim to maintain trough levels of FVIII or FIX (the lowest level before the next infusion) at or above 60% where coagulation factor supply is not constrained. In most cases, carriers of hemophilia A with clotting factor levels of 10% or more can be treated adequately with desmopressin. When clotting factor correction for more than three or four days is required, FVIII concentrates are indicated. Desmopressin should not be administered more than once daily and not for more than two or three days, because of the risks of tachyphylaxis and water intoxication. Carriers with FVIII levels of less than 10% and carriers of hemophilia B are treated with FVIII or FIX concentrates.

Dental extraction
In carriers with clotting factor levels of 30% or more, tranexamic acid administered for a total seven days,

and preferably started the day before surgery will be sufficient to prevent prolonged bleeding after a simple dental extraction (one or two teeth, excluding molars). In hemophilia A carriers with clotting factor levels of 10% or more, tranexamic acid should be administered concomitantly with desmopressin. When FVIII levels are lower than 10% or in non-responders to desmopressin, tranexamic acid should be combined with FVIII concentrates, aiming to achieve clotting factor levels of at least 40%. In hemophilia B carriers, tranexamic acid should be combined with FIX concentrates, also aiming to achieve clotting factor levels of at least 40%. In uncomplicated dental extractions, one dose of desmopressin or clotting factor concentrate will usually be sufficient to form an initial clot; it should be combined with antifibrinolytic therapy (tranexamic acid or epsilon aminocaproic acid) for a total of seven days. The dental surgeon must use local hemostatic measures including the use of oxidized cellulose or similar and sutures as required.

Medical diagnostics and interventions
Complete clotting factor correction is indicated in case of lumbar puncture, puncture of the femoral artery, and during gastro- or colonoscopy. In general, one single full dose, aiming at FVIII or FIX levels of 100%, will be sufficient to prevent bleeding. In the author's experience, complete clotting factor correction is also indicated for skin biopsies.

Conclusion

Carriers of hemophilia A and B with clotting factor levels of less than 60% often have an increased bleeding tendency. Therefore, each known carrier and possible carrier should have her FVIII or FIX levels measured. When a FVIII or FIX level of less than 60% is found, a carrier should be considered and treated as a (mild) hemophilia patient. Carriers with clotting factor levels of less than 30% should be regularly seen at a hemophilia treatment centre.

Clotting factor replacement is indicated in case of bleeding, trauma, and surgery. Carriers with menorrhagia should be treated with tranexamic acid. When this is not sufficient, OC or other hormonal therapy can be prescribed. In persistent menorrhagia, clotting factor correction is indicated.

Recommendations

1. All known and possible carriers of hemophilia A and B should have their FVIII or FIX levels measured.
2. All carriers with pre-existing FVIII levels of less than 50% should have their factor level measured during the third trimester of pregnancy. They should be treated to raise their FVIII levels to 100% at the time of delivery [10].
3. Carriers with decreased FVIII or FIX levels should be treated as (mild) hemophilia.
4. When a carrier has a FVIII or FIX level of less than 60%, clotting factor correction is indicated after trauma, during childbirth, in the presence of bleeding, and before surgery or other medical intervention.
5. Carriers of hemophilia with low clotting factor levels should be followed regularly at a hemophilia treatment centre.

References

1. Kasper CK, Buzin CH. *Genetics of Hemophilia A and B: an Introduction for Clinicians*. 2007.
2. Lyon MF. Sex chromatin and gene action in the mammalian X-chromosome. *Am J Hum Genet* 1962; 14: 135-48.
3. Rizza CR, Rhymes IL, Austen DE, Kernoff PB, Aroni SA. Detection of carriers of haemophilia: a 'blind' study. *Br J Haematol* 1975; 30: 447-56.
4. Bröcker-Vriends AH, Bakker E, Kanhai HH, van Ommen GJ, Reitsma PH, van de Kamp JJ, Briët E. The contribution of DNA analysis to carrier detection of and prenatal diagnosis of hemophilia A and B. *Ann hematol* 1992; 64: 2-11.
5. Tedgard U. Carrier testing and prenatal diagnosis of haemophilia: utilisation and psychological consequences. *Haemophilia* 1998; 4: 365-9.
6. Wahlberg T, Blomback M, Brodin U. Carriers and non carriers of haemophilia A: multivariate analysis of pedigree data, screening blood coagulation and factor VIII variables. *Thromb Res* 1982; 25: 410-14.
7. Kadir RA, Economides DL, Braithwaite J, Goldman E, Lee CA. The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol* 1997; 104: 803-10.

8. Mauser Bunschoten EP, van Houwelingen JC, Sjamsoedin Visser EJM, van Dijken PJ, Kok AJ, Sixma JJ. Bleeding symptoms in carriers of hemophilia A and B. *Thromb Haemost* 1988; 59: 349-52.
9. Plug I, Mauser-Bunschoten EP, Bröcker-Vriends AH, van Amstel HK, van der Bom JG, van Diemen-Homan JE, Willemse J, Rosendaal FR. Bleeding in carriers of hemophilia. *Blood* 2006; 108: 52-6.
10. Chi C, Lee CA, Shiltagh, Khan A, Pollard D, Kadir A. Pregnancy in carriers of haemophilia. *Haemophilia* 2008 ; 14 :56-64.
11. Briët E, Reisner HM, Blatt PM. Factor IX levels during pregnancy in a women with hemophilia B. *Haemostasis* 1982; 11: 87-9.
12. World Federation of Hemophilia. *Guidelines for the Management of Hemophilia*, 2005.
13. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; 90: 2515-21.
14. Mannucci PM. Use of desmopressin (DDAVP) during early pregnancy in factor VIII-deficient women. *Blood* 2005; 105: 3382.
15. Cohen AJ, Kessler CM, Ewenstein BM; Hemophilia Research Society of North America. Management of von Willebrand disease: a survey on current clinical practice from the haemophilia centres of North America. *Haemophilia* 2001; 7: 235-41.
16. Lee CA. Women and inherited bleeding disorders: menstrual issues. *Semin Hematol* 1999; 36(3 Suppl 4): 21-7.
17. Lee CA, Chi C, Pavord SR, Bolton-Maggs PH, Pollard D, Hinchcliffe-Wood A, Kadir RA; UK Haemophilia Centre Doctors' Organization. The obstetric and gynaecological management of women with inherited bleeding disorders: review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2006; 12: 301-36.

Appendix 1

Desired plasma level and dosage for bolus infusions.

Table 1A: Recommended Plasma Factor Level and Duration of Administration (when there is no significant resource constraint)

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired level	**Duration (Days)**	**Desired level**	**Duration (Days)**
Joint	40%–60%	1–2, may be longer if response is inadequate	40%–60%	1–2, may be longer if response is inadequate
Muscle (except iliopsoas)	40%–60%	2–3, sometimes longer if response is inadequate	40%–60%	2–3, sometimes longer if response is inadequate
Iliopsoas • initial • maintenance	 80%–100% 30%–60%	 1–2 3–5, sometimes longer as secondary prophylaxis during physiotherapy	 60%–80% 30%–60%	 1–2 3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head • initial • maintenance	 80%–100 % 50%	 1–7 8–21	 60%–80% 30%	 1–7 8–21
Throat and neck • initial • maintenance	 80%–100% 50%	 1–7 8–14	 60%–80% 30%	 1–7 8–14
Gastrointestinal • initial • maintenance	 80%–100% 50%	 1–6 7–14	 60%–80% 30%	 1–6 7–14
Renal	50%	3–5	40%	3–5
Deep laceration	50%	5–7	40%	5–7
Surgery (major) • Pre-op • Post-op	 80%–100% 60%–80% 40%–60% 30%–50%	 1–3 4–6 7–14	 60%–80% 40%–60% 30%–50% 20%–40%	 1–3 4–6 7–14

Table 1B: Recommended Plasma Factor Level and Duration of Administration (when there is significant resource constraint)

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired level	**Duration (Days)**	**Desired level**	**Duration (Days)**
Joint	10%–20%	1–2, may be longer if response is inadequate	10%–20%	1–2, may be longer if response is inadequate
Muscle (except iliopsoas)	10%–20%	2–3, sometimes longer if response is inadequate	10%–20%	2–3, sometimes longer if response is inadequate
Iliopsoas • initial • maintenance	 20%–40% 10%–20%	 1–2 3–5, sometimes longer as secondary prophylaxis during physiotherapy	 15%–30% 10%–20%	 1–2 3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head • initial • maintenance	 50%–80 % 30%–50% 20%–40%	 1–3 4–7 8–14	 50%–80% 30%–50% 20%–40%	 1–3 4–7 8–14 (or 21 if indicated)
Throat and neck • initial • maintenance	 30%–50% 10%–20%	 1–3 4–7	 30%–50% 10%–20%	 1–3 4–7
Gastrointestinal • initial • maintenance	 30%–50% 10%–20%	 1–3 4–7	 30%–50% 10%–20%	 1–3 4–7
Renal	20%–40%	3–5	15%–30%	3–5
Deep laceration	20%–40%	5–7	15%–30%	5–7
Surgery (Major) • Pre-op • Post-op	 60%–80% 30%–40% 20%–30% 10%–20%	 1–3 4–6 7–14	 50%–70% 30%–40% 20%–30% 10%–20%	 1–3 4–6 7–14