

# 9 SPECIFIC MANAGEMENT ISSUES

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**All statements identified as recommendations are consensus based, as denoted by .**

## 9.1 | Introduction

- People with hemophilia and their families may experience a number of health- or hemophilia-related conditions or management issues over the course of their lives. These include bleeding and reproductive complications that may affect carriers, specific requirements for surgery and other invasive procedures, psychosocial matters, a range of comorbidities due to lifestyle and aging, and other issues.
- As the management of these conditions can sometimes be complex, education aimed at preventing and/or appropriately treating the issues discussed in this chapter should be a primary and ongoing focus of collaboration between people and family members affected by hemophilia and their multidisciplinary healthcare team.

## 9.2 | Carriers

- The most severe forms of hemophilia typically affect males; females have conventionally been designated as “carriers.”
- Carriers often do not show symptoms of hemophilia because, although they have an abnormal *F8* or *F9* gene on one X chromosome, their other X chromosome contains

a normal *F8* or *F9* gene that generally works as normal to produce factor levels in the lower limit of the normal range.

- A proportion of carriers have low factor VIII (FVIII) or factor IX (FIX) activity due to lyonization (the random suppression of one of the two X chromosomes; also called X inactivation), which can result in mild, moderate, or even severe hemophilia in rare instances. Symptomatic females should be designated as having hemophilia of a specified severity, like males with hemophilia.

### Inheritance of hemophilia

- A female who has an *F8* or *F9* pathogenic variant is called an obligate carrier of hemophilia. Obligate carriers can be identified as having a hemophilia gene based on analysis of their family history of hemophilia.
- Obligate carriers include:
  - any biological daughter of a father with hemophilia;
  - any biological mother of a child with hemophilia who also has at least one other family member with hemophilia (i.e., her brother, maternal grandfather, uncle, nephew, or male cousin) or who is a known carrier of hemophilia (i.e., her mother, sister, maternal grandmother, aunt, niece, or female cousin);
  - any biological mother of two or more children with hemophilia.
- Potential carriers include:

- any biological daughter, sister, mother, maternal grandmother, aunt, niece, or female cousin of a carrier of hemophilia;
- a biological mother of a child with hemophilia and no known family history of hemophilia or carriers of hemophilia.

### Factor levels in carriers

- Carriers with FVIII/ FIX levels in the normal range may never require factor replacement therapy. However, some carriers with factor levels in the lower range of normal (i.e., below 50 IU/dL) experience bleeding problems similar to males with mild hemophilia (e.g., hemorrhaging after dental extraction, surgery, or trauma) as well as problems that are specific to women, such as prolonged or heavy menstrual bleeding.<sup>1</sup>
- Carriers who exhibit a greater bleeding tendency than would be predicted by their factor level, as in males, may have a second coagulation defect, such as a von Willebrand factor (VWF) gene variant or a congenital platelet defect.

### RECOMMENDATION 9.2.1:

- **Carriers of hemophilia, irrespective of factor level, should be registered at a hemophilia treatment centre. **CB****

### RECOMMENDATION 9.2.2:

- **Carriers of hemophilia with low factor levels should be treated and managed the same as males with hemophilia. **CB****

### Carrier factor level testing

- All immediate female relatives (mother, sister, or daughter) of a person with hemophilia should have their factor levels measured, especially prior to any invasive procedure, childbirth, or as soon as any abnormal bleeding symptoms occur.<sup>1,2</sup>
- In potential carriers, the diagnosis should be confirmed by genetic testing, if available, as factor levels may be above 50 IU/dL.<sup>3,4</sup>
- In some carriers, levels consistent with moderate or even severe hemophilia may be found on factor level testing as a result of lyonization.<sup>5</sup> (See Chapter 2: Comprehensive Care of Hemophilia – Table 2-1.)

### RECOMMENDATION 9.2.3:

- **All potential and obligate carriers of hemophilia should have their FVIII/ FIX levels measured to establish their baseline levels prior to major procedures, surgery, or pregnancy. **CB****

### Bleeding symptoms

- The most common manifestations among symptomatic carriers include<sup>1</sup>:
  - menorrhagia (heavy menstrual bleeding);
  - dysmenorrhea (pain during menstrual bleeding);
  - postpartum hemorrhage;
  - perimenopausal bleeding (abnormal bleeding during the pre-menopause transition);
  - abnormal bleeding alone, following trauma, or after medical interventions (e.g., dental extraction or surgery).
- Hormonal therapy is useful in managing heavy menstrual bleeding.<sup>6,7</sup> Options include:
  - oral, subcutaneous, or transdermal formulations containing estrogen/progesterone/progestin;
  - the levonorgestrel intrauterine device (IUD).
- Oral antifibrinolytics, e.g., tranexamic acid (15-25 mg/kg every 6-8 hours), may also be helpful in managing heavy menstrual bleeding.<sup>8</sup>

### Genetic counselling

- Genetic counselling is an essential but complex component of comprehensive care for individuals and families with a diagnosis of hemophilia and for those at risk.<sup>9</sup>
- While the scope and availability of services vary among countries<sup>10</sup> and individual hemophilia treatment centres,<sup>11</sup> comprehensive genetic counselling generally involves<sup>9</sup>:
  - collection and analysis of family and medical histories to assess the chance of disease occurrence;
  - education about inheritance, genetic testing, treatment, prevention, and available resources; and
  - counselling to promote informed choices and adaptation to the risk or condition.
- Genetic counselling should take into account the individual's experiences and perceptions, as well as the social, cultural, and religious factors and contexts that may influence decisions and options related to their genetic status.
- Genetic counsellors can help both obligate and potential carriers of hemophilia understand their bleeding and genetic risks and adapt to the medical, psychological, familial, and reproductive implications and consequences of their genetic status.<sup>9</sup>
- The primary role of genetic counsellors is to educate individuals on the natural history of hemophilia, establish their family tree/pedigree, perform risk assessments related to the inheritance of hemophilia, facilitate genetic testing, help them process and integrate genetic information, and discuss relevant reproductive options.<sup>9</sup>

- Where access to trained genetic counsellors is limited, the hemophilia treatment centre and the comprehensive care team members, specifically physicians, nurses, and/or psychosocial professionals,<sup>9</sup> often take responsibility for delivering important genetic information.<sup>2</sup>

### Psychosocial support

- Ongoing psychosocial assessment and counselling should be integrated within case management and comprehensive care for carriers. Carriers may require referral to psychosocial professionals (e.g., psychologists) for further support to address psychological or emotional issues that may arise during the genetic counselling process or at different life stages.
- Collaboration between psychosocial professionals and genetic counsellors can enhance overall patient care.
- Carriers may experience a wide range of emotional and psychosocial impacts, including feelings of guilt, sorrow, and self-blame related to reproductive choices or consequences such as passing on their genetic variant.<sup>12</sup> Such feelings run across generations of a family and may also be experienced by grandmothers who were carriers and fathers with hemophilia.<sup>12</sup>
- It is important for hemophilia treatment centres and healthcare providers (especially genetic counsellors and clinical geneticists), families, and patient organizations to be aware that the experience of being a hemophilia carrier may change with different life stages, and carriers may need genetic and/or psychosocial counselling more than once during their lifetime.<sup>12</sup>
- Comprehensive genetic counselling including a formalized system for the education, management, follow-up, and long-term medical and psychosocial support of carriers should be implemented.<sup>10</sup>

### Genetic testing

- Genetic testing facilitates identification of carriers and prenatal diagnosis. Where available, formal genetic testing should be offered to potential carriers when they are mature enough to understand the consequences of the diagnosis and give consent.<sup>13</sup>
- It is important to be aware of and abide by the relevant laws governing genetic testing and prenatal diagnosis procedures in the country where the service is being provided.
- See also Chapter 4: Genetic Assessment.

#### **RECOMMENDATION 9.2.4:**

- **Carriers of hemophilia should be offered counselling that includes reproductive implications and choices. CB**

### Prenatal diagnosis

- Prenatal diagnosis is usually offered to help with reproductive planning and risk assessment. Determination of whether a male fetus is affected by hemophilia assists parents and healthcare providers in making decisions regarding pregnancy management, such as caesarean delivery of a fetus with severe disease to reduce intracranial hemorrhage (ICH) and maternal anesthesia for childbirth. (See Chapter 4: Genetic Assessment.)

### Pregnancy and prenatal planning

Management of care for all pregnant carriers should involve close cooperation between the hemophilia and obstetric teams. It is important to have a clear plan for delivery that is shared with the carrier and written in her medical file.

#### *Factor levels during pregnancy*

- During pregnancy, FVIII levels can increase significantly in carriers and may completely normalize in the later stages. Levels of FIX, however, do not usually change significantly.<sup>14</sup>
- Even with factor levels above 50 IU/dL in the third trimester, carriers may experience abnormal bleeding during childbirth; therefore, it is critical to obtain a carrier's bleeding history and score, family history of bleeding, and history of bleeding with past childbirth prior to delivery<sup>15</sup> and, if possible, prior to pregnancy.

#### **RECOMMENDATION 9.2.5:**

- **Pregnant carriers of hemophilia should have their FVIII/FIX levels assayed in the third trimester of pregnancy to assess their bleeding risk during delivery and in the postpartum period. CB**

### Labour and delivery

- Regional block anesthesia (epidural) in carriers of hemophilia is not contraindicated if the coagulation screen is normal and the relevant factor level is above 50 IU/dL or raised to above 50 IU/dL by prophylactic treatment.<sup>16</sup> The anesthesia should be performed by an expert anesthetist, taking into account the carrier's coagulation parameters and factor levels, with arrangements for appropriate timing of treatment, if applicable.
- Factor replacement therapy, if required, should be administered to maintain factor levels above 50 IU/dL for labour and delivery and maintained in the normal range for at least 3 days after vaginal delivery and at least 5 days after caesarean delivery.<sup>16,17</sup> Route of delivery for carriers with a fetus without hemophilia should be as per

obstetric indications. Some suggest caesarean delivery to prevent intracranial hemorrhage in an infant expected to be born with severe hemophilia.<sup>18</sup>

- Delivery of infants known or suspected to have hemophilia must be atraumatic, regardless of whether it is by vaginal or caesarean delivery, to decrease the risk of bleeding complications.<sup>14</sup>
- Forceps and vacuum extraction vaginal delivery as well as invasive procedures to the fetus such as fetal scalp blood sampling and internal fetal scalp electrodes should be avoided.<sup>19</sup>
- See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for major and minor surgery.

#### **RECOMMENDATION 9.2.6:**

- **For pregnant carriers of hemophilia, delivery should be in a hospital with access to hemophilia specialists where complications during labour and delivery can be dealt with promptly to maintain the safety of mother and child.** **CB**

#### **RECOMMENDATION 9.2.7:**

- **For pregnant carriers of hemophilia, the WFH recommends against instrumental delivery.** **CB**

#### **Postpartum care**

- Carrier FVIII and VWF levels fall off fairly rapidly after delivery,<sup>5</sup> usually returning to baseline levels in 7-10 days, but sometimes earlier.<sup>20</sup>
- It is important to monitor and maintain factor levels post-delivery as carriers are at increased risk of primary and secondary postpartum hemorrhage.<sup>21</sup> If postpartum hemorrhage occurs, factor replacement therapy, antifibrinolytics (tranexamic acid), and hormonal therapy are the first-line therapies for its management.<sup>5</sup>
- Prophylactic hormonal therapy may be started immediately after delivery and continued for one month in selected carriers deemed to be at higher risk of bleeding.<sup>5</sup>
- Desmopressin (DDAVP) is occasionally used in the postpartum period for hemophilia A.<sup>5</sup> (See Chapter 5: Hemostatic Agents – Other pharmacological options – Desmopressin [DDAVP].)
- Hemoglobin levels in carriers at risk of late postpartum hemorrhage should be checked before discharge from hospital.<sup>22</sup>
- Delayed bleeding up to 35 days postpartum is possible; carriers must be informed of this risk and should be seen 2 weeks postpartum. Follow-up to monitor postpartum bleeding for approximately 1-2 months may be appropriate.<sup>22</sup>

#### **RECOMMENDATION 9.2.8:**

- **Carriers of hemophilia should be monitored for both primary and secondary postpartum hemorrhage, which should be treated with appropriate hemostatic measures.** **CB**

#### **Newborn testing**

- Cord blood should be collected from all male newborn infants of carriers of hemophilia to assess clotting factor levels for early identification and management of hemophilia. The test results should be conveyed to the parents by an appropriate member of the hemophilia team.
- Normally in newborn and pre-term infants without hemophilia, FVIII levels at birth are within the normal adult range or mildly increased. Therefore, it is possible to diagnose most cases of hemophilia A at birth; the exception being in mild hemophilia A, wherein a FVIII result at the lower end of the normal range should be repeated when the infant is around 6 months of age.<sup>23</sup>
- In contrast to FVIII, FIX levels at birth are significantly lower than normal in newborns without hemophilia and even more so in preterm infants.<sup>23</sup> While it is usually possible to make a diagnosis of severe or moderate hemophilia B in the neonatal period, infants who may be mildly affected will require repeat screening at 3-6 months of age.

#### **RECOMMENDATION 9.2.9:**

- **Male babies born to known or potential carriers of hemophilia should have cord blood testing of activated partial thromboplastin time (APTT) or factor levels.** **CB**

#### **Miscarriage management**

- Miscarriage refers to a spontaneous abortion or pregnancy loss before 20 weeks of gestation<sup>24,25</sup> by complete or incomplete expulsion of the products of conception from the uterus, by failure of the embryo to develop, or by death of the fetus in utero.<sup>25</sup>
- Once the determination has been made that the pregnancy has ended because the embryo or fetus has died or because a miscarriage is in progress, the obstetrician will surgically evacuate the uterus or await spontaneous expulsion of the products of conception.
- Surgical management of spontaneous abortion is preferred in patients with a pre-existing hemostatic abnormality such as an inherited bleeding disorder.<sup>24</sup> In such cases, adequate hemostatic treatment is required in accordance with the recommended perioperative protocols. (See 9.5 Surgery and invasive procedures, below, and Chapter 7:

Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for major and minor surgery.)

- Since bleeding in pregnancy is almost always attributed to obstetric bleeding, adequate obstetric management is required. In the case of bleeding in a pregnant carrier, appropriate hemostatic management may also be required.
- Hemostatic management consists of replacement of the deficient clotting factor or other treatment modalities in accordance with protocols for the management of bleeding complications in patients with hemophilia.

### 9.3 | Circumcision

- Circumcision is a widely practiced surgical procedure; up to 30% of the male population in the world are circumcised.<sup>26,27</sup>
- Medical benefits of circumcision include reduced risk of sexually transmitted diseases, reduced risk of carcinoma of the penis, and reduced risk of cervical cancer in sexual partners of circumcised males.<sup>28</sup>
- The accepted medical indications include treatment of phimosis, paraphimosis, recurrent balanitis, and recurrent balanoposthitis.<sup>27,29</sup> Non-medical reasons and indications may be social, cultural, personal, or religious.
- In hemophilia, circumcision is associated with a number of complications including prolonged bleeding, infection, delayed skin healing/increased morbidity, gangrene, human immunodeficiency virus (HIV) and hepatitis infection acquired through contaminated blood products to treat bleeding, risk of neonatal inhibitor development, psychosocial scarring, and risk of mortality.<sup>29,30</sup>
- The key considerations for circumcision in patients with hemophilia include individual patient factors such as inhibitor development, venous access, and wound care, as well as the expertise and resources at the hospital/treatment centre. Patients will invariably bleed when stitches are removed, and this should be managed with clotting factor replacement. (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for minor surgery.)
- A risk–benefit ratio assessment should be performed and discussed with family and other caregivers.

#### RECOMMENDATION 9.3.1:

- **In patients with hemophilia, the circumcision procedure should be performed electively by an experienced surgeon and hematology team in a resourced**

**hematology treatment centre with access to clotting factor concentrates. **CB****

#### RECOMMENDATION 9.3.2:

- **In patients with hemophilia, the plasma factor level should be raised to 80-100 IU/dL just prior to the procedure. **CB****

#### RECOMMENDATION 9.3.3:

- **In patients with hemophilia undergoing circumcision, intraoperative care should be taken to cauterize all bleeding vessels. **CB****

#### RECOMMENDATION 9.3.4:

- **For patients with hemophilia undergoing circumcision, the WFH suggests use of topical fibrin sealant as an adjunctive therapy, using a product manufactured with robust viral reduction/inactivation processes if available, to minimize the risk of bloodborne pathogen transmission. **CB****

#### RECOMMENDATION 9.3.5:

- **For patients with hemophilia undergoing circumcision, the WFH recommends adjusting clotting factor replacement to the clinical course of the procedure. If continued clotting factor replacement is required, the goal would be to maintain factor levels above 50 IU/dL for the first 3 days, and above 30 IU/dL for the subsequent 4-8 days. **CB****

#### RECOMMENDATION 9.3.6:

- **In patients with hemophilia post-circumcision, inhibitor measurement should be repeated if there is intractable bleeding that is poorly responsive to replacement therapy and local hemostatic measures. **CB****

#### RECOMMENDATION 9.3.7:

- **In patients with hemophilia post-circumcision, non-dissolvable stitches (if used) should be removed 10-14 days postsurgery; the inevitable bleeding should be managed with clotting factor replacement. **CB****

#### RECOMMENDATION 9.3.8:

- **In hemophilia patients with intractable bleeding post-circumcision, all angles should be considered, including blood vessel bleeding, clotting factor deficiency, and platelet abnormalities. **CB****

**RECOMMENDATION 9.3.9:**

- In hemophilia patients with intractable bleeding post-circumcision, adjunct and supportive therapy should be used; this includes transfusion and local hemostatic measures, such as the application of topical agents. **CB**

**9.4 | Vaccinations**

- Vaccination against communicable diseases is crucial for disease prevention. People with hemophilia should receive all immunizations recommended for their age group.
- Challenges associated with vaccinations include:
  - route of vaccine administration; and
  - vaccination of patients with compromised immunity (e.g., HIV infection).
- Live virus vaccines may be contraindicated in those with weakened immunity.
- There has been no evidence that vaccinations result in inhibitor development.<sup>31</sup>

**RECOMMENDATION 9.4.1:**

- **Children and adults with hemophilia should be administered the same routine vaccines as the general population; however, they should preferably receive the vaccines subcutaneously rather than intramuscularly or intradermally, as it is as safe and effective as the latter and does not require clotting factor infusion.**
- **REMARK: If intramuscular injection must be the route of administration, a dose of clotting factor concentrate should be given, and the smallest gauge needle available (25-27 gauge) should be used.**
- **REMARK: Additionally, an ice pack should be applied to the injection site for 5 minutes before injection of the vaccine, and pressure should be applied to the site for at least 10 minutes to reduce bleeding and swelling. **CB****

**RECOMMENDATION 9.4.2:**

- **In children and adults with hemophilia and human immunodeficiency virus (HIV) infection, the WFH recommends standard immunizations, including pneumococcal and influenza vaccines and hepatitis A and B immunization. **CB****

**RECOMMENDATION 9.4.3:**

- **In children and adults with hemophilia and HIV infection, the WFH recommends that live virus vaccines (such as chickenpox, yellow fever, rotavirus, oral polio,**

**and combined measles, mumps, and rubella [MMR] vaccines) should be avoided. **CB****

**9.5 | Surgery and invasive procedures**

- Surgery may be required for hemophilia-related complications or unrelated diseases. The issues discussed here are of prime importance when performing surgery on patients with hemophilia.
- Surgery for patients with hemophilia requires additional planning and interaction with the healthcare team compared to what is required for other patients.
- The anesthesiologist should have experience treating patients with bleeding disorders.
- Neuraxial anesthesia requires factor levels above 50 IU/dL to avoid bleeding and ensuing neurological complications.<sup>32</sup>
- Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.
- Adequate quantities of CFCs (or bypassing agents for patients with inhibitors) should be available for the surgery itself and to maintain adequate coverage postoperatively for the length of time required for healing and/or rehabilitation. (For patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor – Surgery and invasive procedures.)
- If CFCs or bypassing agents are not available, adequate blood bank support for plasma components is needed.
- The dosage and duration of CFC or other hemostatic coverage depend on the type of surgery performed. (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2 for CFC replacement for major and minor surgery.)
- Effectiveness of hemostasis for surgical procedures may be assessed as per criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (see Table 9-1).<sup>33</sup>
- Treatment with CFCs or other hemostatic agents should be considered before invasive diagnostic procedures such as lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy.
- DDAVP may be useful hemostatic treatment for surgery and other invasive procedures in responsive patients with mild hemophilia A (without medical contraindications) for minor bleeding or surgery.<sup>34</sup> Limitations of DDAVP include water retention, hyponatremia, and tachyphylaxis. Tachyphylaxis occurs when repeated dosages of DDAVP are given within short time intervals (12-24 hours), with approximately 30% decrease in FVIII activity response from the second dose onwards in the case of a 24-hour

**TABLE 9-1** Definition of adequacy of hemostasis for surgical procedures<sup>33</sup>

<b>Excellent</b>	Intraoperative and postoperative blood loss similar (within 10%) to that in the non-hemophilic patient. <ul style="list-style-type: none"> <li>No extra (unplanned) doses of FVIII/FIX/bypassing agents needed <b>and</b></li> <li>Blood component transfusions required are similar to those in a non-hemophilic patient</li> </ul>
<b>Good</b>	Intraoperative and/or postoperative blood loss slightly increased over expectation for the non-hemophilic patient (between 10% and 25% of expected), but the difference is judged by the involved surgeon/anesthetist to be clinically insignificant. <ul style="list-style-type: none"> <li>No extra (unplanned) doses of FVIII/FIX/bypassing agents needed <b>and</b></li> <li>Blood component transfusions required are similar to those in the non-hemophilic patient</li> </ul>
<b>Fair</b>	Intraoperative and/or postoperative blood loss increased over expectation (25%-50%) for the non-hemophilic patient, and additional treatment is needed. <ul style="list-style-type: none"> <li>Extra (unplanned) dose of FVIII/FIX/bypassing agents needed <b>or</b></li> <li>Increased blood component (within 2-fold) of the anticipated transfusion requirement</li> </ul>
<b>Poor/None</b>	Significant intraoperative and/or postoperative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia. <ul style="list-style-type: none"> <li>Unexpected hypotension or unexpected transfer to ICU due to bleeding <b>or</b></li> <li>Substantially increased blood component (&gt;2-fold) of the anticipated transfusion requirement</li> </ul>

Notes: Apart from estimates of blood loss during surgery, data on pre- and postoperative hemoglobin levels and the number of packed red blood cell units transfused may also be used, if relevant, to estimate surgical blood loss. Surgical hemostasis should be assessed by an involved surgeon and/ or anesthetist, and records should be completed within 72 h post-surgery. Surgical procedures may be classified as major or minor. A major surgical procedure is defined as one that requires hemostatic support for periods exceeding 5 consecutive days.

Abbreviations: FIX, factor IX; FVIII, factor VIII; ICU, intensive care unit.

interval. Due to possible tachyphylaxis, DDAVP may not be a good option for those patients who require adequate hemostasis for longer periods of time, e.g., following major surgery.<sup>35</sup>

- Combined administration of DDAVP and FVIII concentrate may be able to overcome several of the drawbacks of these separate treatment options; however, there is a lack of experience and knowledge with regard to the efficacy and safety of combination treatment.<sup>35</sup>
- When needed, or if CFCs are not available, DDAVP and antifibrinolytics (tranexamic acid or epsilon-aminocaproic acid) are therapeutic options as hemostatic support to the initial replacement treatment.<sup>36</sup> More potent and better tolerated among antifibrinolytics is tranexamic acid. This compound is particularly effective and useful in cases of mucosal bleeds.
- See Chapter 5: Hemostatic Agents – Other pharmacological options – Desmopressin (DDAVP).
- Inhibitors should be assessed prior to surgery and when there is suboptimal response to treatment in the postoperative period. (See Chapter 8: Inhibitors to Clotting Factor – Surgery and invasive procedures.)

#### **RECOMMENDATION 9.5.1:**

- **Patients with hemophilia A and B should have ready access to and be evaluated for acute and elective surgical procedures that could enhance their well-being or quality of life. **CB****

#### **RECOMMENDATION 9.5.2:**

- **The WFH recommends patients with hemophilia requiring surgery should be managed at or in consultation with a comprehensive hemophilia treatment centre. **CB****

#### **RECOMMENDATION 9.5.3:**

- **For patients with hemophilia requiring surgery, sufficient quantities of clotting factor concentrates must be available for the surgery itself and to maintain adequate coverage postoperatively for the duration required for recovery and/or rehabilitation. **CB****

#### **RECOMMENDATION 9.5.4:**

- **The WFH recommends centres providing surgery for patients with hemophilia should have adequate laboratory support for reliable monitoring of clotting factor levels in the perioperative period. **CB****

**RECOMMENDATION 9.5.5:**

- For patients with mild hemophilia A undergoing surgery, the WFH recommends the use of DDAVP for hemostasis if the patient shows good therapeutic response to DDAVP in pre-surgery testing.
- **REMARK:** DDAVP is not recommended for surgical hemostasis in those patients with mild hemophilia A in whom the response to DDAVP (increase of plasma FVIII activity levels) is unsatisfactory or in whom DDAVP is contraindicated (e.g., in those with significant cardiovascular disease).
- **REMARK:** Due to the risk of tachyphylaxis, DDAVP should not be given for more than 3-5 days unless the patient can be monitored closely and switched to clotting factor concentrate if this occurs. Therefore, if the anticipated treatment duration will be longer than 3-5 days (e.g., after major surgery), providers may choose to avoid the use of DDAVP from the outset.
- **REMARK:** DDAVP is the first choice for patients with mild hemophilia A to avoid the cost of CFCs and exposure to FVIII concentrates and the potential risk of inhibitor development, which increases with the number of exposures.
- **REMARK:** Given the need for close monitoring, an experienced hematology team should manage these patients. **CB**

**RECOMMENDATION 9.5.6:**

- For patients with hemophilia undergoing surgery, antifibrinolytics and topical hemostatic agents should be considered if ancillary therapies are required beyond factor replacement. **CB**

**RECOMMENDATION 9.5.7:**

- Pre- and postoperative assessment of all patients with hemophilia A and B should include inhibitor screening and inhibitor assay. **CB**

**RECOMMENDATION 9.5.8:**

- For patients with hemophilia undergoing surgery, the WFH advises against neuraxial anesthesia. If neuraxial anesthesia is required, it should be performed only under adequate clotting factor coverage as the safety of neuraxial procedures has not been established in patients with hemophilia.
- **REMARK:** It is recognized that in some centres, neuraxial anesthesia is acceptable after restoring hemostasis in patients with hemophilia, whereas in other centres

this procedure is discouraged and general anesthesia is preferred. **CB**

**RECOMMENDATION 9.5.9:**

- Patients with mild hemophilia A and all patients with hemophilia receiving intensive factor replacement for the first time are at particular risk of inhibitor development, and therefore should be rescreened for inhibitor presence 4-12 weeks post-operatively. **CB**

**RECOMMENDATION 9.5.10:**

- In surgical patients with hemophilia B requiring intensive replacement therapy, the WFH recommends against use of prothrombin complex concentrate (PCC) due to risk of accumulation of clotting factors II, VII, and X, which can be associated with higher risk of thrombotic complications. **CB**

**RECOMMENDATION 9.5.11:**

- The WFH recommends replacement therapy for a duration of at least 3 days for minor surgical procedures, and at least 7-10 days for major surgical procedures. **CB**

**RECOMMENDATION 9.5.12:**

- For patients with hemophilia A and B undergoing major surgery, the WFH recommends against routine use of pharmacologic thromboprophylaxis. **CB**

## 9.6 | Sexuality

- People with hemophilia are able to have entirely normal sexual lives.<sup>37</sup> Although sexual health has generally been inadequately assessed in routine care of people with hemophilia, recent studies have shown that the prevalence of difficulty with sexual activity is significantly higher compared to the general population.<sup>38</sup>
- Complications of hemophilia can be accompanied by sexual dysfunction, such as lack of libido or impotence. Pain, fear of pain, or analgesia may affect sexual desire, and hemophilic arthropathy may place physical limitations on sexual intercourse.
- Older age, joint bleeding, and joint status contribute to poor sexual health; in addition, poor sexual health is strongly associated with worse general health status.<sup>38</sup>
- People with hemophilia have reported experiencing joint stiffness that affected their sexual life (53%), joint pain from sexual activity (53%), and not having adequate information regarding sexual activity.<sup>39</sup>



- Muscle bleeding (e.g., iliopsoas) may sometimes arise from sexual activity, and this may require active management or specific counselling to reduce recurrence.<sup>40</sup> (See Chapter 10: Musculoskeletal Complications.)
- Sexuality may also be affected by viral complications such as chronic hepatitis C virus (HCV) and HIV infection.<sup>40</sup>
- Age-related diseases such as hypertension and diabetes mellitus may also result in sexuality issues, as well as certain medications to treat comorbidities.
- In some cases, oral phosphodiesterase-5 inhibitors (sildenafil, tadalafil) may be helpful. Note that these medications mildly inhibit platelet aggregation in vitro and may cause epistaxis due to nasal congestion.
- In addition to the physical effects on sexuality, people with hemophilia may experience social and psychological issues surrounding sexual health. Worries about having a bleed due to sexual activity, lack of desire, body image issues, fear of rejection, medication side effects, pain, and tiredness have all been reported to affect the sexual lives of people with hemophilia.<sup>40</sup>
- Cultural influences may play a role in a person's decision about whether to discuss sexual health issues with their healthcare provider. As some individuals may be reluctant to have such discussions, all members of the comprehensive care team should be proficient in initiating and engaging patients in a conversation about their sexual health and quality of life, and this approach should be integrated into routine care.<sup>40</sup>
- Hematospermia (defined as the macroscopic presence of blood in the semen) is not uncommon in people with hemophilia and may cause considerable anxiety in some individuals and their partners.
- Hematospermia is rarely linked to serious dysfunctions; nevertheless, a more serious pathology may be underlying, consequently requiring further investigations.

#### **RECOMMENDATION 9.6.1:**

- **Adult patients with hemophilia should be assessed for sexual health issues as part of routine care to address possible impacts related to age, joint bleeding, joint pain and stiffness, and muscle bleeding (e.g., iliopsoas), which can sometimes arise during sexual activity. **CB****

#### **RECOMMENDATION 9.6.2:**

- **For patients with hemophilia with comorbidities who may experience complications of hemophilia accompanied by sexual dysfunction, the WFH recommends that healthcare providers at hemophilia treatment centres provide a multipronged psychosocial approach that**

**includes communicating openly about sexual activity and quality of life in a consistent and comprehensive manner. **CB****

## **9.7 | Psychosocial issues**

- Severe hemophilia is associated with major psychological and economic burdens for people with hemophilia and their caregivers.<sup>41</sup> As hemophilia can impact many aspects of daily living and family life, psychological and social support are important components of comprehensive care for hemophilia.<sup>42</sup>
- Psychosocial care is an important aspect of healthcare services for individuals and families living with hemophilia and related complications.
- The hemophilia treatment centre social worker and/or other members of the comprehensive care team typically fulfill this role. Key functions include:
  - Provide as much information as possible about all aspects of care, including the physical, psychological, emotional, and economic dimensions of living with hemophilia, in terms the patient/family members can understand.
  - Provide psychosocial support and counselling to patients, their parents, and other family members (including unaffected siblings).
  - Interact and speak directly with children with hemophilia about their treatment, not just with their parents.
  - Assess and address issues related to adherence.
  - Help patients understand and deal with issues and challenges related to school or employment.
  - Encourage patients and family members to build a support network (e.g., by forming or joining support groups at their hemophilia treatment centre and patient organization).
  - Work in partnership with the patient organization to provide education to patients, families, and healthcare providers, and advocate for hemophilia care.
  - Enlist the assistance of local healthcare organizations where social workers are unavailable.
  - Encourage patients, family members and caregivers to discuss issues or challenges with regards to mental health such as depression or anxiety.
  - Recognize warning signs of burnout and depression, which are common with chronic illness, and provide suggestions and resources for coping.

- Encourage patients to engage in productive and fulfilling activities at home and in the workplace.
- See 9.9 Medical issues with aging – Psychosocial issues with aging, below.

#### **RECOMMENDATION 9.7.1:**

- **For patients with severe hemophilia, the WFH recommends the provision of psychological and social support as part of comprehensive hemophilia care, with enlistment of assistance from local healthcare organizations wherever psychologists or social workers are unavailable. **CB****

#### **RECOMMENDATION 9.7.2:**

- **For patients with hemophilia, the WFH recommends that hemophilia treatment centres assist patients and families in forming and joining support groups or networks, and encourage participation in their patient organizations. **CB****

#### **RECOMMENDATION 9.7.3:**

- **For patients with hemophilia, the WFH recommends appropriate programming at hemophilia treatment centres and patient organizations to assist in successful aging through assessment of their developmental progression, assessment and prevention of comorbidities and functional impairments, assessment of cognitive and emotional function, identification of depression and referral for treatment, and reinforcement of social connectedness. **CB****

## **9.8 | Comorbidities**

- The increase in life expectancy for people with hemophilia—due to major advances in hemophilia care, including the availability of safe and effective CFCs—is accompanied by a range of new challenges. An increasing number of people with hemophilia develop significant comorbidities, such as cardiovascular and metabolic diseases, renal disease, and cancer/malignancies.<sup>43</sup>
- As a result, hemophilia treatment centres increasingly require the expertise of specialists rarely needed before, such as cardiologists, endocrinologists, and oncologists.<sup>44</sup>
- In general, the comorbidities occurring in older patients with hemophilia should be treated in consultation with relevant specialists as they would in the unaffected population of the same age, but treatment should be adapted when the risk of bleeding is increased by the use

of invasive procedures or medications that may cause bleeding.<sup>44</sup>

### **Cancer/malignancy**

- The risk of developing cancer increases with age, and the same holds true in aging patients with hemophilia.<sup>45</sup>
- It has been well documented that older patients with hemophilia have a higher incidence of virus-related malignancies caused by HIV (e.g., non-Hodgkin lymphoma, basal cell carcinoma, Kaposi sarcoma) and HCV (e.g., hepatocellular carcinoma) infection.<sup>46-48</sup>
- It is unclear whether hemophilia exerts an impact on the prevalence of other cancers among people with hemophilia, and it is unclear whether hemophilia exerts an impact on the clinical course of malignancy.<sup>49-51</sup>
- More recent analyses suggest that, with the exception of hepatocellular carcinoma due to chronic hepatitis infection, mortality rates from cancer are essentially the same among people with hemophilia and the general population.<sup>52</sup>
- The risk of bleeding in people with hemophilia and cancer is exacerbated by factors including<sup>44</sup>:
  - use of invasive diagnostic and therapeutic procedures;
  - thrombocytopenia induced by chemotherapy and/or radiotherapy.
- Therefore, hemostatic therapy should be provided not only episodically at the time of invasive procedures, but also in the form of ongoing prophylaxis in cases of severe thrombocytopenia due to chemotherapy and/or radiotherapy.<sup>44</sup>
- It is unknown which platelet count is safe in patients with hemophilia and malignancy. Some experts advise considering prophylaxis with replacement of the deficient clotting factor when platelet count is less than 30 G/L apart from management of thrombocytopenia,<sup>44</sup> although previous studies have suggested that prophylaxis should be instituted when platelet counts fall below 50 because of the risk of central nervous system (CNS) and other serious bleeds.<sup>53</sup> (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)
- Since thrombocytopenia is in itself not antithrombotic, antithrombotic prophylaxis should be considered in those types of malignancy that are associated with a high risk of thrombosis.<sup>44</sup>
- For patients with hemophilia who are diagnosed with cancer, which in the general population is accompanied by an increased risk for developing venous thromboembolism (VTE), thromboembolism prophylaxis may not be necessary

as patients with clotting deficiencies are relatively protected from developing VTE.<sup>53,54</sup>

#### **RECOMMENDATION 9.8.1:**

- **In patients with hemophilia, the WFH recommends age-appropriate cancer screening. **CB****

#### **RECOMMENDATION 9.8.2:**

- **For diagnosis and treatment of malignancy in patients with hemophilia, the WFH recommends the provision of adequate factor replacement as necessary to minimize bleeding risk. **CB****

#### **RECOMMENDATION 9.8.3:**

- **In patients with hemophilia, if chemotherapy or radiotherapy is accompanied by severe long-lasting thrombocytopenia, the WFH recommends continuous prophylactic replacement therapy. **CB****

#### **RECOMMENDATION 9.8.4:**

- **Antineoplastic treatments for patients with hemophilia diagnosed with cancer should be the same as recommended for the general population. **CB****

#### **RECOMMENDATION 9.8.5:**

- **For hemophilia patients without inhibitors diagnosed with cancer, the WFH advises that venous thromboembolism prophylaxis management decisions should be based on evaluation of the individual patient's bleeding and thrombotic risk. If used in patients receiving factor concentrates, it must be carefully managed to maintain factor levels below the risk range for VTE.**
- **REMARK: If pharmacologic thromboprophylaxis for hemophilia patients without inhibitors diagnosed with cancer is used, it should mimic what is recommended for the general population, provided that appropriate factor replacement therapy is administered, taking into account that factor replacement to high factor levels above normal is a potential risk factor for VTE. **CB****

#### **Cerebrovascular accident/stroke**

- Patients with hemophilia are prone to hemorrhagic stroke, the most serious type of bleeding in this population; however, ischemic/thrombotic strokes have also been reported.<sup>55,56</sup> (See Chapter 7: Treatment of Specific Hemorrhages – Table 7-2.)

#### **Atrial fibrillation**

- Non-valvular atrial fibrillation (AF) is the most common type of arrhythmia, and it is associated with a significant increase in the risk of embolic stroke. Its prevalence in the general population increases with age, ranging from <0.1% in patients less than 55 years of age to 3% in patients between 65 and 69 years of age, and up to 9% in patients over 80 years of age.<sup>57-59</sup>
- Results of recent studies indicate that the prevalence of atrial fibrillation in patients with hemophilia is similar to that reported in their peers in the general population.<sup>60</sup>
- There is no evidence to suggest that patients with hemophilia and atrial fibrillation are protected from thromboembolic complications.
- Management of non-valvular atrial fibrillation comprises rhythm control strategies such as cardioversion or ablation; however, these strategies do not always obviate the need for therapeutic anticoagulation.<sup>54</sup>
- The selection of patients with hemophilia who have a high chance of successful cardioversion should involve a cardiologist at a hemophilia treatment centre.<sup>44</sup>
- Left atrial appendage occlusion may be an option for patients with non-valvular atrial fibrillation at high risk of bleeding and cardioembolism.<sup>61</sup>
- In patients without bleeding diathesis, treatment decisions regarding anticoagulation in atrial fibrillation are determined by weighing an individual's stroke risk as calculated by the CHA2DS2-VASc score against an estimated bleeding risk occurring as a consequence of anticoagulation therapy (the risk of bleeding associated with anticoagulation for atrial fibrillation in the general population is calculated by the HAS-BLED score).<sup>54</sup>
- There is no evidence to support or reject the hypothesis that the CHA2DS2-VASc and HAS-BLED scores are equally useful in patients with hemophilia.<sup>54,60</sup>
- There are no evidence-based guidelines for the management of atrial fibrillation in patients with hemophilia.

#### **RECOMMENDATION 9.8.6:**

- **Patients with hemophilia and non-valvular atrial fibrillation should be treated by medical teams composed of experienced hematologists and cardiologists. **CB****

#### **RECOMMENDATION 9.8.7:**

- **For patients with severe or moderate hemophilia and atrial fibrillation, the WFH recommends clinical management based on basal FVIII/FIX levels and stroke risk by weighing the patient's stroke risk as calculated by the CHA2DS2-VASc score against an estimated bleeding**

risk occurring as a consequence of anticoagulation therapy, and withholding anticoagulation if stroke risk is deemed to be lower than bleeding risk. **CB**

#### **RECOMMENDATION 9.8.8:**

- For patients with hemophilia and atrial fibrillation at high risk of bleeding and thromboembolism, the WFH recommends left atrial appendage occlusion, particularly if long-term replacement therapy with deficient clotting factor is not feasible.
- **REMARK:** Left atrial appendage occlusion for patients with hemophilia and atrial fibrillation should be preceded by assessments of the individual's risk of bleeding and thromboembolism and implemented under the advisement of a cardiologist. **CB**

#### **RECOMMENDATION 9.8.9:**

- For patients with hemophilia in whom the risk of non-valvular atrial fibrillation-associated stroke is high or outweighs the risk of bleeding complications, the WFH recommends careful consideration of the use of anticoagulants.
- **REMARK:** The choice between direct oral anticoagulants and vitamin K antagonists depends on the local protocols, availability of antidotes for reversal of anticoagulant activity, and feasibility of maintaining adequate trough levels of the deficient clotting factor.
- **REMARK:** Despite the scarcity of evidence-based data for this indication in patients with hemophilia, most experts suggest maintaining trough levels of the deficient clotting factor in the individual patient at  $\geq 15$ -30 IU/dL while on anticoagulant therapy for atrial fibrillation.
- **REMARK:** Because treatment responses to DOACs and VKAs may vary, decisions on anticoagulant therapy should be based on the individual patient in consultation with a cardiologist. **CB**

#### **RECOMMENDATION 9.8.10:**

- In hemophilia patients with inhibitors, antithrombotic therapy is generally contraindicated. **CB**
- More research is needed to better understand the safety of antithrombotic therapy in patients with hemophilia A complicated by FVIII inhibitors who are treated with emicizumab.

#### **Venous thromboembolism/thrombosis**

- Patients with hemophilia are considered to be protected against venous thromboembolism (VTE) by virtue of their coagulation factor deficiency.
- Spontaneous VTE is uncommon among patients with hemophilia, including those with inherited thrombophilia; however, VTE associated with surgical interventions (e.g., total knee or hip replacement or major abdominal surgery for cancer) has been reported. It has been postulated that in this clinical setting, the natural protection against VTE is mitigated by administration of high doses of concentrates of the deficient clotting factor.<sup>62-64</sup>
- Intensive replacement therapy with prothrombin complex concentrate (PCC) in patients with hemophilia B may result in accumulation of clotting factors II, VII, and X, which may be associated with a higher risk of VTE development.<sup>65</sup>
- Intensive therapy with bypassing agents may also be associated with a higher risk of VTE development.<sup>54,65</sup>
- Concomitant use of emicizumab and activated prothrombin complex concentrate (aPCC) may also result in thrombotic complications, including VTE and thrombotic microangiopathy.<sup>66</sup> (See Chapter 8: Inhibitors to Clotting Factor.)
- There is currently a lack of evidence-based consensus on how to manage VTE in patients with hemophilia. It has been suggested that therapeutic doses of anticoagulants may be administered when deficient clotting factor levels are maintained above 30 IU/ dL<sup>44</sup> or above 15 IU/dL.<sup>54</sup>
- Hemostatic response to bypassing agents is often unpredictable; therefore, antithrombotics should only be used in patients with hemophilia and high-responding inhibitors who are at the highest risk of developing thromboses. In rare cases, the risk of untreated thrombosis may outweigh the risk of bleeding complications and therefore justify the use of antithrombotic agents. (For patients with inhibitors, see Chapter 8: Inhibitors to Clotting Factor.)

#### **RECOMMENDATION 9.8.11:**

- In patients with hemophilia undergoing surgical procedures who carry a high risk of developing venous thromboembolism (e.g., in cases of major orthopedic surgery, major abdominal surgery for cancer, or long post-surgery immobilization), the WFH recommends an assessment of individual risk of VTE. **CB**

**RECOMMENDATION 9.8.12:**

- For patients with hemophilia undergoing surgery associated with a high risk of venous thromboembolism and bleeding complications, the WFH recommends consideration of the use of mechanical methods for thromboprophylaxis.
- **REMARK:** In contrast to pharmacological thromboprophylaxis, mechanical methods of thromboprophylaxis are not associated with the risk of bleeding complications. **CB**

**RECOMMENDATION 9.8.13:**

- For patients with hemophilia in whom the balance of the risk of bleeding compared to the risk of developing venous thromboembolism favours pharmacological thromboprophylaxis, the WFH recommends the same practice as that applied in the general population, provided that adequate replacement therapy is administered.
- **REMARK:** Decisions on anticoagulant therapy in a patient with hemophilia should always be preceded by assessments of the individual's bleeding and thrombotic risk. In some patients with hemophilia, the risk of uncontrolled bleeding may outweigh the benefit of anticoagulation. **CB**

**RECOMMENDATION 9.8.14:**

- For patients with hemophilia without inhibitors, the WFH recommends the use of prophylactic doses of anticoagulants only after ensuring hemostatic control with adequate replacement therapy.
- **REMARK:** If the risk of uncontrolled bleeding outweighs the benefit of anticoagulation, anticoagulants should not be used.
- **REMARK:** This recommendation does not apply to patients with hemophilia and inhibitors in whom anticoagulants are generally contraindicated. **CB**

**RECOMMENDATION 9.8.15:**

- In hemophilia patients without inhibitors who experience an acute episode of venous thromboembolism, the WFH recommends the use of high-intensity anticoagulation for the minimal duration and under clotting factor replacement protection and close clinical and laboratory monitoring.
- **REMARK:** This recommendation does not apply to hemophilia patients with inhibitors in whom anticoagulants are generally contraindicated. **CB**

- More research is needed to better understand the safety of antithrombotic therapy in patients with hemophilia A complicated by FVIII inhibitors who are treated with emicizumab.

**Metabolic syndrome**

- Metabolic syndrome is associated with obesity and physical inactivity, both of which are common in older patients with hemophilia due to severe hemophilic arthropathy.<sup>43</sup>
- Obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) is a major health concern in developed countries in both the general population and in patients with hemophilia.<sup>67</sup> The number of patients with hemophilia who are overweight is also increasing.<sup>68</sup>
- Obesity impacts physical activity in both children<sup>69</sup> and adults.<sup>70</sup> Although few studies have assessed the effects of obesity on hemophilia-specific outcomes, there is evidence that excess weight has a significant impact on lower extremity joint range of motion and functional ability, as well as on joint pain, with potentially significant effects on overall quality of life.<sup>71,72</sup>
- Overweight and obesity can affect frequency of bleeding in different ways: some overweight/obese patients have reduced bleeding rates, but this may be due to lower levels of physical activity; conversely, obese patients with hemophilia tend to have more joint bleeds, compared to non-obese patients with hemophilia.<sup>70</sup>
- Venous access is more complex in obese patients with hemophilia, which may inhibit their ability to self-infuse and therefore result in lower compliance with their prophylaxis regimen.<sup>73</sup> Lower compliance with prophylaxis may result in more joint bleeding and ultimately worsen hemophilic arthropathy and osteoarthritis in obese patients with hemophilia.<sup>70</sup>
- Factor recovery is different in patients with hemophilia who are overweight or obese. A median FVIII recovery has been observed in obese children (2.65), compared to those with normal weight (1.94).<sup>74,75</sup>
- For some obese patients, lean body weight dosing may be effective while reducing cost of treatment based on body weight. However, each patient would have to be assessed by pharmacokinetic studies, including trough and peak levels, and factor levels at additional timepoints to establish ideal dosing.
- Weight management should be offered as part of health promotion within hemophilia treatment centres for all patients. This should include:
  - nutritional education for parents of children as well as for adults with hemophilia;

- weight management programs;
  - psychological support;
  - exercise programs (preferably monitored by the centre's physical therapist);
  - pharmacological therapy;
  - bariatric surgery; and
  - collaboration with or referral to obesity medical/surgical teams.
- Bariatric surgery is possible in morbidly obese people with hemophilia.<sup>76</sup>

#### **RECOMMENDATION 9.8.16:**

- **Patients with hemophilia should have regular height and weight measurements to monitor body mass index. **CB****

#### **RECOMMENDATION 9.8.17:**

- **Patients with hemophilia who are overweight or obese should be referred for dietary advice and/or weight management. **CB****

#### **RECOMMENDATION 9.8.18:**

- **Patients with hemophilia who are obese should have FVIII/FIX replacement therapy based on lean body weight after individual pharmacokinetic assessments. **CB****

#### **Diabetes mellitus**

- Little is known about the prevalence of diabetes mellitus in people with hemophilia, but it has been found to be higher in the hemophilia population than in the general population.<sup>43</sup>
- If treatment with insulin is indicated, subcutaneous injections can be administered without bleeding and without the need for factor replacement.<sup>37</sup>
- Higher body weight/BMI is a major risk factor for not only the development of diabetes mellitus, but also for atherosclerosis, cardiovascular disease, and further damage to arthropathic joints. As a result, regular physical activity and physical therapy aimed at preventing further joint deterioration are advisable.<sup>43</sup>

#### **RECOMMENDATION 9.8.19:**

- **Patients with hemophilia should have the same screening for diabetes as the general population. **CB****

#### **RECOMMENDATION 9.8.20:**

- **Patients with hemophilia and diabetes should have the same management strategies to control their diabetes as the general population; if treatment with insulin is indicated, subcutaneous**

**injections can be administered without bleeding and without the need for factor replacement. **CB****

#### **Renal disease**

- A higher incidence of renal disease has been reported in people with hemophilia, compared with the general population. In addition, the likelihood of death from renal failure is about 50 times higher among patients with hemophilia than in the general population.<sup>45</sup>
- The increasing frequency of renal disease in older patients with hemophilia is likely due to a number of concomitant risk factors including<sup>44,45</sup>:
  - older age;
  - non-white population;
  - hypertension;
  - history of renal bleeds and hematuria, potentially resulting in structural renal damage;
  - HIV infection and combined antiretroviral therapy;
  - use of antifibrinolytic amino acids.
- Therefore, the need for dialysis may be increasing in patients with hemophilia.<sup>44</sup>
- In those patients who require renal replacement therapy, the choice between peritoneal dialysis and hemodialysis depends on patient-specific factors, such as the increased risk of infection in patients with cirrhosis and/or ascites.<sup>45</sup>
- Theoretically, peritoneal dialysis is preferable to hemodialysis because it requires factor coverage only at the time of catheter insertion; however, the procedure is associated with a high risk of peritoneal infections, particularly in HCV- and HIV-infected patients. Thus, hemodialysis using heparin and a single dose of CFC before and after each procedure is often preferred.<sup>44</sup>
- If hemodialysis is selected, central venous access is mandatory. Before placement of the device, factor levels should be 80-100 IU/ dL and then maintained between 50 and 70 IU/dL for 3 days after the procedure.<sup>45,77</sup>

#### **Osteoporosis**

- Bone mineral density (BMD) has been shown to be lower in people with hemophilia. An increased number of arthropathic joints, loss of joint movement, and muscle atrophy leading to inactivity are associated with a lower BMD.<sup>78,79</sup>
- It is not clear whether patients with hemophilia require routine monitoring of bone mass; it may be advisable in patients with high risk or multiple risk factors.
- Weight-bearing activities and suitable sports that promote development and maintenance of good bone density should be encouraged for younger patients, if their joint

health permits, to build bone mass and reduce the risk of later osteoporosis.

- Calcium and vitamin D supplements or bisphosphonates should be considered for patients with demonstrated osteopenia, and a dental evaluation should be carried out before initiating long-term bisphosphonate therapy.<sup>80,81</sup>

### Degenerative joint disease

- Joint damage progresses with increasing age in a near-linear fashion not only in patients with severe hemophilia but also in moderate cases.<sup>44</sup>
- Contributing factors include osteoporosis and osteopenia, a sedentary lifestyle, overweight, and obesity.<sup>44</sup>
- Due to the increased rate of joint morbidity, preventive strategies are necessary. While secondary prophylaxis reduces the incidence of bleeding, its efficacy in improving orthopedic function has not been clearly established.<sup>45</sup>
- See also Chapter 10: Musculoskeletal Complications.

#### RECOMMENDATION 9.8.21:

- All patients with hemophilia should be encouraged to engage in regular physical activity and to have adequate calcium and vitamin D intake.
- **REMARK:** Hemophilia patients with musculoskeletal conditions and injuries should have physical therapy and rehabilitation supervised by a physical therapist with hemophilia experience. **CB**

#### RECOMMENDATION 9.8.22:

- Hemophilia patients with osteoporosis, fragility fractures, or who are at increased fracture risk should be treated with individually adjusted anti-osteoporotic medications. **CB**

## 9.9 | Medical issues with aging

- See also 9.8 Comorbidities, above, for discussion of cancer/malignancy, cerebrovascular accident/stroke, atrial fibrillation, venous thromboembolism/thrombosis, metabolic syndrome, diabetes mellitus, renal disease, and degenerative joint disease.
- It is important to provide older patients with regular education and counselling on the importance of informing the hemophilia team of their health issues to ensure appropriate treatment.
- Aging patients with hemophilia require the same access as patients without hemophilia to health education and

preventive strategies to reduce the risk or impact of age-related morbidity.

- The hemophilia team should be closely involved in managing aspects and complications of care related to aging, and ensure close consultation and agreement on treatment plans.
- Patients with mild hemophilia may require specific education and attention to highlight potential issues associated with hemophilia and other illnesses.

#### RECOMMENDATION 9.9.1:

- **The WFH recommends that aging patients with hemophilia be granted the same access to health education and preventive strategies to reduce the risks or impacts of age-related morbidities as the general population. **CB****

#### RECOMMENDATION 9.9.2:

- **The WFH recommends the hemophilia team should be closely involved in managing aspects and complications of care related to aging and ensure close consultation and agreement on treatment plans. **CB****

### Hypertension

- Studies have shown that people with hemophilia have higher mean blood pressure, are twice as likely to have hypertension, and use more antihypertensive medications compared to the general population.<sup>82,83</sup>
- Hypertension is associated with the usual risk factors, such as older age, diabetes mellitus, dyslipidemia, or higher BMI and obesity; however, the causes of the increased prevalence of hypertension in patients with hemophilia remain unclear.<sup>84,85</sup>
- Hypertension is a well-established risk factor for cardiovascular diseases, renal diseases, and intracranial hemorrhage, all of which may pose significant challenges in the management of care for patients with hemophilia.<sup>84</sup>
- In view of the increased risk of bleeding, hypertensive patients with hemophilia should receive appropriate treatment and have their blood pressure checked regularly.
- In the absence of other cardiovascular risk factors, a systolic blood pressure  $\leq 130$  mm Hg and a diastolic blood pressure  $\leq 80$  mm Hg should be maintained.

#### RECOMMENDATION 9.9.3:

- **For all patients with hemophilia, the WFH recommends regular blood pressure measurements as part of their standard care.**

- **REMARK:** This recommendation is based on data indicating a higher prevalence of arterial hypertension among patients with hemophilia irrespective of age as compared with males in the general population. **CB**

#### **RECOMMENDATION 9.9.4:**

- For patients with hemophilia, the WFH recommends the same management of arterial hypertension as that applied in the general population.
- **REMARK:** Patients with hemophilia diagnosed with hypertension may be treated in a hemophilia treatment centre or referred to primary care providers depending on the local healthcare system and practices. **CB**

#### **Coronary artery disease**

- There is evidence that people with hemophilia develop atherosclerosis at similar rates to those in the general population.<sup>86,87</sup>
- By contrast, patients with hemophilia have lower cardiovascular mortality rates compared with the general population (most likely because of lower thrombin generation at the point of plaque rupture).<sup>87,88</sup>
- It is not known whether the increasing use of prophylaxis in aging patients with hemophilia will result in an increase in cardiovascular mortality.<sup>89</sup>
- Individuals with severe, moderate, and mild hemophilia may develop overt ischemic heart disease. The management of such cases should be individualized and requires close cooperation between the hemophilia and cardiology teams.
- Making a decision on antithrombotic therapy in a patient with innate bleeding tendency is particularly difficult; a recent study found that antiplatelet and anticoagulant medications increased severe bleeding in patients with hemophilia (odds ratio [OR] = 3.5).<sup>90</sup>
- When considering antithrombotic therapy in patients with hemophilia, the following aspects should be evaluated<sup>54</sup>:
  - patient bleeding phenotype;
  - intensity of the antithrombotic therapy;
  - duration of the planned therapy; and
  - characteristics of the antithrombotic agent.
- Healthcare providers working with patients with hemophilia should educate them on cardiovascular risk and encourage risk reduction (smoking, obesity, exercise) or optimization (hypertension, hyperlipidemia).<sup>89</sup>

#### **RECOMMENDATION 9.9.5:**

- Patients with hemophilia should receive the same screening and management for individual cardiovascular disease risk factors as the general population. **CB**

#### **RECOMMENDATION 9.9.6:**

- Patients with hemophilia and cardiovascular disease should receive routine care adapted to their individual situation in consultation with a cardiologist. **CB**

#### **RECOMMENDATION 9.9.7:**

- For patients with hemophilia without inhibitors who have been diagnosed with cardiovascular disease, the WFH recommends similar management as that applied to the general population, except for the necessary additional correction of impaired hemostasis with clotting factor concentrates.
- **REMARK:** Decisions on cardiovascular treatment strategy for patients with hemophilia should always be preceded by assessments of the individual's bleeding and thrombotic risks and cardiac disease severity and implemented under the advisement of a cardiologist. **CB**

#### **RECOMMENDATION 9.9.8:**

- Among patients with hemophilia and high-responding inhibitors, the WFH recommends limiting the use of antithrombotics to those patients in whom the risk of untreated thrombosis outweighs the risk of bleeding complications.
- **REMARK:** This recommendation is based on the observation that hemostatic response to bypassing agents is often unpredictable.
- **REMARK:** More research is needed to better understand the safety of antithrombotic therapy in patients treated with emicizumab. **CB**

#### **RECOMMENDATION 9.9.9:**

- Given the scarcity of published data on antiplatelet therapy in patients with hemophilia, the WFH recommends careful evaluation of an individual's bleeding and thrombotic risk.
- **REMARK:** It has been suggested that the trough level of the deficient clotting factor be maintained at  $\geq 15$ -30 IU/dL during dual antiplatelet therapy and at  $\geq 1$ -5 IU/dL during single-agent antiplatelet therapy; however, treatment strategy should be tailored to the individual.
- **REMARK:** The decision on use of antiplatelet therapy in a patient with hemophilia should always be made in consultation with a cardiologist. **CB**

#### **RECOMMENDATION 9.9.10:**

- Given the scarcity of published data on patients with hemophilia undergoing percutaneous coronary



intervention, the WFH recommends careful evaluation of an individual's bleeding and thrombotic risk.

- **REMARK:** It has been suggested that in patients with hemophilia without inhibitors who are undergoing PCI, the deficient clotting factor be maintained at the peak level of 80-100 IU/dL for as long as therapeutic doses of antithrombotics are used; however, treatment strategy should be tailored to the individual.
- **REMARK:** The decision on use of antithrombotic therapy for this indication should always be made in consultation with a cardiologist. **CB**

#### **RECOMMENDATION 9.9.11:**

- Given the scarcity of published data on patients with hemophilia undergoing coronary artery bypass grafting, the WFH recommends careful evaluation of an individual's bleeding and thrombotic risk.
- **REMARK:** It has been suggested that in patients with hemophilia without inhibitors who are undergoing CABG, similarly to other major surgical procedures, the deficient clotting factor be maintained at the peak level of 80-100 IU/dL before, during, and after CABG until sufficient wound healing has taken place; however, treatment strategy should be tailored to the individual.
- **REMARK:** The decision on use of antithrombotic therapy for this indication should always be made in consultation with a cardiologist. **CB**

#### **RECOMMENDATION 9.9.12:**

- Given the scarcity of published data on patients with hemophilia and ST-elevation myocardial infarction in whom early percutaneous coronary intervention is not available, the WFH recommends careful evaluation of an individual's bleeding risk and cardiac disease severity.
- **REMARK:** Use of fibrinolytic therapy may only be considered after complete correction of hemostasis with deficient clotting factor replacement.
- **REMARK:** The decision on use of fibrinolytic therapy for this indication should always be made in consultation with a cardiologist. **CB**

#### **RECOMMENDATION 9.9.13:**

- When heart valve replacement is indicated in patients with hemophilia, a bioprosthetic valve should be the first choice to avoid the need for indefinite anticoagulation. **CB**

#### *Hypercholesterolemia*

- Mean cholesterol levels in patients with hemophilia have been reported to be lower than in the general population.<sup>91</sup>

Cholesterol levels (total cholesterol, HDL, and LDL fraction) should be measured in aging patients with hemophilia at risk of cardiovascular disease.

- Treatment is indicated if cholesterol levels are high. As a general rule, the total cholesterol/HDL ratio should not be higher than 8.

#### **RECOMMENDATION 9.9.14:**

- **In patients with hemophilia, the management of hypercholesterolemia should be the same as for the general population. **CB****

#### **Psychosocial issues with aging**

- For aging patients with hemophilia, crippling, painful arthropathy can affect quality of life and may lead to loss of independence.<sup>92</sup>
- Aging patients may be confronted with unexpected emotional problems due to memories of negative experiences related to hemophilia (e.g., hospitalization) during their youth.<sup>89</sup>
- Adaptations at home or at work and an appropriate pain management regimen are indicated to improve quality of life and preserve independence.
- Active psychosocial support should be provided by a social worker, hemophilia nurse, physician, and/or psychologist.
- The patient's annual checkup at the hemophilia treatment centre is a good time to assess and address changing needs with age. Refer patients to appropriate services and resources as needed and as mutually agreed upon.

#### **RECOMMENDATION 9.9.15:**

- **As adults with hemophilia experience many personal and social changes with aging, the WFH recommends active psychosocial assessments and support for their changing needs. **CB****

#### *Quality of life assessment*

- People with hemophilia may face a variety of psychosocial issues which may impact their well-being. Quality of life assessments can help to:
  - identify patient perceptions of their health status and needs;
  - gather evidence on clinical findings that can lead to improved quality of care;
  - serve as a rapid screening to identify individual patients or populations who might require more detailed assessment of their health and quality of life needs; and

- identify individual and overall patient needs in terms of gaps in knowledge and/or education to facilitate better self-management.
- See also Chapter 11: Outcome Assessment.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.