

Chapter 9: Specific Management Issues

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RECOMMENDATIONS

9.2 | Carriers

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}

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}

Recommendation 9.2.4

Carriers of hemophilia should be offered counselling that includes reproductive implications and choices. ^{CB}

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}

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}

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}

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}

9.3 | Circumcision

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}

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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

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

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).

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- **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 postoperatively. ^{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

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

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}

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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

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}

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.

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- **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 ≥ 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}

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}

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}

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}

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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

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}

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}

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.

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- **REMARK** : It has been suggested that the trough level of the deficient clotting factor be maintained at ≥ 15 -30 IU/dL during dual antiplatelet therapy and at ≥ 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}

Recommendation 9.9.14

In patients with hemophilia, the management of hypercholesterolemia should be the same as for the general population. ^{CB}

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}

CB: Consensus based; APTT, activated partial thromboplastin time; HIV, human immunodeficiency virus; MMR, measles, mumps, and rubella; DAVP, desmopressin; CFCs, clotting factor concentrates; PCC, prothrombin complex concentrate; DOACs, direct oral anticoagulants; VKAS, vitamin K antagonists; VTE, venous thromboembolism; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery.