

5 HEMOSTATIC AGENTS

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

5.1 | Introduction

- Different types of hemostatic agents and coagulation therapies are available for the management of hemophilia. The wide range of product classes and types in use around the world reflects the evolution of hemophilia treatment products and the variations in local healthcare resources and capacities.
- Clotting factor concentrates (CFCs) are the treatment of choice for people with hemophilia as they are very safe and effective for treating and preventing bleeds. There are two main types of CFCs: virally inactivated plasma-derived products made from plasma donated by human blood donors; and recombinant products manufactured using genetically engineered cells and recombinant technology.
- The development of non-factor replacement therapies such as emicizumab has recently begun to offer an alternative treatment approach as such products become available in clinical practice.
- However, access to CFCs and emicizumab is limited in many parts of the world; in some countries, healthcare providers often rely on locally produced blood products such as cryoprecipitate and fresh frozen plasma (FFP) for

hemophilia treatment. However, these blood products are less effective than CFCs and may contain viral and bacterial pathogens.^{1,2} For this reason, where available, viral-inactivated plasma-derived or recombinant CFCs are preferred over cryoprecipitate and FFP.

- Although advances have been made in the safety of such blood products, the WFH's position is that the products of choice for hemophilia treatment are industrially manufactured CFCs where they fulfill the requirements for pharmaceutical Good Manufacturing Practice (GMP).²
- The comprehensive *WFH Guide for the Assessment of Clotting Factor Concentrates* describes the key elements that affect the quality, safety, efficacy, licensing, and regulation of factor products and the important principles involved in selecting suitable products for the treatment of hemophilia.²
- The WFH also publishes and regularly updates the *WFH Online Registry of Clotting Factor Concentrates*, which lists all currently available products and their manufacturing details.³

RECOMMENDATION 5.1.1:

- **For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived clotting factor concentrates.**
- **REMARK: The choice between these classes of product must be made according to local criteria including availability, cost, and patient preferences. **CB****

5.2 | Product selection

- Product selection should evaluate key requirements including product safety and quality, purity, viral inactivation, and efficacy.²

Safety and quality

- Currently manufactured plasma-derived CFCs produced to GMP standards have an exemplary safety record with respect to lipid-enveloped viruses, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV).
- Product safety is the result of comprehensive measures and improvements in several areas including:
 - donor selection (exclusion of at-risk donors);
 - screening of donations, including nucleic acid testing (NAT);
 - a number of in-process viral inactivation and/or removal steps, notably solvent-detergent and heat treatment, and nanofiltration for the removal of some non-enveloped viruses and prions; and
 - post-marketing surveillance.²
- As new information evolves in this field, decision-makers need to always be aware of current scientific recommendations regarding choice of CFCs for people with hemophilia.
- When selecting plasma-derived CFCs, both plasma quality and the manufacturing process need to be considered. The WFH emphasizes the importance of assessment by the official agencies responsible for protecting and promoting public health (i.e., national regulatory authorities, health agencies, or ministries of health) to ensure the quality, safety, and efficacy of plasma-derived treatment products for hemophilia.²
- Two issues require special consideration:
 - purity of product; and
 - viral inactivation/elimination.

Purity

- Purity of CFCs refers to the percentage of the desired ingredient (i.e., factor VIII [FVIII] or factor IX [FIX]) relative to the other ingredients in the product.
- There is no universally accepted classification of products based on purity, and CFCs on the market vary widely in their purity. Their “specific activity” may be expressed in international units (IU) per milligram (mg) and, for example, can range from 10 to >100 IU/mg for FVIII.⁴
- Some products have high or very high purity at one stage in the production process but are subsequently stabilized by albumin, which decreases their final purity.

- In rare cases, lower-purity CFCs may give rise to adverse or allergic reactions.^{5,6} Patients who experience repeated allergic reactions with a particular product may benefit from the administration of an antihistamine immediately prior to infusion or from the use of a higher-purity CFC.
- Plasma-derived FVIII CFCs may contain variable amounts of von Willebrand factor (VWF). Therefore, it is important to ascertain a product’s VWF content (as most commonly measured by VWF activity assay) if it is used for the treatment of von Willebrand disease (VWD) and not hemophilia A.⁷
- For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates (PCCs). PCCs also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture and may predispose the patient to thromboembolism. Current PCCs are considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z.^{8,9} Nevertheless, with intensive treatment (e.g., during perioperative management), prothrombotic clotting factors may accumulate in the plasma and increase the risk for thromboembolic complications.
- The viral safety of CFCs is not related to their purity, provided that adequate viral elimination measures are in place.

Viral inactivation/elimination

- In-process viral inactivation is the single largest contributor to the safety of plasma-derived CFCs.¹⁰
- Typically, two complementary or orthogonal-specific viral reduction steps are incorporated into the CFC manufacturing process. These measures should follow the regulations set by official regulatory agencies.
- Solvent-detergent treatment is highly effective against lipid-enveloped viruses such as hepatitis B virus (HBV), HCV, and HIV, but this treatment does not inactivate non-lipid-enveloped viruses such as hepatitis A virus (HAV) and human parvovirus B19.
- Heat treatment is generally effective against a broad range of viruses, both with and without a lipid envelope, including HAV and human parvovirus B19. However, the degree of inactivation is dependent upon the temperature, time, and whether heating occurs in the dry or wet state.
- As non-enveloped viruses currently pose a greater challenge than enveloped viruses to viral elimination during the manufacturing process,¹¹ any viral reduction/inactivation process should ideally inactivate both lipid-enveloped and non-lipid-enveloped viruses.

- Inactivation of prions in plasma-derived CFCs is not possible because the necessary techniques denature coagulation factors; nor is there a reliable screening test for variant Creutzfeldt–Jakob disease (vCJD). The risk of prion-mediated disease through plasma-derived products is currently being addressed by exclusion of at-risk donors, leukoreduction of donations, and plasma fractionation manufacturing steps including precipitation, chromatography, and filtration.¹⁰

RECOMMENDATION 5.2.1:

- **For people with hemophilia, the WFH recommends the use of products that have been accepted by the official regulatory agencies responsible for protecting and promoting public health with consideration given to the plasma quality (i.e., purity of the product) and the manufacturing process (i.e., viral inactivation/elimination).**
- **REMARK: A plasma-derived product created by a process that incorporates two viral reduction steps should not automatically be considered better than one that only has one specific viral inactivation step. If only one step is used, this step should preferably inactivate viruses with and without lipid envelopes. Most recently, licensed products use two orthogonal viral inactivation/elimination steps.**
- **REMARK: Current prothrombin complex concentrates should be considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. **

Efficacy

- Product potency (the biological activity in terms of the concentration or amount of the drug required to produce a defined effect) and efficacy (the ability of a drug to produce a desired therapeutic effect in patients) are also important features for consideration in product selection.²
- Plasma-derived and conventional recombinant FVIII and FIX CFCs with standard half-life (SHL) have been proven to have similarly high clinical efficacy.²
- Recombinant CFCs with extended half-life (EHL) are engineered to provide longer-lasting therapy than SHL CFCs. (See “Extended half-life products” below.)

5.3 | Clotting factor concentrates (CFCs)

- The main treatment for severe hemophilia is CFC replacement therapy with plasma-derived or recombinant

CFCs as they provide convenient high doses of clotting factor for the treatment and prevention of bleeds.

- See also Chapter 2: Comprehensive Care of Hemophilia, Chapter 6: Prophylaxis in Hemophilia, Chapter 7: Treatment of Specific Hemorrhages, and Chapter 9: Specific Management Issues.

FVIII CFCs

- All currently marketed plasma-derived and recombinant FVIII products are listed in the *WFH Online Registry of Clotting Factor Concentrates*.³ Consult the individual product inserts for details.

Dosage/administration

- FVIII CFCs are available in vials labelled with the product potency expressed in IU, ranging from approximately 250–3000 IU per vial.
- In the absence of an inhibitor, each IU of plasma-derived or recombinant SHL FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level by approximately 2 IU/dL.¹² This raise (also called recovery) is dependent on several individual factors; most importantly, the body mass index (BMI). It is higher in patients with a high BMI and lower in those with a low BMI.¹³
- The half-life of SHL FVIII is approximately 12 hours in adults; its half-life is shorter in younger children and increases with age.
- To calculate dosage, multiply the patient’s weight in kilograms by the FVIII level in IU/dL desired, then multiply by 0.5.
 - Example: 50 kg × 40 (IU/dL level desired) × 0.5 = 1000 IU of FVIII.
- See Chapter 7: Treatment of Specific Hemorrhages and refer to Table 7-2 for CFC replacement for different types of hemorrhage.
- FVIII CFCs should be infused slowly over several minutes as specified in the product insert.¹⁴ The patient’s peak factor level should be measured 15–30 minutes after the infusion to verify the expected FVIII activity level of the dose given.¹²
- For patients undergoing surgery or those with severe bleeds that require frequent infusions, laboratory monitoring of FVIII levels is necessary, including measurement of FVIII trough level to aid in the calculation of subsequent doses. (See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays, and Chapter 9: Specific Management Issues – Surgery and invasive procedures.)
- Subsequent doses should ideally be based on the FVIII half-life and on the factor recovery in the individual

patient for a particular product. However, the half-life in individual patients cannot be predicted simply from patient characteristics such as age and body weight and typically requires empiric determination.

- Guidelines for pharmacokinetic (PK) studies on new FVIII CFCs include 10-11 blood samplings taken over a period of 32-48 hours (additional samplings over up to 96 hours or longer for EHL FVIII). However, for dose tailoring in routine practice, useful PK parameters can be estimated from population PK models which enable Bayesian estimation of individual PK from limited samples.¹⁵
- See Chapter 6: Prophylaxis in Hemophilia and Chapter 7: Treatment of Specific Hemorrhages.

RECOMMENDATION 5.3.1:

- For people with hemophilia receiving FVIII concentrates who would benefit from optimization of prophylaxis, the WFH recommends individualized pharmacokinetic monitoring.
- **REMARK:** Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 32-96 hours), or with limited sampling in combination with population PK estimates. **CB**
- Continuous infusion of CFCs avoids peaks and troughs and may be advantageous and more convenient in certain clinical situations (e.g., major surgery or severe bleeding episodes in patients with low-responding inhibitors). However, the use of specifically designated pumps and knowledge of the stability of the particular CFC after reconstitution within the infusion device are required.¹⁶
- Continuous infusion may allow a reduction in factor clearance, dosage, and the total quantity of CFCs used.¹⁷ It can potentially be more cost-effective for patients with severe hemophilia, depending on the doses used for continuous and intermittent bolus infusions.¹⁸ However, caution should be exercised if considering continuous infusion for patients with mild hemophilia as this has been associated with an increased risk of the development of inhibitors,^{19,20} although the contribution of continuous infusion alone may be confounded by the presence of high-risk pathogenic variants in mild hemophilia A.
- Doses for continuous infusion should be adjusted based on frequent factor assays (usually once a day) and calculation of clearance, noting that clearance of factor may be increased immediately after surgery or with severe bleeding (e.g., blood loss of >500 mL), whereby additional boluses of

CFCs may be required to maintain effective levels. For some CFCs, stability can be demonstrated for up to 12 hours after preparing the solution; thus, continuous infusion over several hours is possible.²¹

RECOMMENDATION 5.3.2:

- For patients with hemophilia receiving FVIII concentrates where steady-state hemostatic correction is necessary for a prolonged period of time (e.g., perioperative management or in the case of a severe bleeding episode in a patient with a low-responding inhibitor), the WFH recommends consideration for use of continuous infusion.
- **REMARK:** Continuous infusion may lead to a reduction in the total quantity of clotting factor concentrates used and can be more cost-effective in patients with severe hemophilia. However, this cost-effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions.
- **REMARK:** Continuous infusion requires the use of specifically designated pumps and knowledge of the stability of the particular clotting factor concentrate after reconstitution within the infusion device, and patients must be monitored frequently for pump failure. **CB**

FIX CFCs

- All currently marketed plasma-derived and recombinant FIX products are listed in the *WFH Online Registry of Clotting Factor Concentrates*.³ Consult the individual product inserts for details.
- FIX CFCs are categorized into two classes:
 - Pure FIX CFCs, which may be plasma-derived or recombinant (see below for information on EHL FIX CFCs);
 - FIX CFCs that also contain factors II, VII, IX, and X, known as prothrombin complex concentrates (PCCs), which are nowadays only rarely used.
- Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B^{8,9} as they are associated with a reduced risk of thrombosis and disseminated intravascular coagulation compared to PCCs, particularly in the following instances:
 - surgery;
 - liver disease;
 - intensive exposure, i.e., prolonged therapy at high doses;
 - previous thrombosis or known thrombotic tendency;
 - concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents.

- See Chapter 9: Specific Management Issues – Surgery and invasive procedures.

RECOMMENDATION 5.3.3:

- For treatment of FIX deficiency in patients with hemophilia B, the WFH recommends a product containing only FIX rather than prothrombin complex concentrates (PCCs), which also contain other clotting factors, such as factors II, VII, and X, some of which may become activated during manufacture and may predispose the patient to thromboembolism.
- **REMARK:** Pure FIX products have reduced risk of thrombosis or disseminated intravascular coagulation, compared to what was observed with large doses of older-generation PCCs.
- **REMARK:** Current PCCs are considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. Nevertheless, in cases of intensive treatment (e.g., perioperative management), prothrombotic clotting factors may accumulate in plasma and may increase the risk for thromboembolic complications. When PCCs are used in high doses in order to normalize FIX levels, thromboprophylaxis should be considered. **CB**

RECOMMENDATION 5.3.4:

- For hemophilia B patients requiring prolonged therapy at high doses, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. **CB**

RECOMMENDATION 5.3.5:

- For hemophilia B patients undergoing surgery, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. **CB**

RECOMMENDATION 5.3.6:

- For hemophilia B patients with liver disease, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. **CB**

RECOMMENDATION 5.3.7:

- For hemophilia B patients with previous thrombosis or known thrombotic tendency, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. **CB**

RECOMMENDATION 5.3.8:

- For hemophilia B patients concomitantly using drugs known to have thrombogenic potential, including antifibrinolytic agents, the use of pure FIX concentrates is recommended over prothrombin complex concentrates.

CB

Dosage/administration

- FIX CFCs are available in vials labelled with the product potency, ranging from approximately 250-4000 IU per vial.
- In the absence of an inhibitor, each IU of plasma-derived or recombinant SHL FIX per kilogram of body weight infused intravenously will raise the plasma FIX level by approximately 1 IU/dL.¹²
- The half-life of SHL FIX is approximately 18-24 hours. Guidelines for PK studies on FIX CFCs include at least 8 blood samplings taken over a period of 72 hours (additional samplings over up to 2 weeks for EHL FIX). However, for dose tailoring in routine practice, useful PK parameters can be estimated from population PK models which enable Bayesian estimation of individual PK from limited samples.¹⁵

RECOMMENDATION 5.3.9:

- For patients with hemophilia B receiving FIX concentrates who would benefit from optimization of prophylaxis, the WFH recommends pharmacokinetic monitoring.
- **REMARK:** Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 1-2 weeks), or with limited sampling in combination with population PK estimates. **CB**
- Unmodified recombinant FIX (rFIX) CFCs have a lower recovery than plasma-derived FIX CFCs, such that each unit of FIX infused per kilogram of body weight will raise FIX activity by approximately 0.8 IU/dL in adults and 0.7 IU/dL in children under 15 years of age.²²
- To calculate dosage, multiply the patient's weight in kilograms by the FIX level in IU/dL desired.
 - Example: 50 kg body weight × 40 (IU/dL level desired) = 2000 IU of plasma-derived FIX.
 - For rFIX, the dose is calculated as 2000 IU ÷ 0.8 (or 2000 IU × 1.25) = 2500 IU for adults, and 2000 IU ÷ 0.7 (or 2000 IU × 1.43) = 2860 IU for children.

- See Chapter 7: Treatment of Specific Hemorrhages and refer to Table 7-2 for practice patterns with CFCs for different types of hemorrhage.
- FIX CFCs should be infused slowly over several minutes as specified in the product insert.¹⁴ The patient's peak FIX level should be measured approximately 15-30 minutes after infusion to verify the expected FIX activity of the dose given.¹²
- For patients undergoing surgery or those with severe bleeds that require frequent infusions, laboratory monitoring of FIX levels is required including measurement of FIX trough level to aid in the calculation of subsequent doses. (See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays, and Chapter 9: Specific Management Issues – Surgery and invasive procedures.)
- Purified FIX CFCs may also be administered by continuous infusion (as with FVIII CFCs).
- Allergic reactions may occur with infusions of both recombinant and plasma-derived FIX CFCs (in approximately 2%-4% of cases). These are often associated with anti-FIX inhibitors.
- The WFH recommendations on EHL products were structured accordingly:
 - The emphasis was on the absence of “clinical safety issues” and not on preclinical observations from animal models with unclear implications.
 - The WFH recognizes that evaluation of both clinical and preclinical observations of EHL products has led to divergence in regulatory approval for some PEGylated products, which has impacted their licensing for prophylaxis and pediatric application in some geographies.
 - Regarding allergic reactions, these are, albeit rarely, observed for all infusion treatment products and have been observed with fusion proteins as well.²⁷
 - Regarding anti-PEG antibodies, there is no published evidence to support that these have clinical safety implications in patients with hemophilia.²⁸

Extended half-life products

Rationale for development of EHL CFCs

- The frequency of infusions using SHL CFCs is associated with an increased burden of treatment and often leads to poor adherence to prophylaxis regimens.²³ Annualized bleeding rates (ABRs) are not always zero with prophylaxis with SHL CFCs, and joint disease can still appear in young adults.^{24,25} EHL products were developed to address the need to reduce the treatment burden of prophylaxis and to maintain higher factor trough levels to improve bleed prevention.

Mechanisms of half-life extension

- Fusion technologies and PEGylation are successful half-life extension strategies in hemophilia.²⁶
- Fusion technologies rescue endocytosed proteins from intracellular degradation pathways through interaction with the neonatal Fc receptor.
- PEGylation reduces interaction with clearance receptors.
- All currently marketed EHL products are listed in the *WFH Online Registry of Clotting Factor Concentrates*.³ Consult the individual product inserts for details.
- Different types of recombinant and modified forms of FVIII and FIX are summarized in Chapter 3: Laboratory Diagnosis and Monitoring – Tables 3-2 and 3-3.

RECOMMENDATION 5.3.10:

- **For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the half-life of clotting factor concentrates.**

CB

Pharmacokinetic properties of EHL products

- For EHL FVIII products, half-life extension has been limited to 1.4- to 1.6-fold (or approximately 19 hours) that of SHL FVIII products. EHL FIX products have a much longer half-life at 3- to over 5-fold that of SHL FIX products.
- The prolonged half-life of EHL products translates to dosing twice per week or every 3 days in most cases for FVIII, and once every 7-14 days for FIX.
- Clearance of EHL products in adolescents and adults is similar, as was observed for SHL products, and half-life is shorter in pediatric populations.²⁹
- EHL FIX products do not demonstrate the lower factor recovery observed with standard rFIX products. Some EHL FIX products show much higher recovery, suggesting extravascular distribution of a lower proportion of EHL FIX.^{30,31} Accordingly, clinical assessment of efficacy should supplement assessment of plasma PK measurements.
- Modification of these molecules has introduced variations in their activity measurements in routine coagulation assays. Thus, clinicians should follow the recommendations accompanying a product's regulatory approval regarding the optimal assays to be used for laboratory monitoring.

(See Chapter 3: Laboratory Diagnosis and Monitoring – Factor assays.)

Safety and efficacy of EHL products

- All registered EHL products have been shown to be efficacious in the prevention and treatment of bleeds in children, adolescents, and adults. Over 90% of bleeds were successfully treated with a single administration, and the efficacy in bleed prevention resulted in ABRs <4-5 across all EHL products. Hemostatic efficacy was demonstrated in a variety of minor and major surgeries.³²
- In previously treated children, adolescents, and adults, no increased risk of new inhibitor development has been observed in those receiving EHL FVIII/FIX products; all clinical trials in previously treated patients (PTPs) have demonstrated either no inhibitor development or very low incidence rates that were within regulatory safety limits.
- EHL products have been given to previously untreated patients (PUPs), either as part of clinical PUP studies or outside of studies. Although inhibitor development has been reported in such settings, no substantial difference in levels of inhibitor development has been observed with EHL compared to SHL products. However, no completed trial in PUPs has yet been published in full.

Approaches to dosing with EHL products

- Although EHL CFCs extend the time until patients reach the minimum trough levels required to avoid spontaneous bleeds, there is significant interpatient variability related to age, body mass, blood group, VWF level, bleeding phenotype, physical activity level, joint status, and compliance. Accordingly, there is no consensus on standardized dosing with EHL CFCs nor management of patients receiving EHL products.^{23,33}
- Each of the following approaches has established efficacy in clinical trials with EHL CFCs:
 - fixed programmatic prophylaxis (fixed dose and interval, e.g., once weekly for FIX, twice weekly for FVIII);
 - PK-tailored prophylaxis (dose tailored to target trough level, given at fixed intervals);
 - phenotypic-tailored prophylaxis (variable dose and interval tailored according to bleeding pattern and activity);
 - dose/frequency-tailored prophylaxis (dose and/or frequency tailored according to target trough level and interval, e.g., higher dose and longer interval).
- To transition from SHL to EHL factor replacement therapy, dose frequency is typically lowered from 3 to 2 times

weekly for FVIII, and from twice weekly to once every 7-10 days for FIX.

- PK-driven dosing allows more individualized prophylaxis. Population PK tools are in development to aid the implementation of individualized prophylaxis in clinical practice. Once an individual's PK profile is generated, the dose and treatment frequency required to obtain a desired trough level can be estimated. The target trough level needs to be customized to the needs of the individual patient within their healthcare system's parameters and flexibilities.
- See Chapter 6: Prophylaxis in Hemophilia – Extended half-life factor prophylaxis.

RECOMMENDATION 5.3.11:

- **Patients with hemophilia who are transitioning from standard half-life clotting factor concentrates to extended half-life clotting factor concentrates would typically require decreased dose frequencies, but EHL products may also be used to maintain higher trough levels to optimize prophylaxis.**
- **REMARK: Pharmacokinetic-guided dosing as per Recommendations and 5.3.9 provides for more individualized prophylaxis. **

5.4 | Bypassing agents

- Bypassing agents are used for the treatment and prevention of bleeding complications in patients with hemophilia A or B who develop FVIII or FIX alloantibodies (called inhibitors) that typically neutralize the function of infused CFCs.³⁴ These agents are based on different mechanisms of action to achieve hemostasis, thereby bypassing the need for FVIII or FIX replacement to treat and prevent bleeds.³⁵

Recombinant activated factor VIIa (rFVIIa)

- Recombinant activated factor VIIa (rFVIIa) is a bypassing agent that promotes coagulation through tissue factor-dependent and independent pathways.³⁵ rFVIIa binds to tissue factor to activate FX and FIX and allows the coagulation cascade to resume.^{36,37}

Activated prothrombin complex concentrate (aPCC)

- Activated prothrombin complex concentrate (aPCC) is used to treat patients with hemophilia A with inhibitors. aPCC contains mainly non-activated FII (prothrombin), FIX, FX, and mainly activated FVII.³⁸⁻⁴⁰

- See Chapter 8: Inhibitors to Clotting Factor for more information on bleed management for patients with inhibitors.

RECOMMENDATION 5.4.1:

- For people with hemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, the WFH recommends that a bypassing agent be used.
- **REMARK: Bypassing agents include recombinant activated factor VIIa or activated prothrombin complex concentrate. CB**

RECOMMENDATION 5.4.2:

- For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used. CB

RECOMMENDATION 5.4.3:

- The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events. CB
- In addition to bypassing agents, non-factor replacement therapies (e.g., emicizumab) are becoming available that offer new treatment paradigms including for the treatment of inhibitors.
- See 5.7 Non-factor replacement therapies, below; and Chapter 6: Prophylaxis in Hemophilia – Prophylaxis using non-factor replacement therapies.

5.5 | Other plasma products

- Cryoprecipitate and FFP are not normally subjected to viral inactivation procedures (such as heat or solvent-detergent treatment) and consequently carry an increased risk of transmission of viral pathogens, which is significant with repeated infusions.^{1,41} However, the WFH recognizes the necessity of the continued use of cryoprecipitate and FFP in some parts of the world where they are the only available or affordable treatment options.^{1,2}
- Certain steps can be taken to minimize the risk of transmission of viral pathogens. These include:
 - quarantining plasma until the donor has been tested or even retested for antibodies to HIV, HCV, and the surface antigens of the hepatitis B virus (HBsAg)—a

practice that is difficult to implement in countries where the proportion of repeat donors is low;

- NAT testing to detect viruses—a technology that has a potentially much greater relevance for the production of cryoprecipitate than for CFCs, as the latter are subjected to viral inactivation steps.⁴²
- Allergic reactions are more common following infusion of cryoprecipitate than CFC.⁴¹ (For use of antihistamine prophylaxis, see “Safety and quality” above.)

RECOMMENDATION 5.5.1:

- For patients with hemophilia, the WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant clotting factor concentrates in preference to cryoprecipitate or fresh frozen plasma.
- **REMARK: The WFH supports the use of CFCs in preference to cryoprecipitate or FFP due to concerns about quality, safety, and efficacy. However, the WFH recognizes the reality that they are still widely used in countries around the world where they are the only available or affordable treatment options. CB**

Fresh frozen plasma (FFP)

- As fresh frozen plasma contains all coagulation factors, it is sometimes used to treat coagulation factor deficiencies.
- Cryoprecipitate is preferable to FFP for the treatment of hemophilia A.⁴³ However, as FFP and cryo-poor plasma contain FIX, albeit in low concentrations, they can be used for the treatment of hemophilia B in countries unable to afford plasma-derived FIX CFCs.

RECOMMENDATION 5.5.2:

- For patients with hemophilia, fresh frozen plasma is not recommended due to concerns about the safety and quality.
- **REMARK: However, the WFH recognizes the as yet unavoidable reality of their continued use in some parts of the world where it is the only available or affordable treatment option. CB**
- It is possible to apply some forms of virucidal treatment to packs of FFP (including solvent-detergent treatment). The use of treated packs is recommended; however, virucidal treatment may have some impact on coagulation factors. The large-scale preparation of pooled solvent-detergent-treated plasma has also been shown to reduce the proportion of the largest multimers of VWF,^{44,45} which is important for VWD, but is irrelevant for treatment of hemophilia A.

Dosage/administration

- One mL of FFP contains 1 unit of factor activity.
- It is generally difficult to achieve FVIII levels higher than 30 IU/ dL with FFP alone.
- FIX levels above 25 IU/dL are difficult to achieve. A starting FFP dose of 15-20 mL/kg is acceptable.⁴³

Cryoprecipitate

- Cryoprecipitate is the insoluble concentrate of high molecular weight plasma proteins that precipitate when frozen plasma is slowly thawed at 1-60°C.
- Cryoprecipitate contains significant quantities of FVIII (about 3-10 IU/mL), VWF, fibrinogen, and FXIII but not FIX nor FXI. The resultant supernatant is called cryo-poor plasma and contains other coagulation factors such as factors VII, IX, X, and XI.
- The use of viral inactivation procedures is strongly encouraged.^{1,43,46,47}
- The manufacture of small pool, viral-inactivated (solvent-detergent-treated) cryoprecipitate has been described, although this provides safety only for lipid-enveloped viruses.⁴⁷

RECOMMENDATION 5.5.3:

- **For patients with hemophilia, cryoprecipitate is not recommended due to concerns about the safety and quality.**
- **REMARK: The use of cryoprecipitate can only be justified in situations where clotting factor concentrates are not available as there is no proven advantage for their use over CFCs. It is strongly encouraged that viral-inactivation procedures be used, if available. **

Dosage/administration

- A bag of cryoprecipitate made from 1 unit of FFP (200-250 mL) may contain 70-80 units of FVIII in a volume of 30-40 mL.

5.6 | Other pharmacological options

- In addition to CFCs, other agents can be of great value in a significant proportion of cases. These include:
 - desmopressin (DDAVP);
 - tranexamic acid; and
 - epsilon aminocaproic acid (EACA).
- See also Chapter 2: Comprehensive Care of Hemophilia, Chapter 7: Treatment of Specific Hemorrhages, and Chapter 9: Specific Management Issues.

Desmopressin (DDAVP)

- Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) is a synthetic analogue of vasopressin that boosts plasma levels of FVIII and VWF.⁴⁸
- DDAVP may be the treatment of choice for patients with mild or moderate hemophilia A when FVIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using CFC including the risk of FVIII inhibitor development.⁴⁸⁻⁵¹
- DDAVP does not affect FIX levels and is of no value in hemophilia B.
- There are significant differences in individual patient response to DDAVP. The response to intranasal DDAVP is more variable and therefore less predictable.^{48,49}
- DDAVP is particularly useful in the treatment and prevention of bleeding in carriers of hemophilia A.⁵²
- DDAVP is not licensed for use in pregnancy, but it has been used with caution in pregnant carriers during labour and delivery. Its use should be avoided in preeclampsia and eclampsia because of the already high levels of VWF.^{53,54} (See Chapter 9: Specific Management Issues – Carriers.)
- The decision to use DDAVP must be based on both the patient's baseline FVIII activity, the increment achieved, and the duration of treatment required.

Dosage/administration

- Though DDAVP may be given subcutaneously, it is primarily administered by intravenous infusion or nasal spray. It is important to choose the correct preparation of DDAVP because some lower-dose preparations are used for other medical purposes.
- Appropriate preparations include:
 - 4 µg/mL for intravenous use;
 - 15 µg/mL for intravenous and subcutaneous use;
 - 150 µg per metered dose as nasal spray.
- A single dose of 0.3 µg/kg body weight, either via intravenous or subcutaneous administration, can be expected to boost the FVIII level 3- to 6-fold.^{48,55}
- For intravenous use, DDAVP is usually diluted in at least 50-100 mL of physiological saline and given by slow infusion over 20-30 minutes.
- The peak response is seen approximately 60 minutes after either intravenous or subcutaneous administration.
- Children should generally not be given DDAVP more than once per day; in adults under close supervision, twice-daily dosing may be considered. With subsequent dosing, therapeutic response decreases (tachyphylaxis) and the risk of complications rises; thus, in general, DDAVP should not be used for more than 3 consecutive days.

- CFCs may be needed when higher factor levels are required for a prolonged period.⁵⁶
- Rapid DDAVP infusion may result in tachycardia, flushing, tremor, and abdominal discomfort.
- A single metered intranasal DDAVP spray of 1.5 mg/mL in each nostril is appropriate for an adult. For patients with a body weight of less than 40 kg, a single dose in one nostril is sufficient.^{57,58}
- Some patients may find the intranasal preparation of DDAVP difficult to use, and it may be less efficacious than DDAVP given subcutaneously.
- Because DDAVP is an antidiuretic agent, water retention, hyponatremia, and even seizures may occur in patients receiving large amounts of hypotonic intravenous or oral fluids, necessitating fluid restriction during DDAVP treatment.⁵⁹ This is especially important in the context of home treatment of minor bleeding episodes and peri-operatively, when large quantities of infusions are used—patients/caregivers should be instructed to restrict fluids after DDAVP use.⁵⁹
- DDAVP should be used with caution in young children, and it is contraindicated in children under 2 years of age. For young pediatric inpatients (i.e., postoperative patients), hypotonic intravenous fluids should be avoided and total fluid intake should be reduced to 75% of maintenance requirements in the 24 hours after use of DDAVP.⁵⁹ Plasma osmolality and sodium levels should be measured before and after DDAVP use in young children, especially if more than one dose is used over a 24-hour period.^{48,59-61}
- Hyponatremia is uncommon in most adults treated with DDAVP. However, hypotension is commonly observed in both children and adults, and children under 2 years of age have an increased risk of seizures secondary to cerebral edema caused by water retention/ hyponatremia.^{61,62} Other side effects of DDAVP include headache, flushing, fatigue, and tachycardia. Given the vasoactive effect of DDAVP, caution should be exercised if it is used in patients with hypertension that is not completely controlled by therapy. These side effects may occur more often after intravenous administration.^{63,64}
- There are case reports of thrombosis (including myocardial infarction) after infusion of DDAVP. It should be used with caution in patients with a history or risk of cardiovascular disease.⁵⁵

RECOMMENDATION 5.6.1:

- **For patients with mild or moderate hemophilia A and carriers of hemophilia A, the WFH recommends**

considering desmopressin (DDAVP) as an option for treatment.

- **REMARK:** The WFH recommends testing DDAVP prior to therapeutic use to evaluate the individual FVIII response. The decision to use DDAVP must be based on the patient's baseline FVIII activity, the increment achieved, and the duration of treatment required.
- **REMARK:** In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion, and are mostly mild and transient. However, hypotension and/or severe hyponatremia can also occur.
- **REMARK:** For pregnant women during labour and delivery, the WFH recommends caution in the use of DDAVP, and it should be avoided in pre-eclampsia and eclampsia.
- **REMARK:** With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period. **CB**

RECOMMENDATION 5.6.2:

- **For adults, the WFH recommends DDAVP not be used for more than 3 consecutive days and only under close supervision. If DDAVP is administered twice in a single day, subsequent daily dosing should be limited to once per day.**
- **REMARK:** In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion. However, hypotension and/or hyponatremia can also occur.
- **REMARK:** With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period. **CB**

RECOMMENDATION 5.6.3:

- **For children, the WFH recommends using no more than 1 dose of DDAVP per day for no more than 3 consecutive days.**
- **REMARK:** In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion. However, hypotension and/or hyponatremia can also occur.

- **REMARK: With more than 3 consecutive days of dosing, the therapeutic response may decrease (tachyphylaxis) and the risk of complications rises; thus, clotting factor concentrates may be needed when higher factor levels are required for a prolonged period. CB**

RECOMMENDATION 5.6.4:

- **For children under 2 years of age, the WFH alerts that DDAVP is contraindicated due to increased risk of seizures as consequences of water retention and hyponatremia. CB**

RECOMMENDATION 5.6.5:

- **For patients at risk of cardiovascular disease or thrombosis, the WFH recommends that DDAVP should be used with caution due to the risk of thromboembolism and myocardial infarction. CB**

Tranexamic acid

- Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin. It promotes clot stability and is useful as adjunctive therapy for some types of hemophilic bleeding.⁶⁵
- Treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia.⁶⁵
- Tranexamic acid is useful for treating superficial soft tissue and mucosal bleeds (e.g., oral bleeding, epistaxis, and menorrhagia).⁶⁶⁻⁶⁸
- Tranexamic acid is particularly valuable in the setting of dental surgery and may be used to control oral bleeding associated with eruption or shedding of teeth.^{67,69}
- See also Chapter 2: Comprehensive Care of Hemophilia and Chapter 7: Treatment of Specific Hemorrhages.

Dosage/administration

- Tranexamic acid is usually given as oral tablets (25 mg/kg/dose) 3-4 times daily. It can also be given by intravenous infusion (10 mg/kg/dose) 2-3 times daily. It is also available as an oral rinse.
- Gastrointestinal upset (nausea, vomiting, or diarrhea) may rarely occur as a side effect of tranexamic acid, but these symptoms usually resolve if the dosage is reduced. When administered intravenously, tranexamic acid must be infused slowly as rapid injection may result in dizziness and hypotension.
- A syrup formulation of tranexamic acid is also available for pediatric use. If this is not obtainable, a tablet can be crushed finely and dissolved in clean water for topical use on bleeding mucosal lesions.

- Tranexamic acid is commonly prescribed for 7 days following dental extractions to prevent postoperative bleeding.
- Tranexamic acid is excreted by the kidneys, and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.
- The use of tranexamic acid is contraindicated for the treatment of hematuria as its use may prevent dissolution of clots in the ureter, leading to serious obstructive uropathy and potentially permanent loss of renal function.
- Tranexamic acid is also contraindicated in the setting of thoracic surgery where it may result in the development of insoluble hematomas.
- Tranexamic acid may be given alone or together with standard doses of CFCs including bypassing agents such as aPCC and rFVIIa.⁷⁰⁻⁷²
- Tranexamic acid is contraindicated in patients with hemophilia B receiving PCCs, as it increases the risk of thromboembolism.⁷³

RECOMMENDATION 5.6.6:

- **For patients with hemophilia, the WFH recommends that antifibrinolytics are a valuable alternative to use alone or as adjuvant treatment, particularly in controlling mucocutaneous bleeding (e.g., epistaxis, oral and gastrointestinal bleeding, and menorrhagia) and for dental surgery and eruption or shedding of teeth.**
- **REMARK: Antifibrinolytics can be used with standard doses of clotting factor concentrates, including bypassing agents. However, they should not be used with prothrombin complex concentrates due to the increased risk of thromboembolism. CB**

RECOMMENDATION 5.6.7:

- **For patients with hematuria, the WFH recommends against the use of antifibrinolytics, as it is contraindicated in these patients due to increased risk of obstructive uropathy. CB**

RECOMMENDATION 5.6.8:

- **For patients with renal impairment, the WFH recommends reduced dosing of antifibrinolytics and close monitoring. CB**

Epsilon aminocaproic acid

- Epsilon aminocaproic acid is similar to tranexamic acid but is less widely used as it has a shorter plasma half-life, lower potency, and higher toxicity.⁶⁵

- See also Chapter 2: Comprehensive Care of Hemophilia and Chapter 7: Treatment of Specific Hemorrhages.

Dosage/administration

- In adults, EACA is typically administered orally (100 mg/kg/dose up to a maximum of 2 g/dose) or intravenously (100 mg/kg/dose up to a maximum of 4 g/dose) every 4-6 hours up to a maximum of 24 g/day.
- A 250 mg/mL syrup formulation of EACA is also available.
- Gastrointestinal upset is a common complication with EACA use; reducing the dose often alleviates this side effect.
- Myopathy is a rare adverse reaction specifically reported in association with EACA therapy (but not tranexamic acid) and typically occurs after administration of high doses for several weeks.
- The myopathy associated with EACA use is often painful and associated with elevated levels of creatine kinase and even myoglobinuria. Full resolution may be expected once EACA treatment is stopped.

5.7 | Non-factor replacement therapies

- For the past five decades, the focus of hemophilia therapies has been on replacing the missing clotting factor protein; however, recombinant technology combined with improved basic understanding of coagulation biochemistry is currently shifting the treatment paradigm.

Rationale and mechanisms of action

- New and emerging innovative therapeutics have been developed with alternative modes of delivery (e.g., subcutaneous), targets that overcome the limitations of current clotting factor replacement therapy (i.e., intravenous administration, short half-life, risk of inhibitor formation), and markedly improved PK profiles with a very low burden of administration (e.g., up to monthly dosing), which may increase compliance.

Substitution therapy

- Substitution therapy differs from factor replacement therapy in that it is based on the use of an alternative hemostatic agent to substitute for clotting factor. The factor mimetic, emicizumab, is the first and only licensed substitution therapy at the time of this publication.
- Emicizumab is a chimeric bispecific antibody directed against the enzyme FIXa and the zymogen FX that mimics the cofactor function of FVIII in patients with hemophilia A, with or without inhibitors. Emicizumab binds to FIX,

FIXa, FX, and FXa; however, it is its affinity to FIXa and FX that promotes FIXa-catalyzed FX activation and tenase formation.^{74,75}

- The key benefits of emicizumab are its subcutaneous route of administration, long half-life, high efficacy in bleed prevention, and reduction of the frequency of bleeding episodes in patients with or without FVIII inhibitors.
- As emicizumab differs biochemically from FVIII, many questions remain regarding its long-term impact on joint pathology and immunogenicity in non-inhibitor patients.
- Emicizumab is not intended to treat acute bleeding episodes. Caution is required when treating breakthrough bleeding episodes while on emicizumab as several patients have developed either venous thromboembolism or thrombotic microangiopathy with concomitant administration of aPCC.⁷⁶ Consult the hemophilia treatment centre and risk management guidance.

RECOMMENDATION 5.7.1:

- **For patients with hemophilia A with an inhibitor, the WFH recommends that emicizumab should be used for regular prophylaxis.**
- **REMARK: For patients with hemophilia A with no inhibitor, the WFH recommends that emicizumab can be used for regular prophylaxis. CE**

Hemostatic rebalancing agents

- The hemostatic system regulates the balance between procoagulants (e.g., clotting factors) and natural anticoagulants (e.g., antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C). Bleeding disorders result from a deficiency of the procoagulants, whereas deficiencies of the natural anticoagulants are associated with increased thrombotic risk.
- Hemophilia has typically been treated by replacing the missing procoagulant protein or with bypassing agents (i.e., when inhibitors are present). However, inhibiting the natural anticoagulants can also restore hemostasis. This has been observed naturally as co-inheritance of thrombophilic risk factors can moderate the clinical phenotype of severe hemophilia A. In addition, thrombin generation is increased with co-inheritance of hemophilia with some forms of thrombophilia (e.g., protein C deficiency).
- Fitusiran is an RNA interference therapy that specifically targets antithrombin messenger RNA to suppress the production of antithrombin in the liver.⁷⁷ This therapy has the advantage of subcutaneous administration, prolonged duration of action and, due to its mechanism of action, it

could be used in both hemophilia A and B patients with or without inhibitors.

- For prevention of bleeding, suppression of antithrombin by 75% is most effective. Breakthrough bleeding can be treated with FVIII/FIX replacement or with bypassing agents, but lower doses must be used to minimize the risk of excessive procoagulant activity.
- Anti-TFPI antibodies represent another modality in clinical trials. Different anti-TFPI antibodies are currently in development, all of which bind to the K2 domain or to both the K1 and K2 domains of TFPI, thus rescuing FXa and FVIIa from inhibition.⁷⁸ These therapies may also be administered subcutaneously and restore hemostasis in both hemophilia A and B patients with or without inhibitors, but their duration of action is limited by target-mediated drug disposition. The use of fitusiran requires close monitoring to minimize risk of thrombosis. Two anti-TFPI clinical programs are ongoing, while two others have seen evidence of thrombotic complications. One clinical program has been stopped and one halted due to these adverse events.
- See also Chapter 2: Comprehensive Care of Hemophilia, Chapter 6: Prophylaxis in Hemophilia, Chapter 8: Inhibitors to Clotting Factor, and Chapter 9: Specific Management Issues.

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SUPPORTING INFORMATION

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