

## Chapter 5: Hemostatic Agents

Steven W. Pipe, Manuel Carcao, Kim Chew, Radoslaw Kaczmarek, Steve Kitchen, Johnny Mahlangu, Margareth C. Ozelo, Ekawat Suwantaraj, Jerzy Windyga, Glenn F. Pierce, Alok Srivastava

### RECOMMENDATIONS

#### 5.1 | Introduction

##### 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. <sup>CB</sup>

#### 5.2 | Product selection

##### 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. <sup>CB</sup>

#### 5.3 | Clotting factor concentrates (CFCs)

##### 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. <sup>CB</sup>

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

##### 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. <sup>CB</sup>

## Chapter 5: Hemostatic Agents

• **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. <sup>CB</sup>

### 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. <sup>CB</sup>

### Recommendation 5.3.5

For hemophilia B patients undergoing surgery, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. <sup>CB</sup>

### Recommendation 5.3.6:

For hemophilia B patients with liver disease, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. <sup>CB</sup>

### 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. <sup>CB</sup>

### 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. <sup>CB</sup>

### 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. <sup>CB</sup>

### 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. <sup>CB</sup>

### 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 5.3.1 and 5.3.9 provides for more individualized prophylaxis. <sup>CB</sup>

## 5.4 | Bypassing agents

### 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. <sup>CB</sup>

### 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. <sup>CB</sup>

### Recommendation 5.4.3

The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events. <sup>CB</sup>

## Chapter 5: Hemostatic Agents

### 5.5 | Other plasma Products

#### 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. <sup>CB</sup>

#### 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. <sup>CB</sup>

#### 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. <sup>CB</sup>

### 5.6 | Other pharmacological options

#### 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. <sup>CB</sup>

#### 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. <sup>CB</sup>

#### 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. <sup>CB</sup>

#### 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. <sup>CB</sup>

## Chapter 5: Hemostatic Agents

### 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. <sup>CB</sup>

### 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. <sup>CB</sup>

### 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. <sup>CB</sup>

### Recommendation 5.6.8

For patients with renal impairment, the WFH recommends reduced dosing of antifibrinolytics and close monitoring. <sup>CB</sup>

## 5.7 | Clotting factor concentrates (CFCs)

### 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. <sup>CB</sup>