4 HEMOSTATIC AGENTS

4.1 Clotting factor concentrates

1. **The WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate or fresh frozen plasma for the treatment of hemophilia and other inherited bleeding disorders. (Level 5) [1,2]**
2. The comprehensive WFH *Guide for the Assessment of Clotting Factor Concentrates* reviews factors affecting the quality, safety, licensing, and assessment of plasma-derived products and the important principles involved in selecting suitable products for the treatment of hemophilia [2].
3. The WFH also publishes and regularly updates a *Registry of Clotting Factor Concentrates*, which lists all currently available products and their manufacturing details [3].
4. The WFH does not express a preference for recombinant over plasma-derived concentrates and the choice between these classes of product must be made according to local criteria.
5. Currently manufactured plasma-derived concentrates produced to Good Manufacturing Practice (GMP) standards have an exemplary safety record with respect to lipid-coated viruses, such as HIV and HCV.
6. Product safety is the result of efforts in several areas:
   - improved donor selection (exclusion of at-risk donors)
   - improved screening tests of donations, including nucleic acid testing (NAT)
   - type and number of in-process viral inactivation and/or removal steps
7. The risk of prion-mediated disease through plasma-derived products exists. In the absence of a reliable screening test for variant Creutzfeldt-Jakob disease (vCJD), and with no established manufacturing steps to inactivate the vCJD prion, this problem is currently being handled by excluding plasma from all donors perceived to be at risk. As new information evolves in this field, constant awareness of current scientific recommendations is needed for those involved in making decisions regarding choice of clotting factor concentrate for people with hemophilia.

Product selection

When selecting plasma-derived concentrates, consideration needs to be given to both the plasma quality and the manufacturing process. Two issues deserve special consideration:

- Purity of product
- Viral inactivation/elimination

Purity

1. Purity of concentrates refers to the percentage of the desired ingredient (e.g. FVIII), relative to other ingredients present.
2. There is no universally agreed classification of products based on purity.
3. Concentrates on the market vary widely in their purity.
4. Some products have high or very high purity at one stage of the production process but are subsequently stabilized by albumin, which lowers their final purity. Generally speaking, products with higher purity tend to be associated with low manufacturing yields. These concentrates are, therefore, costlier.
5. Concentrates of lower purity may give rise to allergic reactions [4,5]. Patients who experience these repeatedly with a particular product may benefit from the administration of an antihistamine immediately prior to infusion or from use of a higher purity concentrate.
6. Plasma-derived FVIII concentrates may contain variable amounts of von Willebrand factor (VWF). It is therefore important to ascertain a product's VWF content (as measured by ristocetin cofactor activity) if it is used for the treatment of VWD [6].
7. **For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates, which also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture. Products containing activated clotting factors may predispose to thromboembolism. (Level 2) [7,8]**
8. The viral safety of products is not related to purity, as long as adequate viral elimination measures are in place.

Viral inactivation/elimination

1. In-process viral inactivation is the single largest contributor to the safety of plasma-derived concentrates [9].
2. There is a growing tendency to incorporate two specific viral-reducing steps in the manufacturing process of concentrates.
   - Heat treatment is generally effective against a broad range of viruses, both with and without a lipid envelope, including HIV, HAV, HBV, and HCV.
   - Solvent/detergent treatment is effective against HBV, HCV, and HIV but does not inactivate non-enveloped viruses such as HAV.
3. Some viruses (such as human parvovirus B19) are relatively resistant to both types of process. None of the current methods can inactivate prions.
4. Nano (ultra) filtration can be used to remove small viruses such as parvovirus but filtration techniques currently in use do not eliminate the risk of transmission [10].
5. A 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.
6. If only one step is used, this step should preferably inactivate viruses with and without lipid envelopes.

FVIII concentrates

1. FVIII concentrates are the treatment of choice for hemophilia A.
2. All plasma-derived products currently in the market are listed in the WFH *Registry of Clotting Factor Concentrates* [3]. Consult the product insert for specific details.

Dosage/administration

1. Vials of factor concentrates are available in dosages ranging from approximately 250 to 3000 units each.
2. **In the absence of an inhibitor, each unit of FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level approximately 2 IU/dl. (Level 4) [11]**
3. The half-life of FVIII is approximately 8-12 hours.

4. **The patient's factor level should be measured 15 minutes after the infusion to verify the calculated dose. (Level 4) [11]**
5. The dose is calculated by multiplying the patient's weight in kilograms by the factor level in IU/dl desired, multiplied by 0.5.

   Example: *50 kg × 40 (IU/dl level desired) × 0.5 = 1,000 units of FVIII. Refer to Tables 7-1 and 7-2 for suggested factor level and duration of replacement required based on type of hemorrhage.*
6. **FVIII should be infused by slow IV injection at a rate not to exceed 3 ml per minute in adults and 100 units per minute in young children, or as specified in the product information leaflet. (Level 5) [12]**
7. Subsequent doses should ideally be based on the half-life of FVIII and on the recovery in an individual patient for a particular product.
8. It is best to use the entire vial of FVIII once reconstituted, though many products have been shown to have extended stability after reconstitution.
9. **Continuous infusion avoids peaks and troughs and is considered by some to be advantageous and more convenient. However, patients must be monitored frequently for pump failure. (Level 3) [13,14]**
10. 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 [15]. However, this cost-effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions [16].
11. Dose for continuous infusion is adjusted based on frequent factor assays and calculation of clearance. Since FVIII concentrates of very high purity are stable in IV solutions for at least 24-48 hours at room temperature with less than 10% loss of potency, continuous infusion for a similar number of hours is possible.

FIX concentrates

1. FIX concentrates are the treatment of choice for hemophilia B.
2. All plasma-derived products currently in the market are listed in the WFH *Registry of Clotting Factor Concentrates* [3]. Consult the product information guide for specific details.
3. FIX concentrates fall into two classes:
   - Pure FIX concentrates, which may be plasma-derived or recombinant.
   - FIX concentrates that also contain factors II, VII, IX, and X, also known as prothrombin complex concentrates (PCCs), are only rarely used.
4. **Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B as opposed to PCC (Level 2) [7,8],** particularly in the following instances:
   - Surgery
   - Liver disease
   - Prolonged therapy at high doses
   - Previous thrombosis or known thrombotic tendency
   - Concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents
5. Pure FIX products are free of the risks of thrombosis or disseminated intravascular coagulation (DIC), which may occur with large doses of PCCs.

Dosage/administration

1. Vials of FIX concentrates are available in doses ranging from approximately 250 to 2000 units each.
2. **In absence of an inhibitor, each unit of FIX per kilogram of body weight infused intravenously will raise the plasma FIX level approximately 1 IU/dl. (Level 4) [11]**
3. The half-life is approximately 18–24 hours.
4. **The patient's FIX level should be measured approximately 15 minutes after infusion to verify calculated doses. (Level 4) [11]**

5. Recombinant FIX (rFIX) has a lower recovery than plasma-derived products, such that each unit of FIX per kg body weight infused will raise the FIX activity by approximately 0.8 IU/dl in adults and 0.7 IU/dl in children under 15 years of age. The reason for the lower recovery of rFIX is not entirely clear [17].
6. To calculate dosage, multiply the patient's weight in kilograms by the factor level desired.

   Example: *50 kg × 40 (IU/dl level desired) = 2000 units of plasma-derived FIX. For rFIX, the dosage will be 2000 ÷ 0.8 (or 2000 × 1.25) = 2500 units for adults, and 2000 ÷ 0.7 (or 2000 × 1.43) = 2860 units for children. Refer to Tables 7-1 and 7-2 for suggested factor level and duration of replacement therapy based on type of hemorrhage.*
7. **FIX concentrates should be infused by slow IV injection at a rate not to exceed a volume of 3 ml per minute in adults and 100 units per minute in young children, or as recommended in the product information leaflet. (Level 5) [12]**
8. **If used, PCCs should generally be infused at half this rate. Consult the product information leaflet for instructions. (Level 2) [18]**
9. Purified FIX concentrates may also be administered by continuous infusion (as with FVIII concentrates).
10. Allergic reactions may occur with infusions of FIX concentrates in patients with anti-FIX inhibitors. In such patients, infusions may need to be covered with hydrocortisone [19]. Changing the brand of clotting factor concentrate sometimes reduces symptoms.

4.2 Other plasma products

1. **The WFH supports the use of coagulation factor concentrates in preference to cryoprecipitate or fresh frozen plasma (FFP) due to concerns about their quality and safety. However, the WFH recognizes the reality that they are still widely used in countries around the world where it is the only available or affordable treatment option. (Level 5) [1,2]**
2. Cryoprecipitate and FFP are not subjected to viral inactivation procedures (such as heat or solvent/detergent treatment), leading to an increased risk of transmission of viral pathogens, which is significant with repeated infusions [1].
3. 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, hepatitis C, and HBsAg—a practice that is difficult to implement in countries where the proportion of repeat donors is low.
   - Nucleic acid testing (NAT) to detect viruses—a technology that has a potentially much greater relevance for the production of cryoprecipitate than for factor concentrates, as the latter are subjected to viral inactivation steps [20].
4. Allergic reactions are more common following infusion of cryoprecipitate than concentrate [21].

Fresh frozen plasma (FFP)

1. As FFP contains all the coagulation factors, it is sometimes used to treat coagulation factor deficiencies.
2. **Cryoprecipitate is preferable to FFP for the treatment of hemophilia A. (Level 4) [22]**
3. **Due to concerns about the safety and quality of FFP, its use is not recommended, if avoidable (Level 4) [23].** However, as FFP and cryo-poor plasma contain FIX, they can be used for the treatment of hemophilia B in countries unable to afford plasma-derived FIX concentrates.
4. It is possible to apply some forms of virucidal treatment to packs of FFP (including solvent/detergent treatment) and 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 [24,25].

Dosage/administration

1. One ml of fresh frozen plasma contains 1 unit of factor activity.
2. It is generally difficult to achieve FVIII levels higher than 30 IU/dl with FFP alone.
3. FIX levels above 25 IU/dl are difficult to achieve. **An acceptable starting dose is 15–20 ml/kg. (Level 4) [22]**

Cryoprecipitate

1. Cryoprecipitate is prepared by slow thawing of fresh frozen plasma (FFP) at 4°C for 10-24 hours. It appears as an insoluble precipitate and is separated by centrifugation.
2. Cryoprecipitate contains significant quantities of FVIII (about 3-5 IU/ml), VWF, fibrinogen, and FXIII *but not FIX or FXI*. The resultant supernatant is called cryo-poor plasma and contains other coagulation factors such as factors VII, IX, X, and XI.
3. **Due to concerns about the safety and quality of cryoprecipitate, its use in the treatment of congenital bleeding disorders is not recommended and can only be justified in situations where clotting factor concentrates are not available. (Level 4) [1,22,26]**
4. Although the manufacture of small pool, viral-inactivated cryoprecipitate has been described, it is uncertain whether it offers any advantage with respect to overall viral safety or cost benefit over conventionally manufactured large pool concentrates [27].

Dosage/administration

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

4.3 Other pharmacological options

1. In addition to conventional coagulation factor concentrates, other agents can be of great value in a significant proportion of cases. These include:
   - desmopressin
   - tranexamic acid
   - epsilon aminocaproic acid

Desmopressin (DDAVP)

1. 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 [28].
2. **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 a clotting factor concentrate. (Level 3) [28,29]**
3. Desmopressin *does not affect FIX levels* and is of no value in hemophilia B.
4. **Each patient's response should be tested prior to therapeutic use, as there are significant differences between individuals. The response to intranasal desmopressin is more variable and therefore less predictable. (Level 3) [28,29]**
5. **DDAVP is particularly useful in the treatment or prevention of bleeding in carriers of hemophilia. (Level 3) [30]**
6. **Although DDAVP is not licensed for use in pregnancy, there is evidence that it can be safely used during delivery and in the post-partum period in an otherwise normal pregnancy. Its use should be avoided in pre-eclampsia and eclampsia because of the already high levels of VWF. (Level 3) [31,32]**
7. Obvious advantages of DDAVP over plasma products are the much lower cost and the absence of any risk of transmission of viral infections.
8. DDAVP may also be useful to control bleeding and reduce the prolongation of bleeding time associated with disorders of hemostasis, including some congenital platelet disorders.

9. The decision to use DDAVP must be based on both the baseline concentration of FVIII, the increment achieved, and the duration of treatment required.

Dosage/administration

1. Though desmopressin is given subcutaneously in most patients, it can also be administered by intravenous infusion or by nasal spray. It is important to choose the correct preparation of desmopressin because some lower-dose preparations are used for other medical purposes.
2. 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
3. **A single dose of 0.3 μg /kg body weight, either by intravenous or subcutaneous route, can be expected to boost the level of FVIII three- to six-fold. (Level 4) [28,33]**
4. For intravenous use, DDAVP is usually diluted in at least 50–100 ml of physiological saline and given by slow intravenous infusion over 20–30 minutes.
5. The peak response is seen approximately 60 minutes after administration either intravenously or subcutaneously.
6. **Closely spaced repetitive use of DDAVP over several days may result in decreased response (tachyphylaxis). Factor concentrates may be needed when higher factor levels are required for a prolonged period. (Level 3) [34]**
7. Rapid infusion may result in tachycardia, flushing, tremor, and abdominal discomfort.
8. **A single metered intranasal spray of 1.5 mg/ml in each nostril is appropriate for an adult. For an individual with a bodyweight of less than 40 kg, a single dose in one nostril is sufficient. (Level 4) [35,36]**
9. Though the intranasal preparation is available, some patients find it difficult to use and it may be less efficacious than when given subcutaneously.
10. **As a result of its antidiuretic activity, water retention and hyponatremia can be a problem. When repeated doses are given, the plasma osmolality or sodium concentration should be measured. (Level 4) [28,37]**
11. In most adults hyponatremia is uncommon.
12. **Due to water retention, DDVAP should be used with caution in young children and is contraindicated in children under two years of age who are at particular risk of seizures secondary to cerebral edema due to water retention. (Level 4) [38,39]**
13. **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 who are at risk, of cardiovascular disease. (Level 4) [33]**

Tranexamic acid

1. Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin.
2. It promotes clot stability and is useful as adjunctive therapy in hemophilia and some other bleeding disorders [40].
3. **Regular treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia. (Level 4) [40]**
4. **It is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g. oral bleeding, epistaxis, menorrhagia). (Level 2) [41-43]**
5. **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. (Level 4) [42,44]**

Dosage/administration

1. Tranexamic acid is usually given as an oral tablet three to four times daily. It can also be given by intravenous infusion two to three times daily, and is also available as a mouthwash.

2. Gastrointestinal upset (nausea, vomiting, or diarrhea) may rarely occur as a side effect, but these symptoms usually resolve if the dosage is reduced. When administered intravenously, it must be infused slowly as rapid injection may result in dizziness and hypotension.
3. A syrup formulation is also available for pediatric use. If this is not available, a tablet can be crushed and dissolved in clean water for topical use on bleeding mucosal lesions.
4. Tranexamic acid is commonly prescribed for seven days following dental extractions to prevent post-operative bleeding.
5. Tranexamic acid is excreted by the kidneys and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.
6. *The use of tranexamic acid is contraindicated for the treatment of hematuria* as its use may prevent dissolution of clots in the ureters, leading to serious obstructive uropathy and potential permanent loss of renal function.
7. Similarly, the drug is contraindicated in the setting of thoracic surgery, where it may result in the development of insoluble hematomas.
8. **Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrates. (Level 4) [45]**
9. **Tranexamic acid should *not* be given to patients with FIX deficiency receiving prothrombin complex concentrates, as this will exacerbate the risk of thromboembolism. (Level 5) [46]**
10. **If treatment with both agents is deemed necessary, it is recommended that at least 12 hours elapse between the last dose of APCC and the administration of tranexamic acid. (Level 5) [46]**
11. **In contrast, thromboembolism is less likely when tranexamic acid is used in combination with rFVIIa to enhance hemostasis. (Level 4) [47]**

Epsilon aminocaproic acid

1. Epsilon aminocaproic acid (EACA) is similar to tranexamic acid but is less widely used as it has a shorter plasma half-life, is less potent, and is more toxic [40].

Dosage/administration

1. EACA is typically administered to adults orally or intravenously every four to six hours up to a maximum of 24 g/day in an adult.
2. A 250 mg/ml syrup formulation is also available.
3. Gastrointestinal upset is a common complication; reducing the dose often helps.
4. Myopathy is a rare adverse reaction specifically reported in association with aminocaproic acid therapy (but not tranexamic acid), typically occurring after administration of high doses for several weeks.
5. The myopathy is often painful and associated with elevated levels of creatine kinase and even myoglobinuria.
6. Full resolution may be expected once drug treatment is stopped.

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