General

Guideline Title

Guidelines for the management of hemophilia.

Bibliographic Source(s)

Guidelines for the management of hemophilia. 2nd ed. Montreal (Quebec): World Federation of Hemophilia; 2012. 74 p. [324 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Guidelines for the management of hemophilia. Montreal (Quebec): World Federation of Hemophilia; 2005. 56 p.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): In addition to the evidence-based "position statements" below, the guidelines working group also identifies recommendations based on expert opinion in the full-text guideline document.

Levels of evidence (1-5) are defined at the end of the "Major Recommendations" field.

General Care and Management of Hemophilia

Principles of Care

Acute bleeds should be treated as quickly as possible, preferably within two hours. If in doubt, treat. (Level 4) (Ingram et al., 1979)

To facilitate appropriate management in emergency situations, all patients should carry easily accessible identification indicating the diagnosis, severity of the bleeding disorder, inhibitor status, type of treatment product used, initial dosage for treatment of severe, moderate, and mild bleeding, and contact information of the treating physician/clinic. (Level 5) (Singleton, Kruse-Jarres, & Leissinger, 2010)

Administration of desmopressin (DDAVP) can raise coagulation factor VIII (FVIII) level adequately (three to six times baseline levels) to control bleeding in patients with mild, and possibly moderate, hemophilia A. Testing for DDAVP response in individual patients is appropriate. (Level 3) (Castaman et al., 2009; Franchini, Zaffanello, & Lippi, 2010; Mannucci, 2000)

Comprehensive Care

Comprehensive care promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality. (Level 3) (Berntorp et

al., 1995; Kasper et al., 1992; Soucie et al., 2000)

Comprehensive Care Team

The wide-ranging needs of people with hemophilia and their families are best met through the coordinated delivery of comprehensive care by a multidisciplinary team of healthcare professionals, in accordance with accepted protocols that are practical and national treatment guidelines, if available. (Level 5) (Colvin et al., 2008; Evatt, 2006; Evatt et al., 2004)

Functions of a Comprehensive Care Program

To provide or coordinate inpatient (i.e., during hospital stays) and outpatient (clinic and other visits) care and services to patients and their family.

- Patients should be seen by all core team members at least yearly (children every six months) for a complete hematologic, musculoskeletal, and psychosocial assessment and to develop, audit, and refine an individual's comprehensive management plan. Referrals for other services can also be given during these visits. (Level 5) (Canadian Hemophilia Standards Group, 2007; de Moerloose et al., 2012)

Fitness and Physical Activity

Physical activity should be encouraged to promote physical fitness and normal neuromuscular development, with attention paid to muscle strengthening, coordination, general fitness, physical functioning, healthy body weight, and self-esteem. (Level 2) (Gomis et al., 2009)

For patients with significant musculoskeletal dysfunction, weight-bearing activities that promote development and maintenance of good bone density should be encouraged, to the extent their joint health permits. (Level 3) (Iorio et al., 2010)

Target joints can be protected with braces or splints during activity, especially when there is no clotting factor coverage. (Level 4) (Philpott, Houghton, & Luke, 2010; Querol et al., 2002)

Prophylactic Factor Replacement Therapy

Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. (Level 2) (Aronstam et al., 1976; Astermark et al., 1999; Feldman et al., 2006; Fischer et al., 2002; Gringeri et al., 2011; Manco-Johnson et al., 2007)

In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for 4 to 8 weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis. (Level 3) (Kavakli et al., 2008; Luchtman-Jones et al., 2006)

Administration and Dosing Schedules

Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury. (Level 4) (Seuser et al., 2007; Luchtman-Jones et al., 2006; Petrini & Seuser, 2009)

Home Therapy

Home therapy allows immediate access to clotting factor and hence optimal early treatment, resulting in decreased pain, dysfunction, and long-term disability and significantly decreased hospital admissions for complications. (Level 3) (Soucie et al., 2001; Teitel et al., 2004)

Home treatment must be supervised closely by the comprehensive care team and should only be initiated after adequate education and training. (Level 3) (Soucie et al., 2001; Teitel et al., 2004)

An implanted venous access device (Port-A-Cath) can make injections much easier and may be required for administering prophylaxis in younger children. (Level 2) (Neunert et al., 2008; Valentino et al., 2004)

However, the risks of surgery, local infection, and thrombosis associated with such devices need to be weighed against the advantages of starting intensive prophylaxis early. (Level 2) (Ljung, 2007; Ragni, Journeycake, & Brambilla, 2008)

Monitoring Health Status and Outcome

Regular standardized evaluation at least every 12 months allows longitudinal assessment for individual patients and can identify new or potential problems in their early stages so that treatment plans can be modified. (Level 3) (de Moerloose et al., 2012; Feldman et al., 2006; Su et al., 2007)

Pain Management

Pain Due to Chronic Hemophilic Arthropathy

Treatment includes functional training, adaptations, and adequate analgesia as suggested in Table 1-5 in the original guideline document. (Level 2) (Gomis et al., 2009; Vallejo et al., 2010)

Cyclooxygenase-2 (COX-2) inhibitors have a greater role in this situation. (Level 2) (Rattray, Nugent, & Young, 2006; Tsoukas et al., 2006)

Other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided. (Level 2) (Eyster et al., 2007)

When pain is disabling, orthopedic surgery may be indicated. (Level 5) (Rodriguez-Merchan, 2010)

Surgery and Invasive Procedures

A hemophilia patient requiring surgery is best managed at or in consultation with a comprehensive hemophilia treatment centre. (Level 3) (Batorova & Martinowitz, 2000; Hermans, et al., 2009)

Pre-operative assessment should include inhibitor screening and inhibitor assay, particularly if the recovery of the replaced factor is significantly less than expected. (Level 4) (Mathews et al., 2005; Teitel, et al., 2009)

Patients with mild hemophilia A, as well as patients receiving intensive factor replacement for the first time, are at particular risk of inhibitor development and should be re-screened 4–12 weeks post-operatively. (Level 4) (Kempton et al., 2010)

Dental Care and Management

Treatment can be safely carried out under local anesthesia using the full range of techniques available to dental surgeons. Infiltration, intra-papillary, and intra-ligamentary injections are often done under factor cover (20%-40%) though it may be possible for those with adequate experience to administer these injections without it. (Level 4) (Frachon et al., 2005; Hewson et al., 2011)

Dental extraction or surgical procedures carried out within the oral cavity should be done with a plan for hemostasis management, in consultation with the hematologist. (Level 3) (Hermans et al., 2009)

Tranexamic acid or epsilon aminocaproic acid (EACA) is often used after dental procedures to reduce the need for replacement therapy. (Level 4) (Coetzee, 2007; Franchini et al., 2005)

Special Management Issues

Carriers

Immediate female relatives (mother, sisters, and daughters) of a person with hemophilia should have their clotting factor level checked, especially prior to any invasive intervention, childbirth, or if any symptoms occur. (Level 3) (Plug et al., 2006; Ljung & Tedgård, 2003)

Genetic Testing/Counselling and Prenatal Diagnosis

Where available and possible, genetic testing for carrier status should be offered to at-risk female family members of people with hemophilia to facilitate genetic counselling, and if desired by the family, prenatal diagnosis. (Level 4) (Dunn et al., 2008)

Chorionic villus sampling (CVS), or biopsy, is the main method of prenatal diagnosis and is best done between 9 and 14 weeks of gestation. Biopsy carried out earlier may be associated with increased complications including fetal limb abnormalities. (Level 1) (Evans & Andriole, 2008; Jauniaux, Pahal, & Rodeck, 2000; Tabor & Alfirevic, 2010; Wapner, 2005)

All invasive methods used for prenatal diagnosis may cause feto-maternal hemorrhage. Anti-D immunoglobulin should be given if the mother is RhD negative. (Level 3) (Katiyar et al., 2007)

Delivery of Infants with Known or Suspected Hemophilia

FVIII levels usually rise into the normal range during the second and third trimesters and should therefore be measured in carriers during the third trimester of pregnancy to inform decisions for factor coverage during delivery. (Level 3) (Chi et al., 2008)

In carriers with significantly low factor levels (<50 IU/dl), clotting factor replacement is necessary for surgical or invasive procedures including delivery. (Level 3) (Chi et al., 2008)

Delivery of infants with known or suspected hemophilia should be atraumatic, regardless of whether it is vaginal or cesarean, to decrease the risk of bleeding. (Level 3) (Chi et al., 2008)

Vaccinations

Persons with bleeding disorders should be vaccinated, but should preferably receive the vaccine subcutaneously rather than intramuscularly or intradermally, unless covered by infusion of clotting factor concentrates. (Level 4) (Kulkarni & Lusher, 2001)

Immunization to hepatitis A and B is important for all persons with hemophilia. These immunizations may not be as effective in those with human immunodeficiency virus (HIV) infection. (Level 4) (Miller et al., 1989; Steele et al., 2009)

Ageing Hemophilia Patients

Diabetes Mellitus

If treatment with insulin is indicated, subcutaneous injections can be administered without bleeding complications. (Level 5) (Mauser-Bunschoten, Fransen Van De Putte, & Schutgens, 2009)

Cardiovascular Disease

For acute coronary syndromes requiring percutaneous cardiac intervention (PCI):

- Adequate correction with clotting factor concentrates before PCI and until 48 hours after PCI is required. (Level 4) (Schutgens et al., 2009; Mannucci et al., 2009; Coppola, Tagliaferri, & Franchini, 2010)
- Radial artery access site, if technically possible, is preferred over femoral, in order to minimize retroperitoneal or groin bleeds. (Level 4) (Schutgens et al., 2009; Mannucci et al., 2009; Coppola, Tagliaferri, & Franchini, 2010)

Laboratory Diagnosis

Knowledge and Expertise in Coagulation Laboratory Testing

Technical Aspects

Inhibitor Testing

The Nijmegen modification of the FVIII inhibitor assay offers improved specificity and sensitivity over the original Bethesda assay. (Level 1) (Meijer & Verbruggen, 2009; Verbruggen, van Heerde, & Laros-van Gorkom, 2009)

Hemostatic Agents

Clotting Factor Concentrates

The World Federation of Hemophilia (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) (Evatt, et al., 1999; Farrugia, 2008)

Product Selection

Purity

For treatment of factor IX (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) (Kim et al., 1992; Lippi & Franchini, 2008)

FVIII Concentrates

Dosage/Administration

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) (Björkman & Berntorp, 2001)

The patient's factor level should be measured 15 minutes after the infusion to verify the calculated dose. (Level 4) (Björkman & Berntorp, 2001)

FVIII should be infused by slow intravenous (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) (Hemophilia of Georgia, 2012)

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) (Batorova & Martinowitz, 2000; Martinowitz et al., 2009)

FIX Concentrates

Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B as opposed to prothrombin complex concentrates (PCC) (Level 2) (Kim et al., 1992; Lippi & Franchini, 2008), 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

Dosage/Administration

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) (Björkman & Berntorp, 2001)

The patient's FIX level should be measured approximately 15 minutes after infusion to verify calculated doses. (Level 4) (Björkman & Berntorp, 2001)

FIX concentrates should be infused by slow intravenous 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) (Hemophilia of Georgia, 2012)

If used, PCCs should generally be infused at half this rate. Consult the product information leaflet for instructions. (Level 2) (Ruiz-Sáez et al., 2005)

Other Plasma Products

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) (Evatt et al., 1999; Farrugia, 2008)

Fresh Frozen Plasma (FFP)

Cryoprecipitate is preferable to FFP for the treatment of hemophilia A. (Level 4) (Stanworth, 2007)

Due to concerns about the safety and quality of FFP, its use is not recommended, if avoidable (Level 4) (Kasper, 2005). 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.

Dosage/Administration

An acceptable starting dose is 15−20 ml/kg. (Level 4) (Stanworth, 2007)

Cryoprecipitate

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) (Evatt et al., 1999; Stanworth, 2007; Chuansumrit et al., 1999)

Other Pharmacological Options

Desmopressin (DDAVP)

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) (Mannucci, 1997; Franchini et al., 2005)

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) (Mannucci, 1997; Franchini et al., 2005)

DDAVP is particularly useful in the treatment or prevention of bleeding in carriers of hemophilia. (Level 3) (Leissinger, et al., 2001)

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 von Willebrand

factor (VWF). (Level 3) (Mannucci, 2005; Trigg et al., 2012)

Dosage/Administration

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) (Mannucci, 1997; Castaman, 2008)

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) (Mannucci, Bettega & Cattaneo, 1992)

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) (Khair et al., 2007; Rose & Aledort, 1991)

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) (Mannucci, 1997; Sica & Gehr, 2006)

Due to water retention, DDAVP 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) (Das, Carcao, & Hitzler, 2005; Smith et al., 1989)

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) (Castaman, 2008)

Tranexamic Acid

Regular treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia. (Level 4) (Mannucci, 1998)

It is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g., oral bleeding, epistaxis, menorrhagia). (Level 2) (Coetzee, 2007; Frachon et al., 2005; Kouides et al., 2009)

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) (Frachon et al., 2005; Franchini, Zaffanello, & Lippi, 2010)

Dosage/Administration

Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrates. (Level 4) (Hvas et al., 2007)

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) (Luu & Ewenstein, 2004)

If treatment with both agents is deemed necessary, it is recommended that at least 12 hours elapse between the last dose of activated prothrombin complex concentrates (APCC) and the administration of tranexamic acid. (Level 5) (Luu & Ewenstein, 2004)

In contrast, thromboembolism is less likely when tranexamic acid is used in combination with recombinant factor VIIa (rFVIIa) to enhance hemostasis. (Level 4) (Giangrande et al., 2009)

Treatment of Specific Hemorrhages

Joint Hemorrhage (Hemarthrosis)

Administer the appropriate dose of factor concentrate to raise the patient's factor level suitably (refer to Tables 7-1 and 7-2 in the original guideline document). (Level 2) (Aronstam et al., 1980; Aronstam et al., 1983; Hermans et al., 2011; Mathews et al., 2005)

Instruct the patient to avoid weight-bearing, apply compression, and elevate the affected joint. (Level 3) (Hermans et al., 2011)

If bleeding does not stop, a second infusion may be required. If so, repeat half the initial loading dose in 12 hours (hemophilia A) or 24 hours (hemophilia B). (Level 3) (Hermans et al., 2011)

Rehabilitation must be stressed as an active part of the management of acute joint bleeding episodes. (Level 2) (Hermans et al., 2011; Gomis et al., 2009; Mulder, 2006)

Arthrocentesis

Arthrocentesis (removal of blood from a joint) may be considered in the following situations:

- A bleeding, tense, and painful joint which shows no improvement 24 hours after conservative treatment
- Joint pain that cannot be alleviated
- Evidence of neurovascular compromise of the limb
- Unusual increase in local or systemic temperature and other evidence of infection (septic arthritis) (Level 3) (Hermans et al., 2011; Ingram, Mathews, & Bennett, 1972; Rodriguez-Merchan, 2012)

When necessary, arthrocentesis should be performed under factor levels of at least 30–50 IU/dl for 48–72 hours. Arthrocentesis should not be done in circumstances where such factor replacement is not available. In the presence of inhibitors, other appropriate hemostatic agents should be used for the procedure, as needed. (Level 3) (Hermans et al., 2011)

Muscle Hemorrhage

Raise the patient's factor level as soon as possible, ideally when the patient recognizes the first signs of discomfort or after trauma. If there is neurovascular compromise, maintain the levels for five to seven days or longer, as symptoms indicate (refer to Tables 7-1 and 7-2 in the original guideline document). (Level 3) (Aronstam et al., 1983; Beyer, Ingerslev, & Sørensen, 2010; Railton & Aronstam, 1987)

Repeat infusions are often required for two to three days or much longer in case of bleeds at critical sites causing compartment syndromes and if extensive rehabilitation is required. (Level 5) (Rodriguez-Merchan, 2010; Singleton, Kruse-Jarres, & Leissinger, 2010)

The patient should be monitored continuously for neurovascular compromise; fasciotomy may be required in some such cases. (Level 5) (Llinás et al., 2010; Rodriguez-Merchan, 2008)

Physiotherapy should begin as soon as pain subsides and should be progressed gradually to restore full muscle length, strength, and function. (Level 4) (Beyer, Ingerslev, & Sørensen, 2010; Blamey et al., 2010)

Iliopsoas Hemorrhage

Immediately raise the patient's factor level. Maintain the levels for five to seven days or longer, as symptoms indicate (refer to Tables 7-1 and 7-2 in the original guideline document). (Level 4) (Ashrani et al., 2003; Balkan, Kavakli, & Karapinar, 2005; Fernandez-Palazzi et al., 1996)

Hospitalize the patient for observation and control of pain. Maintain *strict* bed rest. Ambulation with crutches is *not* permitted, as ambulation requires contraction of the muscle. (Level 4) (Ashrani et al., 2003; Balkan, Kavakli, & Karapinar, 2005; Fernandez-Palazzi et al., 1996)

It is useful to confirm the diagnosis and monitor recovery with an imaging study (ultrasonography, computed tomography [CT] scan, or magnetic resonance imaging [MRI]). (Level 4) (Ashrani et al., 2003; Balkan, Kavakli, & Karapinar, 2005; Fernandez-Palazzi et al., 1996)

Limit the patient's activity until pain resolves and hip extension improves. A carefully supervised program of physiotherapy is key to restoring full activity and function and preventing re-bleeding. Restoration of complete hip extension before returning to full activity is recommended. (Level 4) (Ashrani et al., 2003; Balkan, Kavakli, & Karapinar, 2005; Fernandez-Palazzi et al., 1996)

Central Nervous System Hemorrhage/Head Trauma

Immediately raise the patient's factor level when significant trauma or early symptoms occur. Further doses will depend on imaging results. Maintain factor level until etiology is defined. If a bleed is confirmed, maintain the appropriate factor level for 10-14 days (refer to Tables 7-1 and 7-2 in the original guideline document). (Level 4) (Ljung, 2008; Nakar, Cooper, & DiMichele, 2010)

Intracranial hemorrhage may be an indication for prolonged secondary prophylaxis (three to six months), especially where a relatively high risk of recurrence has been observed (e.g., in the presence of HIV infection). (Level 3) (Ljung, 2008; Patiroglu et al., 2011; Zanon et al., 2012)

Immediate medical evaluation and hospitalization is required. A CT scan or MRI of the brain should be performed. Neurological consultation should be sought early. (Level 4) (Traivaree et al., 2007; Witmer et al., 2009)

Throat and Neck Hemorrhage

Immediately raise the patient's factor level when significant trauma or symptoms occur. Maintain the factor levels until symptoms resolve (refer to Tables 7-1 and 7-2 in the original guideline document). (Level 4) (Singleton, Kruse-Jarres, & Leissinger, 2010; Bush & Roy, 1995; Guthrie Jr & Sacra, 1980)

Hospitalization and evaluation by a specialist is essential. (Level 5) (Singleton, Kruse-Jarres, & Leissinger, 2010)

Acute Gastrointestinal Hemorrhage

Immediately raise the patient's factor levels. Maintain the factor level until hemorrhage has stopped and etiology is defined (refer to Tables 7-1 and 7-2 in the original guideline document). (Level 4) (Kouides & Fogarty, 2010; Mittal et al., 1985)

Acute Abdominal Hemorrhage

Immediately raise the patient's factor levels. Maintain the factor levels (refer to Tables 7-1 and 7-2 in the original guideline document) until the etiology can be defined, then treat appropriately in consultation with a specialist. (Level 4) (Singleton, Kruse-Jarres, & Leissinger, 2010; Bush & Roy, 1995; Guthrie Jr & Sacra, 1980)

Ophthalmic Hemorrhage

Immediately raise the patient's factor level. Maintain the factor level as indicated (refer to Tables 7-1 and 7-2 in the original guideline document). (Level 4) (Singleton, Kruse-Jarres, & Leissinger, 2010; Bush & Roy, 1995; Guthrie Jr & Sacra, 1980)

Renal Hemorrhage

Treat painless hematuria with complete bed rest and vigorous hydration (3 litres/m^2 body surface area) for 48 hours. Avoid DDAVP when hydrating intensively. (Level 4) (Quon & Konkle, 2010)

Raise the patient's factor levels (refer to Tables 7-1 and 7-2 in the original guideline document) if there is pain or persistent gross hematuria and watch for clots and urinary obstruction. (Level 4) (Quon & Konkle, 2010; Ghosh, Jijina, & Mohanty, 2003)

Do not use antifibrinolytic agents. (Level 4) (Quon & Konkle, 2010)

Oral Hemorrhage

Antifibrinolytic agents should not be used systemically in patients with FIX deficiency that are being treated with large doses of prothrombin complex concentrates or in patients with inhibitors being treated with APCC. (Level 4) (Kane et al., 1988; Mannucci, 1998)

Oral EACA or tranexamic acid should be used if appropriate. (Level 4) (Franchini et al., 2005; Vinall & Stassen, 2008)

Lacerations and Abrasions

For deep lacerations, raise the factor level (refer to Tables 7-1 and 7-2 in the original guideline document), and then suture. (Level 4) (Singleton, Kruse-Jarres, & Leissinger, 2010; Bush & Roy, 1995; Guthrie Jr & Sacra, 1980)

Complications of Hemophilia

Musculoskeletal Complications

Synovitis

The goal of treatment is to deactivate the synovium as quickly as possible and preserve joint function (Level 5) (Rodriguez-Merchan, 2012; Seuser, Berdel, & Oldenburg, 2007). Options include:

- Factor concentrate replacement, ideally given with the frequency and at dose levels sufficient to prevent recurrent bleeding (Level 2) (Aronstam et al., 1976; Feldman et al., 2006; Gringeri et al., 2011; Manco-Johnson et al., 2007)
- Physiotherapy (Level 2) (Blamey et al., 2010; Gomis et al., 2009)
- A course of NSAIDs (COX-2 inhibitors), which may reduce inflammation (Level 2) (Rattray, Nugent, & Young, 2006; Tsoukas et al., 2006)

Synovectomy

Synovectomy should be considered if chronic synovitis persists with frequent recurrent bleeding not controlled by other means. Options for synovectomy include chemical or radioisotopic synoviorthesis, and arthroscopic or open surgical synovectomy. (Level 4) (Llinás, 2008; Yoon et al., 2005)

Radioisotopic synovectomy using a pure beta emitter (phosphorus-32 or yttrium-90) is highly effective, has few side effects, and can be accomplished in an out-patient setting. (Level 4) (Thomas et al., 2011; van Kasteren et al., 1993)

Chronic Hemophilic Arthropathy

Pain should be controlled with appropriate analgesics. Certain COX-2 inhibitors may be used to relieve arthritic pain (see 'Pain Management', above). (Level 2) (Rattray, Nugent, & Young, 2006; Tsoukas et al., 2006)

Supervised physiotherapy aiming to preserve muscle strength and functional ability is a very important part of management at this stage. Secondary prophylaxis may be necessary if recurrent bleeding occurs as a result of physiotherapy. (Level 2) (Blamey et al., 2010; Gomis et al., 2009)

Adequate resources, including sufficient factor concentrates and post-operative rehabilitation, must be available in order to proceed with any surgical procedure. (Level 3) (Hermans et al., 2009; Lobet et al., 2008; Mathews et al., 2005)

Pseudotumours

Management depends on the site, size, rate of growth, and effect on adjoining structures. Options include factor replacement and monitoring, aspiration, and surgical ablation.

- A six-week course of treatment with factor is recommended, followed by repeat MRI. If the tumour is decreasing, continue with factor and repeat MRI for three cycles. (Level 4) (D'Young, 2009; Rodriguez-Merchan, 1995)
- Aspiration of the pseudotumour followed by injections of fibrin glue, arterial embolization, or radiotherapy may heal some lesions. Surgery may be needed for others. (Level 4) (Alcalay & Deplas, 2002; Espandar, Heidari, & Rodriguez-Merchan, 2009)

Fractures

Treatment of a fracture requires immediate factor concentrate replacement. (Level 4) (Rodriguez-Merchan, 2002; Lee et al., 2007; Mortazavi & Heidari, 2008)

Clotting factor levels should be raised to at least 50% and maintained for three to five days. (Level 4) (Rodriguez-Merchan, 2012; Rodriguez-Merchan, 2002; Lee et al., 2007; Mortazavi & Heidari, 2008)

Circumferential plaster should be avoided; splints are preferred. (Level 4) (Rodriguez-Merchan, 2002)

Prolonged immobilization, which can lead to significant limitation of range of movement in the adjacent joints, should be avoided. (Level 4) (Rodriguez-Merchan, 2002; Lee et al., 2007)

Principles of Orthopedic Surgery in Hemophilia

Performing multiple site elective surgery in a simultaneous or staggered fashion to use clotting factor concentrates judiciously should be considered. (Level 3) (Schild et al., 2009)

Local coagulation enhancers may be used. Fibrin glue is useful to control oozing when operating in extensive surgical fields. (Level 3) (Hermans et al., 2009; Kavakli, 1999; Serban et al., 2009)

Post-operative care in patients with hemophilia requires closer monitoring of pain and often higher doses of analgesics in the immediate post-operative period. (Level 5) (Hermans et al., 2009)

Inhibitors

Confirmation of the presence of an inhibitor and quantification of the titre is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay (see 'Inhibitor testing', above). (Level 1) (Meijer & Verbruggen, 2009; Verbruggen, van Heerde, & Laros-van Gorkom, 2009)

For children, inhibitors should be screened once every five exposure days until 20 exposure days, every 10 exposure days between 21 and 50 exposure days, and at least two times a year until 150 exposure days. (Level 5) (de Moerloose et al., 2012)

For adults with more than 150 exposure days, apart from a 6-12 monthly review, any failure to respond to adequate factor concentrate replacement therapy in a previously responsive patient is an indication to assess for an inhibitor. (Level 3) (Kempton et al., 2010; Berntorp et al., 2011; Hay et al., 2006; McMillan et al., 1988)

Inhibitor measurement should also be done in all patients who have been intensively treated for more than five days, within four weeks of the last infusion. (Level 4) (Hay et al., 2006; Sharathkumar et al., 2003)

Inhibitors should also be assessed prior to surgery or if recovery assays are not as expected, and when clinical response to treatment of bleeding is sub-optimal in the post-operative period. (Level 2) (Astermark et al., 2010; Hay et al., 2006; Teitel et al., 2009)

Management of Bleeding

Management of bleeding in patients with inhibitors must be in consultation with a centre experienced in their management. (Level 5) (Hay et al., 2006; Colvin et al., 2008)

Choice of treatment product should be based on titre of inhibitor, records of clinical response to product, and site and nature of bleed. (Level 4) (Hay et al., 2006; Teitel et al., 2007)

Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralize the inhibitor with excess factor activity and stop bleeding. (Level 4) (Hay et al., 2006; Teitel et al., 2007)

Patients with a history of a high responding inhibitor but with low titres may be treated similarly in an emergency until an anamnestic response occurs, usually in three to five days, precluding further treatment with concentrates that only contain the missing factor. (Level 4) (Hay et al., 2006; Teitel et al., 2007)

The efficacy of two doses of rFVIIa and one dose of APCC for management of joint bleeding has been shown to be essentially equivalent. (Level 2) (Astermark et al., 2007)

Notably, however, some patients respond better to one agent than the other, highlighting the need to individualize therapy. (Level 2) (Astermark et al., 2007; Berntorp et al., 2006)

Allergic Reactions in Patients with Hemophilia B

Newly diagnosed hemophilia B patients, particularly those with a family history and/or with genetic defects predisposed to inhibitor development, should be treated in a clinic or hospital setting capable of treating severe allergic reactions during the initial 10-20 treatments with FIX concentrates. Reactions can occur later but may be less severe. (Level 4) (Chitlur et al., 2009; Recht et al., 2011)

Immune Tolerance Induction (ITI)

In patients with severe hemophilia A, eradication of inhibitors is often possible by ITI therapy. (Level 2) (Coppola, Di Minno, & Santagostino, 2010; DiMichele et al., 2007)

Before ITI therapy, high-responding patients should avoid FVIII products to allow inhibitor titres to fall and to avoid persistent anamnestic rise. As noted, some patients may develop an anamnestic response to the inactive FVIII molecules in APCC as well. (Level 2) (DiMichele, 2011)

Patients Switching to New Concentrates

Patients switching to a new factor concentrate should be monitored for inhibitor development. (Level 2) (Astermark et al., 2010)

Transfusion-transmitted and Other Infection-related Complications

Principles of Management of HIV Infection in Hemophilia

As part of the hemovigilance program, all people with hemophilia treated with plasma-derived products that are not adequately virus-inactivated should be tested for HIV at least every 6-12 months and whenever clinically indicated. (Level 4) (Evatt et al., 1999)

The diagnosis, counselling, initiation of treatment, and monitoring of HIV, as well as the treatment of HIV-associated complications in infected people with hemophilia, should be the same as in the non-hemophilic population. (Level 2) (Mannucci et al., 1994; Ragni et al., 1995)

None of the currently available classes of anti-HIV drugs are contraindicated in people with hemophilia. (Level 5) (Humphreys, Chang, & Harris, 2010; Spaulding, Rutherford, & Siegfried, "Tenofovir," 2010; Spaulding, Rutherford, & Siegfried, "Stavudine," 2010)

Principles of Management of Hepatitis C Virus (HCV) Infection in Hemophilia

The current standard of treatment for HCV is pegylated interferon (PEG-INF) and ribavirin, which give sustained virological response in 61% of people with hemophilia. (Level 1) (Denholm et al., 2009; Franchini et al., 2008; Hartwell et al., 2011; Operskalski & Kovacs, 2011; Posthouwer et al., 2006; Schulze Zur Wiesch et al., 2009)

Where HCV eradication cannot be achieved, regular monitoring (every 6-12 months) for end-stage liver complication is recommended. (Level 3) (Santagostino et al., 2003)

Principles of Management of Hepatitis B Virus (HBV) Infection in Hemophilia

All people with hemophilia treated with plasma-derived products that are not adequately virus-inactivated should be screened for hepatitis B

antigen and anti-hepatitis B at least every 6-12 months and whenever clinically indicated. (Level 4) (Steele et al., 2009)

Those without HBV immunity should be given the anti-HBV vaccine. Protective seroconversion should be rechecked following vaccination. (Level 4) (Steele et al., 2009; Miller et al., 1989; Pillay et al., 1994)

People with hemophilia who do not seroconvert should be revaccinated with double the hepatitis B vaccine dose. (Level 4) (Steele et al., 2009; Mannucci et al., 1988)

Plasma Factor Level and Duration of Administration

Choice of Factor Replacement Therapy Protocols

Commonly-used dosage for prophylactic factor replacement is 25-40 IU/kg 2-3 times weekly in countries with less resource constraints (see General Care and Management of Hemophilia, above, for details). (Astermark et al., 1999; Blanchette, 2010; Gringeri, et al., 2011)

In situations where there are greater constraints on supply of factor concentrates, prophylaxis may be initiated with lower doses of 10-20 IU/kg 2-3 times per week. (Level 2) (Fischer et al., 2001; Wu et al., 2011)

See Tables 7-1 and 7-2 in the original guideline document for suggested plasma factor peak level and duration of administration, both when there is no significant resource constraint (Table 7-1) and when there is significant resource constraint (Table 7-2).

Definitions:

Oxford Centre for Evidence-Based Medicine, 2011 Levels of Evidence (OCEBM-2)

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5*)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if therapy is not added? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5*)
What is the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*Level may be graded down on the basis of study quality, imprecision, indirectness (study Patient-Intervention-Comparison-Outcome [PICO] does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

**As always, a systematic review is generally better than an individual study.

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hemophilia

Other Disease/Condition(s) Addressed

- Diabetes mellitus
- Hypercholesterolemia
- Hypertension
- Obesity
- Osteoporosis

Guideline Category

Assessment of Therapeutic Effectiveness

Diagnosis

Management

Prevention

Rehabilitation

Screening

Treatment

Clinical Specialty

Allergy and Immunology

Dentistry

Emergency Medicine

Family Practice

Geriatrics

Hematology

Infectious Diseases

Internal Medicine

Medical Genetics

Neurology

Nursing

Obstetrics and Gynecology

Orthopedic Surgery

Pediatrics

Physical Medicine and Rehabilitation

Preventive Medicine

Psychology

Rheumatology

Surgery

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Clinical Laboratory Personnel

Dentists

Health Care Providers

Nurses

Occupational Therapists

Patients

Physical Therapists

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Public Health Departments

Social Workers

Guideline Objective(s)

- To offer practical recommendations on the diagnosis and general management of hemophilia, as well as the prevention and management of complications including musculoskeletal issues, inhibitors, and transfusion-transmitted infections
- To assist healthcare providers seeking to initiate and/or maintain hemophilia care programs, encourage practice harmonization around the world and, where recommendations lack adequate evidence, stimulate appropriate studies

Target Population

Patients with confirmed or suspected hemophilia

Interventions and Practices Considered

Diagnosis

1. Ensuring knowledge and expertise in laboratory coagulation testing (including use of the Nijmegen modification of the factor VIII inhibitor assay)
2. Use of the correct equipment and reagents
3. Quality assurance

Management/Treatment

1. General care and management:
    - Principles of care (treating acute bleeds as quickly as possible, easily accessible patient identification with information about the bleeding disorder and treatment used, use of desmopressin [DDAVP] for mild-moderate hemophilia)
    - Coordinated comprehensive care team
    - Encouragement of physical fitness and activity while protecting target joints
    - Prophylactic factor replacement therapy
    - Home therapy, including use of implanted venous access device (Port-A-Cath)
    - Regular monitoring of health status and outcome
    - Management of pain due to chronic hemophilic arthropathy (avoiding aspirin and non-steroidal anti-inflammatory drugs [NSAIDs])
    - Performing surgery at or in consultation with a comprehensive hemophilia treatment centre
    - Dental care with plan for hemostatic management (use of tranexamic acid or epsilon aminocaproic acid)
2. Special management issues:
    - Testing clotting factor levels of potential carriers (e.g., female relatives of hemophilia patient)
    - Genetic testing for carrier status of at-risk female family members of people with hemophilia
    - Chorionic villus sampling (CVS) or biopsy for prenatal diagnosis of hemophilia
    - Delivery of infants with known or suspected hemophilia
    - Vaccinations, including immunization to hepatitis A and B
    - Considerations for care of hemophilia patients with comorbid conditions
3. Hemostatic agents: viral-inactivated plasma-derived or recombinant clotting factor concentrates (factor VIII, factor IX), cryoprecipitate, fresh frozen plasma, DDAVP, tranexamic acid, epsilon aminocaproic acid
4. Treatment of specific hemorrhages: joint, muscle, throat and neck, gastrointestinal, acute abdominal, ophthalmic, renal, oral, soft tissue, and central nervous system hemorrhages; head trauma; epistaxis; and lacerations and abrasions
5. Management of complications of hemophilia:
    - Management of musculoskeletal complications
    - Assessment and quantification of inhibitor levels and management of complications related to inhibitors
    - Management of transfusion-transmitted and other infection-related complications including human immunodeficiency virus (HIV), hepatitis B, and hepatitis C
6. Plasma factor level and duration of administration

7. Choice of factor replacement therapy protocols

Major Outcomes Considered

- Efficacy of treatments to prevent or manage bleeding or to prevent treatment adverse effects/complications
- Amount of treatment product required
- Level of function
- Level of pain, dysfunction, or long-term disability
- Frequency of hospital admissions
- Need for replacement therapy
- Sensitivity, specificity, and reliability of diagnostic tests
- Adverse effects of treatments
- Safety of treatments
- Morbidity and mortality
- Quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Oxford Centre for Evidence-Based Medicine 2011 (OCEBM-2) Level of Evidence table (see the "Rating Scheme for the Strength of the Evidence" field) was used to help find the best evidence in "real time." Through a series of decision-making "steps" to guide each literature search, the OCEBM-2 table is used to conduct a relatively rapid appraisal. The searches start at the highest (strongest) evidence level, i.e., based on systematic reviews, and then move "down" to randomized trials, cohort studies, case control studies/case series, case reports, and, finally, "mechanistic" reasoning.

Evidence for each practice statement in the guideline was gathered by searching Medline, EMBASE (both on Ovid), and the Systematic Review and CENTRAL databases of the Cochrane Library from 2005 onwards. However, because data in the field is thin, the search was subsequently extended to include all the high quality evidence that exists. Databases were searched between mid-January through mid-July 2011.

The query syntax for practice statements is usually based on a combination of natural language and thesaurus controlled terminology – EMTREE (for EMBASE) and MeSH (for Medline and the CL databases). For some practice statements the guideline authors used standard Scottish Intercollegiate Guidelines Network (SIGN) hedges and/or McMaster hedges.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Oxford Centre for Evidence-Based Medicine, 2011 Levels of Evidence (OCEBM-2)

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5*)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if therapy is not added? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
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Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*Level may be graded down on the basis of study quality, imprecision, indirectness (study Patient-Intervention-Comparison-Outcome [PICO] does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

**As always, a systematic review is generally better than an individual study.

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Although the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM-2) table (see the "Rating Scheme for the Strength of the Evidence" field) is intended as a search heuristic rather than a strict hierarchy, normative judgments about strength of evidence are obviously implied. The table can be used for initial assessment of evidence quality, although further appraisal and judgment must be used. The search strategy is designed so that types of evidence further to the left in the table are likely to be stronger than types of evidence further to the right (although there will be exceptions to this rule of thumb). Step 1-5 corresponds to evidence level 1-5 in the OCEBM-2 table. Evidence levels maybe be graded down on the basis of study quality, imprecision, indirectness, inconsistency between studies, or because the absolute effect size is very small. They may be graded up if there is a large or very large effect size.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Many of the recommendations are based on expert opinion. These guidelines also contain recommendations regarding the clinical management of people with hemophilia (practice statements, in bold in the original guideline document). All such statements are supported by the best available evidence in the literature, which were graded as per the 2011 Oxford Centre for Evidence-Based Medicine (see the "Rating Scheme for the Strength of the Evidence" field). Where possible, references for recommendations that fell outside the selection for practice statements were also included. These references have not been graded.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Given the fact that many recommendations are based on expert opinion, a draft version of these guidelines was circulated to many other opinion leaders involved in hemophilia care outside of the writing group, from around the world. The authors are grateful to those who provided detailed comments.

In addition, the guidelines were peer reviewed upon submission for publication in *Haemophilia*, according to the journal's own policies and practices.

Evidence Supporting the Recommendations

References Supporting the Recommendations

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Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of hemophilia

Potential Harms

- Adverse effects of hemostatic agents:

- 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.
- *Clotting factor concentrates* of lower purity may give rise to allergic reactions.
- *Cryoprecipitate and fresh frozen plasma* 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. Allergic reactions are more common following infusion of cryoprecipitate than concentrate.
- As a result of its antidiuretic activity, water retention and hyponatremia can be a problem with *desmopressin (DDAVP)*. When repeated doses are given, the plasma osmolality or sodium concentration should be measured. 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.
- 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, it must be infused slowly as rapid injection may result in dizziness and hypotension.
- Gastrointestinal upset is a common complication of epsilon *aminocaproic acid*; reducing the dose often helps. 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. The myopathy is often painful and associated with elevated levels of creatine kinase and even myoglobinuria.

- The risks of surgery, local infection, and thrombosis associated with implanted venous access device (Port-A-Cath) need to be weighed against the advantages of starting intensive prophylaxis early.
- All invasive methods used for prenatal diagnosis may cause feto-maternal hemorrhage. Anti-D immunoglobulin should be given if the mother is RhD negative.

Contraindications

Contraindications

- Live virus vaccines (such as oral polio vaccine; measles, mumps, and rubella [MMR]) may be contraindicated in those with human immunodeficiency virus (HIV) infection.
- Due to water retention, desmopressin (DDAVP) 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.
- Due to concerns about the safety and quality of fresh frozen plasma (FFP), its use is not recommended, if avoidable.
- 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.
- Similarly, tranexamic acid is contraindicated in the setting of thoracic surgery, where it may result in the development of insoluble hematomas.
- Tranexamic acid should not be given to patients with factor IX (FIX) deficiency receiving prothrombin complex concentrates, as this will exacerbate the risk of thromboembolism.
- Antifibrinolytic agents should not be used systemically in patients with FIX deficiency that are being treated with large doses of prothrombin complex concentrates or in patients with inhibitors being treated with activated prothrombin complex concentrates (APCC).
- Drugs that affect platelet function, particularly acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs), except certain cyclooxygenase-2 (COX-2) inhibitors, should be avoided in hemophilia patients.

Qualifying Statements

Qualifying Statements

- The World Federation of Hemophilia (WFH) does not endorse particular treatment products or manufacturers; any reference to a product name is not an endorsement by the WFH. The WFH does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimens are continually revised and new side-effects recognized. These guidelines are intended to help develop basic standards of care for the management of hemophilia and do not replace the

advice of a medical advisor and/or product insert information. Any treatment must be designed according to the needs of the individual and the resources available.

- A question often raised when developing a guideline document such as this is its universal applicability given the diversity of health services and economic systems around the world. The strongly held view of the guideline authors is that the principles of management of hemophilia are the same all over the world. The differences are mainly in the doses of clotting factor concentrates (CFC) used to treat or prevent bleeding, given that the costs of replacement products comprise the major expense of hemophilia care programs. Recognizing this reality, these guidelines continue to include a dual set of dose recommendations for CFC replacement therapy. These are based on published literature and practices in major centres around the world. It should be appreciated, however, that the lower doses recommended may not achieve the best results possible and should serve as the starting point for care to be initiated in resource-limited situations, with the aim of gradually moving towards more optimal doses, based on data and greater availability of CFC.
- The recommendations in these guidelines that are based on low levels of evidence should not be taken as final positions on those subjects. The need for further studies in these fields to create better levels of evidence on which to base practice cannot be overemphasized.

Implementation of the Guideline

Description of Implementation Strategy

The World Federation of Hemophilia (WFH) encourages distribution of its materials for educational purposes. These guidelines are available on the *Haemophilia* journal website for free download as well the website of the WFH. The bleeding disorders community has also been informed through more targeted means of communication, which is a continuing process.

The WFH provides support to its national member organizations in their efforts to establish and/or maintain hemophilia care programs, through development programs including the Global Alliance for Progress, the International Hemophilia Treatment Centre fellowship program, the Hemophilia Treatment Centre Twinning Program, and the Advocacy in Action program.

Implementation Tools

Foreign Language Translations

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

Guidelines for the management of hemophilia. 2nd ed. Montreal (Quebec): World Federation of Hemophilia; 2012. 74 p. [324 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

World Federation of Hemophilia - Nonprofit Organization

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Guideline Committee

Treatment Guidelines Working Group

Composition of Group That Authored the Guideline

Working Group Members: Dr. Alok Srivastava (*Chair*), Department of Hematology, Christian Medical College, Vellore, Tamil Nadu, India; Dr. Andrew K. Brewer, Department of Oral Surgery, The Royal Infirmary, Glasgow, Scotland; Dr. Eveline P. Mauser-Bunschoten, Van Creveldkliniek and Department of Hematology, University Medical Center Utrecht, Utrecht, the Netherlands; Dr. Nigel S. Key, Department of Medicine, University of North Carolina, Chapel Hill, NC, U.S.A.; Dr. Steve Kitchen, Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK; Dr. Adolfo Llinas, Department of Orthopaedics and Traumatology, Fundación Santa Fe University Hospital Fundación, Cosme y Damián and Universidad de los Andes and Universidad del Rosario, Bogotá, Colombia; Dr. Christopher A. Ludlam, Comprehensive Care Haemophilia and Thrombosis Centre, Royal Infirmary, Edinburgh, UK; Dr. Johnny N. Mahlangu, Hemophilia Comprehensive Care Centre, Johannesburg Hospital and Department of Molecular Medicine and Haematology, Faculty of Health Sciences, National Health Laboratory Services and University of the Witwatersrand, Johannesburg, South Africa; Kathy Mulder, Department of Physiotherapy, Child Heath, and Manitoba Bleeding Disorders Clinic, Health Sciences Center, Winnipeg, Canada; Dr. Man-Chiu Poon, Departments of Medicine, Pediatrics and Oncology, and Southern Alberta Rare Blood and Bleeding Disorders Comprehensive Care Program, University of Calgary, Foothills Hospital and Calgary Health Region, Alberta, Canada; Dr. Alison Street, Department of Haematology, Alfred Hospital Melbourne, Australia

Financial Disclosures/Conflicts of Interest

Dr. Srivastava has received competitive peer reviewed grant support from the Bayer Hemophilia Awards Program and also serves on their Grants Review and Awards Committee.

Dr. Key has acted as a paid consultant to Novo Nordisk and has received grant funding from Baxter.

Dr. Kitchen has acted as a paid consultant to Novo Nordisk, Pfizer, and Bayer. Dr. Llinas has lectured for Baxter, Novo Nordisk, Pfizer, and Bayer and has performed clinical trials for Bayer and Baxter.

Dr. Ludlam has received an educational grant from Novo Nordisk, has acted as medical advisor for Ipsen, a consultant for Biogen Idec and Baxter as well as Bayer, from which he has also received funding to attend medical conferences.

Dr. Mauser-Bunschoten has received unrestricted research funding from CSL Behring, is a speaker for Bayer, Sanquin Bloedvoorziening, and Novo Nordisk, and has received funding for postmarketing surveillance by Wyeth, Baxter and Sanquin Bloedvoorziening. She is also the principal investigator for a FIX long-acting product trial sponsored by NovoNordisk.

Dr. Poon has attended advisory board meetings of CSL Behring, Novo Nordisk, Octapharma, and Pfizer. He has attended sponsored meetings on behalf of Baxter and Bayer, is a speaker for Pfizer, and acted as chair of Novo Nordisk's expert panel on Glanzmann's Thrombasthenia registry.

Dr Mahlangu has performed clinical research for Biogen, Bayer and NovoNordisk. He has participated in scientific advisory board meetings and has lectures for Bayer, Amgen and NovoNordisk.

The other authors have no competing interests to declare.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Guidelines for the management of hemophilia. Montreal (Quebec): World Federation of Hemophilia; 2005. 56 p.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the World Federation of Hemophilia (WFH) Web site .

Copies can be purchased in Chinese and French from the WFH Web site .

Availability of Companion Documents

A compendium of assessment tools: an evaluation of various assessment tools, including the Hemophilia Joint Health Score (HJHS), World Federation of Hemophilia (WFH) Physical Examination Score (Gilbert score), Haemophilia Activities List (HAL), Haemophilia Activities List – Pediatric (PedHAL), and Functional Independence Score in Hemophilia (FISH), as well as the tools themselves, are available from the World Federation of Hemophilia (WFH) Web site .

Patient Resources

The following is available:

- What is hemophilia? Available from the World Federation of Hemophilia (WFH) Web site .

NGC Status

This NGC summary was completed by ECRI Institute on March 11, 2013. The information was verified by the guideline developer on April 12, 2013. This summary was updated by ECRI Institute on September 18, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs).

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