A practical approach to hemophilia care in children

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Hemophilia A and B are the most common of the severe bleeding disorders. The present article focuses on the practical aspects of the management of neonates and children diagnosed with hemophilia, and is based on questions frequently posed to paediatric hematologists. It highlights the importance of early diagnosis, the principle of early intervention and the role of comprehensive care hemophilia treatment centres.

Key words: *Hemophilia; Neonates; Paediatrics*

Une démarche pratique des soins aux enfants hémophiles

Les hémophilies A et B sont les principaux troubles de saignement graves. Le présent article porte sur les aspects pratiques de la prise en charge des nouveau-nés et des enfants atteints d'hémophilie diagnostiquée et découle de questions souvent posées aux hématologues pédiatriques. Il met en lumière l'importance de poser un diagnostic rapidement, le principe d'intervention précoce et le rôle des centres de traitement global aux hémophiles.

Hemophilia A (HA) (factor VIII [FVIII] deficiency) and hemophilia B (HB) (factor IX [FIX] deficiency) are both rare disorders, but are the most common, severe inherited bleeding disorders. HA affects fewer than one in 10,000 people, or approximately 2500 Canadians. HB is less common, affecting approximately one in 50,000 people, or approximately 500 Canadians (1). HA and HB are X-linked inherited disorders; however, 30% of cases occur as a spontaneous mutation, and therefore, there is no family history of the disease (2). Hemophilia is classified according to the baseline plasma level of FVIII or FIX into severe (factor level lower than 1 U/dL or less than 1%), moderate (factor level between 1 U/dL and 5 U/dL, or between 1% and 5%) and mild (factor level higher than 5 U/dL or greater than 5%). This classification system serves as a guide to the expected frequency of bleeding. If there is a suspicion of hemophilia in a patient, a factor level should be determined, because in mild cases, the activated partial thromboplastin time may be normal. Female carriers may be symptomatic, underscoring the importance of determining a baseline factor level even in carriers.

CLINICAL MANIFESTATIONS OF HEMOPHILIA

Patients with hemophilia experience a spectrum of bleeding manifestations, which usually, but not always, are in keeping with their baseline level of FVIII or FIX. Examples of bleeding include intracranial hemorrhage, deep muscle and joint hemorrhage, hematomas, retroperitoneal hemorrhage, bleeding following teeth extraction, postsurgical bleeding, easy bruising and mucosal bleeding. Patients' susceptibility to musculoskeletal hemorrhage can lead to recurrent hemarthroses and development of target joints. The definition of a target joint is controversial; within Canada, the generally accepted criterion is a minimum of three bleeds into a single joint within a consecutive three-month period (3). It should be noted that even patients with mild hemophilia who develop trauma-related musculoskeletal bleeds can develop permanent damage to a particular muscle group or joint if not treated promptly.

TREATMENT OF HEMOPHILIA

The treatment of hemophilia consists of on-demand therapy or prophylaxis to prevent bleeding. Long-term prophylaxis is the standard of care for treatment of children with severe hemophilia in developed countries. The definition of prophylaxis is the regular infusion of factor concentrates with the aim of preventing bleeding, starting within the first two years of life (4).

A general rule of emergency treatment is 'factor first', ie, if in doubt, administer factor replacement immediately before any further investigations are carried out. The Factor First Program was developed by the Canadian Hemophilia Society to support the emergency care of individuals with bleeding disorders. A product of this program is the Factor First card, which is a wallet-sized document stating the treatment recommendations for a particular patient (5).

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TABLE 1
Calculation of the replacement dose of factor VIII (FVIII) and factor IX (FIX)

Factor	Dose calculation
FVIII	FVIII (U) = Per cent desired rise in plasma FVIII × body weight (kg) × 0.5*
FIX	FIX (U) = Per cent desired rise in plasma FIX × body weight (kg) × 1.4*

**Calculate to the closest vial size and do not discard any factor. Data from references 10 and 11*

TABLE 2
Dosing suggestions of factor VIII (FVIII) and factor IX (FIX) for different clinical conditions

	Initial dose of FVIII (U/kg of body weight)*	Initial dose of FIX (U/kg of body weight)*
Minor bleeding	10–15	25–35
Early joint or muscle bleeding		
Severe nose bleed		
Persistent blood in urine		
Mouth bleed that does not respond to antifibrinolytics		
Major bleeding	20–30	45–70
Advanced joint or muscle bleed		
Bleed into neck, tongue or throat		
Prophylaxis following severe trauma without bleeding		
Life-threatening bleeding	40–50	95–120
Severe head injury		
Surgery (except dental)		
Bleeding after major trauma		
Bleeding into the abdomen		
Dental extraction	10–15	25–35

**Vial sizes are typically 250 U, 500 U and 1000 U. Check with blood bank regarding availability of vial sizes*

Calculation of the dose required to achieve a hemostatic level of FVIII and FIX is given in Table 1. In Canada, both FVIII and FIX concentrates are recombinant products. A guide to the suggested doses of FVIII and FIX in different clinical scenarios is provided in Table 2. Superficial bleeding and bruising do not require factor replacement. The principle of 'more is better' does not necessarily apply in the treatment of hemophiliacs, because the advantages of giving either FVIII or FIX have to be weighed against the awareness of the development of inhibitors to FVIII and FIX.

Other drugs used in the management of hemophilia are outlined in Table 3. Desmopressin (DDAVP, Ferring Pharmaceuticals, USA) is the treatment of choice in patients with mild hemophilia who have shown an adequate response to the drug in a therapeutic trial. DDAVP may also be given to these patients as prophylaxis, 30 min to 60 min before a procedure, to ensure adequate hemostasis. Hyponatremia is a rare side effect of DDAVP therapy; fluid intake should be restricted to maintenance for 24 h post-DDAVP. Patients with mild hemophilia who do not respond adequately to DDAVP may be treated on demand with factor concentrates. Antifibrinolytic therapy (eg, tranexamic acid) is effective in controlling mucosal bleeding. The dose of tranexamic acid is given in Table 3.

TABLE 3
Other drugs used in the management of hemophilia

Drug	Dose	Indication
Tranexamic acid*	25 mg/kg po q 6–8 h or 10 mg/kg IV q 6–8 h	Mild/moderate mucosal hemorrhage
Desmopressin (DDAVP)†	0.3 µg/kg (maximum 20 µg/kg) SC or IV	Treatment of bleeds or prophylaxis preprocedures in mild hemophilia

*For intravenous (IV) administration, desmopressin is given in 20 mL to 50 mL normal saline over 30 min.*Tranexamic acid is available in 500 mg capsules, and there is no elixir available in Canada; †Ferring Pharmaceuticals, USA. po Oral; q Every; SC Subcutaneous*

DIAGNOSIS AND MANAGEMENT OF HEMOPHILIA IN NEONATES

Neither FVIII nor FIX cross the placenta; therefore, hemophilia can be diagnosed on a cord blood sample. All levels of severity of HA can be diagnosed at birth, because neonatal FVIII levels are that of adult values (0.5 U/mL to 1.5 U/mL). FIX levels reach adult values by day 90; therefore, mild HB cannot be diagnosed at birth (6). It is imperative that all male infants born to known carriers have baseline factor level testing, because the prothrombin time and activated partial thromboplastin time may be normal in mild hemophilia. Labour and delivery pose a bleeding threat. Communication among the obstetrician, neonatologist and hematologist during the pregnancy of a carrier cannot be overemphasized. Vaginal delivery is recommended with avoidance of vacuum extraction and forceps, because caesarian section does not eliminate the risk of bleeding (7). Intracranial hemorrhage has been reported in 1% to 4% of hemophiliac newborns and occurs due to birth trauma, irrespective of the mode of delivery (8). The majority of hemophiliacs do not bleed in the newborn period. A neonate presenting with intracranial hemorrhage, subgaleal hemorrhage, cephalohematoma, puncture-related bleeding, joint bleed, visceral organ bleed, bleeding from umbilical stump and/or bleeding after circumcision should have FVIII and FIX levels determined. In the event of severe hemorrhage, the principle of 'factor first' should be observed, and the administration of recombinant clotting factor concentrates to raise the factor level to 100% is preferred over plasma or plasma-derived products. If intramuscular (IM) vitamin K is given, pressure should be applied to the site for 5 min to 10 min. Hepatitis B vaccine can be given subcutaneously rather than through IM injection. Further IM immunizations should be given using a 25- or 27-gauge needle, depending on the muscle mass of the child, and pressure

should be applied to the site for 5 min to 10 min. In the case of patients with severe hemophilia, it is advisable to administer IM injections on the day of their regular prophylaxis.

THE IMPORTANCE OF COMPREHENSIVE CARE TREATMENT CENTRES

Hemophilia treatment centres (HTCs) offer a comprehensive approach through a team of specialized health professionals. The team primarily consists of a hematologist, nurse coordinator, physiotherapist and social worker. Other disciplines are consulted as needed. A comprehensive approach provides ongoing assessments and continuity of care, thereby decreasing the amount of complications for individuals with hemophilia. Furthermore, studies have shown that there are increased mortality and hospitalization rates in hemophilia patients treated outside of HTCs (9). Information on treatment (including the Factor First Program), research and genetic counselling is provided. The clinic promotes the maintenance of a healthy lifestyle, including regular physical activity, regular dental review and adherence to immunization schedules.

SPORTING ACTIVITIES AND HEMOPHILIA

Physical activity is encouraged and supported. Considerations to be taken into account when boys with hemophilia choose to partake in a sporting activity include the severity of hemophilia, use of prophylaxis, history of an inhibitor and presence of target joints. Advice on the use of protective equipment, conditioning exercises and the type of exercise regimens are vital to discuss. Sports that involve high speed, heavy contact and collision, such as football and hockey, are not recommended. Communication with the HTC is very important before undertaking any sporting activities.

HELPFUL WEB SITES

- Canadian Hemophilia Society – www.hemophilia.ca
- World Federation of Hemophilia – www.wfh.org
- National Hemophilia Foundation – www.hemophilia.org
- Association of Hemophilia Clinic Directors of Canada – www.ahcdc.ca
- Hemophilia Emergency Care – www.hemophiliaemergencycare.com

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