2 SPECIAL MANAGEMENT ISSUES

2.1 Carriers

1. Hemophilia is an X-linked disorder that typically affects males, while females are carriers.
2. Obligate carriers are:
   - daughters of a person with hemophilia
   - mothers of one son with hemophilia and who have at least one other family member with hemophilia
   - mothers of one son with hemophilia and who have a family member who is a known carrier of the hemophilia gene
   - mothers of two or more sons with hemophilia
3. The expected mean clotting factor level in carriers of hemophilia is 50% of the levels found in the healthy population [1,2].
4. Most carriers are asymptomatic.
5. Carriers with clotting factor levels of 40-60% of normal may have an increased bleeding tendency [3].
6. A few carriers may have clotting factor levels in the hemophilia range—mostly in the mild category—but in rare instances, carriers can be in the moderate or severe range due to extreme lyonization (see Table 1-1).
7. Carriers with clotting factor levels in the hemophilia range may be symptomatic with bleeding manifestations commensurate with their degree of clotting factor deficiency, particularly during trauma and surgery [3].
8. Menorrhagia and bleeding after medical interventions are the most common manifestations among carriers with significantly low factor levels [3].
9. Carriers with low clotting factor levels should be categorized as having hemophilia of appropriate severity and managed accordingly.
10. Birth control pills and antifibrinolytic agents are useful in controlling symptoms of menorrhagia.
11. Levels of factor VIII increase significantly in pregnancy. Levels of factor IX, however, do not usually change significantly [4].
12. **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) [3,5]**

2.2 Genetic testing/counselling and prenatal diagnosis

1. **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) [6]**
2. DNA-based mutation analysis to identify the specific mutation responsible for hemophilia in a particular family is becoming technically easier and more widely available. This facilitates identification of carriers and prenatal diagnosis for male fetuses.
3. Genetic counselling is key to helping people with hemophilia, carriers, and their families make more informed choices.
4. Prenatal diagnosis is usually offered when termination of the pregnancy would be considered if an affected fetus was identified. However, it may also be done to help the family prepare and to plan delivery. Assisted delivery is best avoided in an affected fetus.
5. Fetal gender can be determined using Y chromosome-specific PCR in maternal plasma/serum after 7-9 weeks of gestation [7,8] or by ultrasonography beginning week 11 of gestation [9].
6. **Chorionic villus sampling (CVS), or biopsy, is the main method of prenatal diagnosis and is best done between 9-14 weeks of gestation. Biopsy carried out earlier may be associated with increased complications including fetal limb abnormalities. (Level 1) [10-13]**
7. Amniocentesis can be done at 15-17 weeks of gestation [11].
8. It is important to be aware of and to follow the relevant laws governing such procedures in the country where the service is being provided.
9. For carriers with low factor levels (< 50 IU/dl), hemostatic support may be required to prevent maternal bleeding during prenatal diagnosis procedures.
10. **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) [14]**
11. Pre-implantation genetic diagnosis allows selection of embryos without specific mutation to be implanted into the uterus [15].

2.3 Delivery of infants with known or suspected hemophilia

1. **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) [4]**
2. **In carriers with significantly low factor levels (< 50 IU/dl), clotting factor replacement is necessary for surgical or invasive procedures including delivery. (Level 3) [4]**
3. The need for clotting factor replacement should be planned in the prenatal period.
4. Route of delivery in carriers with a normal fetus should be as per obstetric indications**.**
5. **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) [4]**
6. Forceps and vacuum extraction should be avoided in vaginal delivery, as well as invasive procedures to the fetus such as fetal scalp blood sampling and internal fetal scalp electrodes [16].

2.4 Vaccinations

1. **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) [17]**
2. If intramuscular injection is to be given:
   - It is best done soon after a dose of factor replacement therapy.
   - An ice pack can be applied to the injection area for five minutes before injection.
   - The smallest gauge needle available (usually 25-27 gauge) should be used.
   - Pressure should be applied to the injection site for at least five minutes [18].
3. Live virus vaccines (such as oral polio vaccine, MMR) may be contraindicated in those with HIV infection.
4. People with hemophilia who have HIV should be given pneumococcal and annual influenza vaccines.
5. **Immunization to hepatitis A and B is important for all persons with hemophilia. These immunizations may not be as effective in those with HIV infection. (Level 4) [19,20]**

2.5 Psychosocial issues

1. Patients and their families should be provided with psychological and social support [21,22].
2. Hemophilia is also a financial burden that places restrictions on several aspects of normal living [23].
3. The social worker and/or other members of the comprehensive care team should:
   - provide as much information as possible about the physical, psychological, emotional, and economic dimensions of hemophilia, in terms the patient/parents can understand.
   - be open and honest about all aspects of care.
   - allow the patient/parents to work through their emotions and ask questions. Provide care and support patiently.
   - talk to affected children, not just their parents. Children can often understand a good deal about their illness and can work with the physician if properly informed and educated.
   - remind parents not to ignore siblings that are healthy.
   - be able to recognize warning signs of burnout and depression, which are common with chronic illness, and provide suggestions for coping.
   - recognize that cultural background may affect patients' views of illness.
   - encourage patients to engage in productive and leisure activities at home and in the workplace.
   - work in partnership with the patient organization to advocate for hemophilia care and to provide education to families and members of the community.
   - enlist the assistance of local groups and organizations where social workers are unavailable.

2.6 Sexuality

1. Patients with hemophilia can have normal sexual intercourse [24].
2. Muscle bleedings (for e.g. iliopsoas) may sometimes be the result of sexual activity.
3. Complications of hemophilia can be accompanied by sexual dysfunction, which may include lack of libido or impotence.
4. Pain or fear of pain may affect sexual desire, and hemophilic arthropathy may place limitations on sexual intercourse.

5. Sexuality is also affected by chronic HCV and HIV infection, age-related diseases like hypertension and diabetes mellitus, and certain medications.
6. In some cases, oral phosphodiesterase-5 inhibitors (sildenafil, tadalafil) may be helpful. These medications mildly inhibit platelet aggregation *in vitro*, and may cause epistaxis due to nasal congestion.

2.7 Ageing hemophilia patients

1. Ageing patients with hemophilia will inevitably suffer from age-related diseases [24,25].
2. Comorbidities in ageing hemophilia patients should be managed appropriately as they may accentuate problems associated with hemophilia and impact the patient's physical and psychosocial health, and thus their quality of life.

Osteoporosis

1. Bone mineral density (BMD) is decreased in people with hemophilia [26,27].
2. An increased number of arthropathic joints, loss of joint movement, and muscle atrophy leading to inactivity are associated with a lower BMD [27].
3. Weight-bearing activities (suitable sports) that promote development and maintenance of good bone density should be encouraged if joint health permits.
4. Calcium and vitamin D supplementation are also important and bisphosphonate therapy may be required. A dental evaluation is advisable before initiating long-term bisphosphonate therapy [28,29].

Obesity

1. The prevalence of overweight (BMI 25-30 kg/m^2) and obesity (BMI > 30kg/m^2) is increasing [30].
2. Lack of activity may contribute to an increase in BMI and increased body weight.
3. A high BMI has been associated with:
   - a significant limitation in range of motion (ROM) [31]
   - increased arthropathic pain
   - increased risk of developing target joints [32]
   - increased risk of diabetes mellitus, atherosclerosis, and cardiovascular disease, which may further damage arthropathic joints.
4. Regular physical activity should be advised.
5. If functional limitations restrict daily activities, a physiotherapist familiar with hemophilia may be able to suggest appropriate alternatives.
6. In some cases referral to a dietician may be indicated.

Hypertension

1. Hemophilia patients have a higher mean blood pressure, are twice as likely to have hypertension, and use more anti-hypertensive medication compared to the general population [33,34].
2. In view of increased risk of bleeding, hypertensive patients with hemophilia should be treated adequately and have their blood pressure checked regularly.
3. In the absence of other cardiovascular risk factors, a systolic blood pressure ≤140 mmHg and a diastolic pressure ≤90 mmHg should be maintained.

Diabetes mellitus (DM)

1. The prevalence of DM in hemophilia is not well documented, but was observed to be higher in a cohort of mild hemophilia [35].
2. In ageing hemophilia patients, especially among those who are overweight, glucose levels should be checked annually.
3. **If treatment with insulin is indicated, subcutaneous injections can be administered without bleeding complications. (Level 5) [24]**

Hypercholesterolemia

1. Mean cholesterol levels in patients with hemophilia have been reported to be lower than in the general population [36].
2. Cholesterol levels (total cholesterol, HDL, and LDL fraction) should be measured in ageing hemophilia patients at risk of cardiovascular disease.
3. Treatment is indicated if cholesterol levels are high. As a general rule, the total cholesterol/HDL ratio should not be higher than 8.

Cardiovascular disease

1. Hemophilia patients appear to have a reduced risk of mortality from ischemic cardiovascular disease, but the number of deaths from this cause is increasing [34,37,38].
2. A possible association between the occurrence of myocardial infarction and previous administration of clotting factor concentrates has been described [39,40].
3. Hemophilia patients with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist [41,42].
4. 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) [40,41,43]**
   - High factor levels should be avoided in order to prevent occlusive thrombi. During complete correction:
     - Heparin can be administered according to standard cardiologic treatment protocols.
     - Glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban) used in PCI with stenting can be administered.
   - **Radial artery access site, if technically possible, is preferred over femoral, in order to minimize retroperitoneal or groin bleeds. (Level 4) [40,41,43]**
   - Factor concentrates should be given for the duration of dual antiplatelet therapy, usually about two weeks, aiming at trough levels of 30 IU/dl [41].
   - Prolonged use of aspirin is not recommended in severe hemophilia. Its use in patients on regular intensive prophylaxis is possible, though the data available is inadequate [41].

Psychosocial impact

1. In the ageing patient, the presence of crippling, painful arthropathy can affect quality of life and may lead to loss of independence [44].
2. Patients may be confronted with unexpected emotional problems due to memories of negative experiences related to hemophilia (such as hospitalization) during their youth.
3. Adaptations at home or at work and an adequate pain schedule are indicated to improve quality of life and preserve independence.
4. Active psychosocial support should be provided by a social worker, hemophilia nurse, physician and/or psychologist.

2.8 Von Willebrand disease and rare bleeding disorders

1. The WFH is committed to providing support and information to patients, families, and clinicians on other hereditary bleeding disorders and many such patients are cared for in hemophilia treatment centres.
2. These guidelines are intended for the treatment of hemophilia. Recent publications that address the principles of diagnosis and treatment of von Willebrand disease (VWD) and rare bleeding disorders include:
   - Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2004;10(3):218.231.

- The Diagnosis, Evaluation and Management of von Willebrand Disease. US Dept of Health and Human Services, National Heart, Lung and Blood Institute NIH Publication no. 08-5832, December 2007. www.nhlbi.nih.gov
- Von Willebrand Disease: An Introduction for the Primary Care Physician. David Lillicrap and Paula James, World Federation of Hemophilia Treatment of Hemophilia monograph No 47, January 2009. www.wfh.org
- Rare Bleeding Disorders. Peyvandi F, Kaufman R, Selighson U et al. *Haemophilia* 2006 Jul; 12 Suppl: 137-42.
- The Rare Coagulation Disorders. Paula Bolton-Maggs, World Federation of Hemophilia Treatment of Hemophilia No 39, April 2006. www.wfh.org

References

1. Lee CA, Chi C, Pavord SR, Bolton-Maggs PH, Pollard D, Hinchcliffe-Wood A, Kadir RA; UK Haemophilia Centre Doctors' Organization. The obstetric and gynaecological management of women with inherited bleeding disorders--review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2006 Jul;12(4):301-36.
2. Rizza CR, Rhymes IL, Austen DE, Kernoff PB, Aroni SA. Detection of carriers of haemophilia: a 'blind' study. *Br J Haematol* 1975;30(4):447-56.
3. Plug I, Mauser-Bunschoten EP, Brocker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood* 2006;108(1):52-6.
4. Chi C, Lee CA, Shiltagh N, Khan A, Pollard D, Kadir RA. Pregnancy in carriers of hemophilia. *Haemophilia* 2008;14(1):56-64.
5. Ljung R, Tedgård U. Genetic counseling of hemophilia carriers. *Semin Thromb Hemost* 2003;29(1):31-6.
6. Dunn NF, Miller R, Griffioen A, Lee CA. Carrier testing in haemophilia A and B: adult carriers' and their partners' experiences and their views on the testing of young females. *Haemophilia* 2008;14(3):584-92.
7. Mortarino M, Garagiola I, Lotta LA, Siboni SM, Semprini AE, Peyvandi F. Non-invasive tool for foetal sex determination in early gestational age. *Haemophilia* 2011 Nov;17(6):952-6.
8. Rijnders RJ, van der Luijt RB, Peters ED, Goeree JK, Van Der Schoot CE, Ploos Van Amstel JK, Christiaens GC. Earliest gestational age for fetal sexing in cell-free maternal plasma. *Prenat Diagn* 2003;23(13):1042-4.
9. Chi C, Hyett JA, Finning KM, Lee CA, Kadir RA. Non-invasive first trimester determination of fetal gender: a new approach of prenatal diagnosis of haemophilia. *BJOG* 2006;113(2):239-42.
10. Evans MI, Andriole S. Chorionic villus sampling and amniocentesis in 2008. *Curr Opin Obstet Gynecol* 2008;20(2):164-8.
11. Jauniaux E, Pahal GS, Rodeck CH. What invasive procedure to use in early pregnancy? *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;14(4):651-62.
12. Tabor A, Alfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. *Fetal Diagn Ther* 2010;27(1):1-7.
13. Wapner RJ.Invasive prenatal diagnostic techniques. *Semin Perinatol* 2005;29(6):401-4.
14. Katiyar R, Kriplani A, Agarwal N, Bhatla N, Kabra M. Detection of fetomaternal hemorrhage following chorionic villus sampling by Kleihauer Betke test and rise in maternal serum alpha feto protein. *Prenat Diagn* 2007;27(2):139-42.
15. Lavery S. Preimplantation genetic diagnosis of haemophilia. *Br J Haematol* 2009;144:303-307.
16. Kletzel M, Miller CH, Becton DL, Chadduck WM, Elser JM. Postdelivery head bleeding in hemophilic neonates: Causes and management. *Am J Dis Child* 1989;143:1107-10.
17. Kulkarni R, Lusher J. Perinatal management of newborns with haemophilia. *Br J Haematol* 2001 Feb;112(2):264-74.
18. Evans DI, Shaw A. Safety of intramuscular injection of hepatitis B vaccine in haemophiliacs. *BMJ* 1990;300:1694–95.
19. Miller EJ, Lee CA, Karayiannis P, Holmes S, Thomas HC, Kernoff PB. Immune response of patients with congenital coagulation disorders to hepatitis B vaccine: suboptimal response and human immunodeficiency virus infection. *J Med Virol* 1989;28:96–100.
20. Steele M, Cochrane A, Wakefield C, et al. Hepatitis A and B immunization for individuals with inherited bleeding disorders. *Haemophilia* 2009;15(2):437-47.
21. Cassis F. Psychosocial care for people with hemophilia. Treatment of Hemophilia monograph no 44. Montreal: World Federation of Hemophilia, 2007.
22. Miller R. Counselling about diagnosis and inheritance of genetic bleeding disorders: haemophilia A and B. *Haemophilia* 1999;5(2):77-83.
23. Bullinger M, von Mackensen S. Psychosocial determinants of quality of life in children and adolescents with haemophilia: a cross-cultural approach. *Clin Psychol Psychother* 2008;15(3):164-72.

24. Mauser-Bunschoten EP, Fransen Van De Putte DE, Schutgens RE. Co-morbidity in the ageing haemophilia patient: the down side of increased life expectancy. *Haemophilia* 2009 Jul;15(4):853-63.
25. Siboni SM, Mannucci PM, Gringeri A, et al. Health status and quality of life of elderly persons with severe haemophilia born before the advent of modern replacement therapy. *J Thromb Haemost* 2009;7(5):780-6.
26. Iorio A, Fabbriciani G, Marcucci M, Brozzetti M, Filipponi P. Bone mineral density in haemophilia patients: A meta-analysis. *Thromb Haemost* 2010 Mar;103(3):596-603.
27. Wallny TA, Scholz DT, Oldenburg J, et al. Osteoporosis in haemophilia - an underestimated comorbidity? *Haemophilia* 2007;13(1):79-84.
28. Kovacs CS. Hemophilia, low bone mass, and osteopenia/osteoporosis. *Transfus Apher Sci* 2008;38(1):33-40.
29. Scottish Dental Clinical Effectiveness Programme, Oral Health Management of Patients Prescribed Bisphosphonates: Dental Clinical Guidance. Dundee: Scottish Dental Clinical Effectiveness Programme, April 2011.
30. Hofstede FG, Fijnvandraat K, Plug I, Kamphuisen PW, Rosendaal FR, Peters M. Obesity: a new disaster for haemophilic patients? A nationwide survey. *Haemophilia* 2008;14(5):1035-38.
31. Soucie JM, Cianfrini C, Janco RL, et al. Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. *Blood* 2004;103(7):2467-73.
32. Carpenter SL, Chrisco M, Johnson E. The effect of overweight and obesity on joint damage in patients with moderate to severe hemophilia. *Blood* 2006;108:ASH Annual Meeting Abstracts 4064.
33. Biere-Rafi S, Baarslag MA, Peters M, Kruip MJ, Kraaijenhagen RA, Den Heijer M, Büller HR, Kamphuisen PW. Cardiovascular risk assessment in haemophilia patients. *Thromb Haemost* 2011 Feb 1;105(2):274-8.
34. Lim MY, Pruthi RK. Cardiovascular disease risk factors: prevalence and management in adult hemophilia patients. *Blood Coagul Fibrinolysis* 2011 Jul;22(5):402-6.
35. Walsh M, Macgregor D, Stuckless S, Barrett B, Kawaja M, Scully MF. Health-related quality of life in a cohort of adult patients with mild hemophilia A. *J Thromb Haemost* 2008;6(5):755-61.
36. Rosendaal FR, Briet E, Stibbe J, van Herpen G, Leuven JA, Hofman A, Vandenbroucke JP. Haemophilia protects against ischaemic heart disease: a study of risk factors. *Br J Haematol* 1990;75(4):525-30.
37. Kulkarni R, Soucie JM, Evatt BL; Hemophilia Surveillance System Project Investigators. Prevalence and risk factors for heart disease among males with hemophilia. *Am J Hematol* 2005;79(1):36-42.
38. Ragni MV, Moore CG. Atherosclerotic heart disease: prevalence and risk factors in hospitalized men with haemophilia A. *Haemophilia* 2011 Nov;17(6):867-71.
39. Girolami A, Ruzzon E, Fabris F, Varvarikis C, Sartori R, Girolami B. Myocardial infarction and other arterial occlusions in hemophilia A patients: a cardiological evaluation of all 42 cases reported in the literature. *Acta Haematol* 2006;116(2):120-5.
40. Schutgens RE, Tuinenburg A, Roosendaal G, Guyomi SH, Mauser-Bunschoten EP. Treatment of ischaemic heart disease in haemophilia patients: an institutional guideline. *Haemophilia* 2009;15(4):952-58.
41. Mannucci PM, Schutgens RE, Santagostino E, Mauser-Bunschoten EP. How I treat age-related morbidities in elderly patients with hemophilia. *Blood* 2009;114 (26):5256-63.
42. Tuinenburg A, Mauser-Bunschoten EP, Verhaar MC, Biesma DH, Schutgens RE. Cardiovascular disease in patients with hemophilia. *J Thromb Haemost* 2009;7(2):247-54.
43. Coppola A, Tagliaferri A, Franchini M. The management of cardiovascular diseases in patients with hemophilia. *Semin Thromb Hemost* 2010;36(1):91-102.
44. Street A, Hill K, Sussex B, Warner M, Scully MF. Haemophilia and ageing. *Haemophilia* 2006;12(Suppl 3): 8-12.