

Editorial

Together we care: new challenges for global haemophilia treatment centers

Haemophilia A and B are rare inherited bleeding disorders characterized in the most severe form by spontaneous bleeding into joint and muscles associated with invalidating arthropathy, as well as by more serious bleeds, namely intracranial haemorrhage¹. Although inherently challenging, the management of haemophiliacs has been dramatically improved over the last decades. The main breakthrough in the management of haemophilia A was the discovery by Judith Pool of the cryoprecipitate, which paved the way for the development of factor VIII (FVIII) concentrates in the 1970s². The advent of an effective treatment for haemophilia led to a significant impact in both expectancy and quality of life of haemophiliacs in developed countries, enabling the treatment of joint bleeds at the earliest symptoms. However, this first golden era was relatively short, since it was suddenly interrupted by the dramatic epidemics of human immunodeficiency (HIV) and hepatitis C (HCV) viruses transmitted by non-virus inactivated clotting factor concentrates. These viruses were responsible for the great majority of deaths (*i.e.*, acquired immunodeficiency syndrome-AIDS, HIV related lymphomas, end-stage liver diseases, including HCV related hepatocellular carcinoma) during the 1980s and 1990s, decimating haemophiliacs and thus causing a new drop in their median life expectancy^{3,4}. This catastrophe led the impulse to the implementation of viral inactivation techniques for the production of plasma-derived factor concentrates. However, the most important advance in this field was represented by recombinant gene technology (FVIII gene was cloned in 1984 and the first haemophilic patient was infused in 1987) and protein purification techniques, which enabled the development of highly purified recombinant factor VIII (rFVIII) products. Indeed, the viral safety of

rFVIII concentrates dramatically improved the quality of life of children with haemophilia and their families, permitting regular infusion of factor concentrate replacement therapy by infusion of factor concentrate to prevent bleeding and resultant joint damage (*i.e.*, primary prophylaxis), home treatment and ultimately a near normal lifestyle⁵. Thus, in developed countries, the early treatment of bleeding episodes and home therapy rapidly became the primary management option for haemophiliacs. In parallel, training and education of patients about disease management became necessary, so that specific programmes were implemented and delivered by haemophilia treatment centers which provided comprehensive services based on an integrated public health approach.

The haemophilia comprehensive care model, which is defined as the continuing supervision of all medical and psychosocial factors affecting patients and their families, has been a cornerstone and one of the most successful health programmes in developed countries, resulting in a significant improvement of health and, ultimately, of life expectancy for haemophilia community^{6,7}. There are several reasons for the importance of a such an approach for the management of haemophilia. First of all, as haemophilia care involves many medical and surgical areas; it requires a multidisciplinary team approach. Thus, a well trained and experienced medical staff is needed for the appropriate care to haemophilic patients. The leading tasks to be covered by the comprehensive care team include diagnosis, education of the patient and his/her family, prenatal counselling, treatment of bleeding episodes, education to home therapy, routine follow up, perioperative management of patients undergoing surgical or invasive procedures, and psychosocial support. For example, the referral team operating at

our haemophilia center includes a medical director (a haematologist), a nurse coordinator, a physiotherapist, a psychologist and expertise from a number of surgical (dentistry, orthopaedic surgery), medical (paediatrics, rheumatology, infectious diseases) and diagnostic (genetics, laboratory medicine, radiology) specialties. In addition, optimization of the efficiency of this system can be achieved by the concentration of haemophilia care into specialized centers, where specialists can work cooperatively within the same facility and with teams of other haemophilia centers. The aim of this organization is to form a specialized treatment network to establish continuous and dynamic evaluation of treatment trends in the light of new discoveries and modify the standards of treatments to incorporate the new discoveries into the management of haemophiliacs. Prevention of the complications of haemophilia is an additional key aspect in the comprehensive care organization. This can be achieved with prophylaxis and early home treatment, as well as with the use of safe products (*i.e.*, virus-inactivated plasma-derived concentrates and recombinant products) that minimize the risk of transmission of blood-borne viruses.

Thanks to considerable improvement in quality and safety of replacement therapy, the life span of haemophiliacs has substantially increased over the last decade, so that it is now approaching that of the males in the general population. However, in parallel with the increased life expectancy, haemophiliacs now develop medical and surgical diseases, such as cardiovascular diseases and cancers, not previously observed in this group⁸. However, as above mentioned, these considerations are only valid for the western developed countries. Indeed, while in this area the most serious and challenging complication of coagulation factor replacement therapy is the development of inhibitory alloantibodies⁹, 75 per cent of haemophiliacs in developing countries have no or inadequate treatment, and often do not survive to adulthood. The World Federation of Haemophilia (WFH) is a non-profit organization founded in 1963 with the aim of improving global haemophilia care to all people with haemophilia, wherever they live. Its actions are mainly directed towards the worldwide improvement of diagnosis, expertise in management and adequate amounts of safe treatment products. This last point is particularly crucial because the availability of treatment products is not only important for the treatment of bleeding episodes but also for prophylaxis in childhood, which has been demonstrated to be effective in minimizing the joint disease¹⁰. The WFH

greatly contributes to the widespread diffusion of factor concentrates through humanitarian aid programmes that channel donations of factor concentrates to treatment centers in developing countries. The WFH also collaborates with several National Member Organizations worldwide to improve haemophilia care in their countries in several ways. Indeed, it has launched training programme at designated International Haemophilia Training Centers (IHTCs) of developed countries to transfer expertise, experience, skills and resources to medical and paramedical staff of developing countries. It has also organized several multidisciplinary conferences and workshops which have significantly contributed to improve the global comprehensive haemophilia care. Annually, WFH development programmes provide supports in nearly 100 countries, affecting the lives and helping to achieve sustainable care for tens of thousands of people with bleeding disorders worldwide. In this context, an ambitious project identified as the Global Alliance for Progress (GAP) was launched in 2003 by WFH, with the aim of greatly improving the number of people with haemophilia diagnosed and receiving treatment in up to 40 developing countries over a 10-year period. Globally, 41,395 new patients with bleeding disorders have been diagnosed since the 2003, including 31,189 with haemophilia. Training all the members of a multidisciplinary comprehensive care team is another strategic goal of the GAP. Within the GAP, the WFH has provided specialized training to 2,478 haemophilia care team members and more generalized education on bleeding disorders to another 4,438¹¹ so far.

The importance of the comprehensive haemophilia care worldwide has been further emphasized this year by the WFH, when this theme has been chosen for the World Haemophilia Day 2009 (17 April). "Together we care" will be the mainstay of the managed care of haemophiliacs for the years to come, since this will be the basis for improving the quality of health assistance to all patients and, ultimately, their quality of life and life expectancy.

Massimo Franchini⁺ & Giuseppe Lippi^{}**

^{*}Immunohematology & Transfusion Center-
Department of Pathology & Laboratory Medicine
University Hospital of Parma, Parma &

^{**}Section of Clinical Chemistry
Department of Biomedical & Morphological Sciences
University of Verona
Verona, Italy

⁺For correspondence:
massimo.franchini@azosp.vr.it

References

1. Mannucci PM, Tuddenham EG. The haemophilias - from royal genes to gene therapy. *N Engl J Med* 2001; 344 : 1773-9.
2. Pool JG, Shannon AE. Production of high-potency concentrates of antihemophilic globulin in a closed-bag system. *N Engl J Med* 1965; 273 : 1443-7.
3. Mejia-Carvajal C, Czapek EE, Valentino LA. Life expectancy in haemophilia outcome. *J Thromb Haemost* 2006; 4 : 507-9.
4. Mannucci PM. Back to the future: a recent history of haemophilia treatment. *Haemophilia* 2008; 14 (Suppl 3): 10-8.
5. Leissinger CA. Prophylaxis in haemophilia patients with inhibitors. *Haemophilia* 2006; 12(Suppl 6): 67-73.
6. Colvin BT, Astermark J, Fischer K, Gringeri A, Lassila R, Schramm W, *et al*; Inter Disciplinary Working Group. European principles of haemophilia care. *Haemophilia* 2008; 14 : 361-74.
7. Soucie JM, Nuss R, Evatt B, Abdelhak A, Cowan L, Hill H, *et al*. Mortality among males with haemophilia: relations with source of medical care. The Haemophilia Surveillance System Project Investigators. *Blood* 2000; 96 : 437-42.
8. Franchini M, Tagliaferri A, Mannucci PM. The management of haemophilia in elderly patients. *Clin Interv Aging* 2007; 2 : 361-8.
9. Key NS. Inhibitors in congenital coagulation disorders. *Br J Haematol* 2004; 127 : 379-91.
10. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, *et al*. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia. *N Engl J Med* 2007; 357 : 535-44.
11. Skinner MW. WFH-the cornerstone of global development: 45 years of progress. *Haemophilia* 2008; 14(Suppl 3) : 1-9.