

Management of haemophilia and its complications in developing countries

K. GHOSH *Institute of Immunohaematology, KEM Hospital, Parel, Mumbai, India*

Summary Eighty per cent of people with haemophilia live in developing countries, where technical expertise and health care facilities may be less than optimal. Haemophilia is a relatively rare disease and high-cost, technology-intensive therapy is not a high priority for the governments of developing countries. The rapid spread of transfusion-related viral infections in many developing countries presents further problems for haemophiliacs. However, it is possible to manage haemophiliacs patients with limited resources. Strategies for conserving factor concentrates, include education of doctors and patients, prenatal diagnosis, increasing the use of anti-fibrinolytic agents, physiotherapy, the use of fibrin glue, and simple orthotics and prosthetic measures. These approaches are helpful in the majority of these patients. Meanwhile, with the help of the World Federation of Haemophilia (WFH), all developing countries are gradually improving management skills for this relatively rare but disabling disease. The present review broadly describes the management of various aspects of severe haemophilia in developing countries.

Keywords Complications, developing countries, haemophilia, management, review

Introduction

Eighty per cent of severe haemophiliacs live in developing countries, where appropriate health resources are severely limited. In most of these countries, health insurance schemes are non-existent and where they do exist, they do not cover diseases such as haemophilia, which are expensive to treat.

India, with a population of over a billion would be expected to have 100 000 patients with severe haemophilia, assuming the incidence of severe haemophilia A to be 1 : 10 000, and severe haemophilia B to be 1 : 40 000. However, a recent survey by the Haemophilia Federation of India (HFI) found only about 10 000 severe haemophiliacs throughout the country, suggesting a severe problem of under-diagnosis and ineffective management. It could be argued that the incidence of haemophilia is lower in developing countries, but studies

have shown a remarkable constancy in the incidence of haemophilia B in the world population (Feng *et al.*, 2002). Thus, the majority of haemophiliacs in developing countries hardly receive any treatment at all! Experience in India, which is probably similar to that in other developing countries, shows a society stratified financially into three tiers (Chandy, 1995). First, there is a very small proportion of extremely rich people who can afford high-cost health care, which they seek in their own countries or abroad. We will not discuss these patients, as they receive standard haemophilia care, as described elsewhere (Bernthrop *et al.*, 1995; Haemophilia of Georgia, 2000). Secondly, there is a substantial minority of people living in large cities, who can afford limited treatment if they are fortunate enough to have access to a government-owned specialized centres or a charitable hospital. Haemophiliacs in this class can afford occasional use of factor concentrates and many are educated and therefore able to understand the importance of physiotherapy for their well-being. Our review will concentrate mainly on the management of these patients in a developing country. The third group, the majority of patients, comes from the rural population, of whom most are extremely poor, do not have

Accepted for publication 20 October 2003

Correspondence: Kanjaksha Ghosh, Institute of Immunohaematology, 13th Floor, KEM Hospital, Parel, Mumbai – 400012, India. Fax: +91 22 – 24138518; E-mail: kanjakshaghosh@hotmail.com

access to the health care system and usually do not even have a proper diagnosis. To reach these patients, they must first be identified through structured programmes, which also include training of medical manpower in this area.

This review draws on our experience of managing approximately 700 haemophiliacs in our Comprehensive Haemophilia Care Center over the past 7 years, supplemented with literature references and personal communications from other experts working in developing countries.

Clinical presentations in haemophilia

A. Acute bleeding

- (i) Superficial, e.g. cutaneous, epistaxis, gum bleeding due to loss of deciduous teeth.
- (ii) Deeper mucosal bleeds, e.g. genito-urinary tract and gastro-intestinal tract.
- (iii) Acute joint bleeding (major joints, e.g. knee, elbow, ankle are most often affected).
- (iv) Bleeding comprising
 - (a) musculo-skeletal bleeds;
 - (b) compartment syndromes – Volkman's contracture;
 - (c) femoral nerve palsy or other nerve palsy.

B. Life-threatening bleeding

- (i) bleeding in the central nervous system;
- (ii) road traffic accident and multiple trauma;
- (iii) severe bleeding from the gastro-intestinal tract.

C. Consequences of repeated acute or chronic bleeding

- (i) anaemia;
- (ii) chronic synovitis;
- (iii) chronic haemophilic arthropathy;
- (iv) contractures, caused by repeated joint bleeds and abnormal postures;
- (v) unequal length of limbs, because of repeated joint bleeds resulting in varus or valgus deformity;
- (vi) chronic haematoma leading to pseudocyst formation.

D. Haemophiliacs needing surgical intervention.

E. Inhibitor development in haemophiliacs.

F. Transfusion-transmitted disease in haemophiliacs.

Acute bleeding

Minor and superficial bleeding, such as gum bleeding, epistaxis etc. are managed by local measures. Antifibrinolytic agents, such as epsilon amino caproic acid (EACA) and tranexamic acid (Cyclokapron^R) are not very expensive and can be diluted and used as a mouth wash

(250 mg EACA/5 ml water or 100 mg EACA/5 ml water every 1–4 h) (Rizza, 1980). For control of epistaxis, a variety of local agents may be used. These include bovine thrombin solution (not available in our country), human thrombin solution (available in India, through the Plasma Fractionation Center in Mumbai), and the snake venom (Botropase^R, obtained from *Bothrops atrox*). Bleeding from superficial cuts can similarly be managed by local application of haemostatic agents. In patients with mild to moderate haemophilia A, desmopressin, 1 deaminocysto-8D Arginine–Vasopressin (DDAVP) (0.3 µg/kg) may be given as an infusion in saline over 15–30 min (Mannucci, 2000). DDAVP is relatively inexpensive (\$2.5/4 µg ampoule in India) and is not associated with viral or other microbial transmission, as occurs with various other blood products. Unfortunately DDAVP is not effective in severe haemophilia A and is likely to be ineffective in haemophilia B, although it was found to be useful in some haemophilia B cases (Ehl, Severin & Sutor, 2000). Bleeding from the genitourinary tract in patients with haemophilia is not uncommon (McMillan *et al.*, 1982) and most of the time, these patients respond to bed rest, urine alkalinization and hydration therapy (2.5 l/m² of liquid input/day). However, a smaller percentage of patients require DDAVP or factor concentrate therapy for 2–3 days. For local pain, antispasmodic analgesics such as Paracetamol, Dextropropoxyphene, Buscopan may be used. Antifibrinolytic agents are generally contraindicated in cases of persistent genitourinary bleeding, but the administration of prednisolone, 0.5 mg/kg for 5–6 days is useful, with rapid tapering off. This has been observed in most of our patients, when bleeding persisted for more than 48 h and no cause for urinary bleeding was found (i.e. urinary tract infection, stones etc.). In haemophiliacs where genitourinary bleeding is persistent or recurrent, a thorough investigation of the genitourinary tract is indicated. In 19 such patients investigated, six were found to have urinary tract stones (Ghosh *et al.*, 2003a,b; Ghosh, Jijina & Mohanty, 2003c). If bleeding persists for more than 48 h, administration of factor concentrates for 2–3 days, raising the plasma factor level to 50–60%, usually stops the bleeding.

Acute bleeding into major joints such as the knees, ankles and elbows is a common presentation of severe haemophilia and may occur up to 2–3 times/week when a child is growing. This is seen in >90% severe haemophiliacs. Although these patients should ideally be on prophylactic therapy with factor concentrate, this is not financially possible in developing countries. Treatment starts with rest, application of crushed ice over the affected joints in a thick cloth (Dietrich, 1996) and pain relief with

Paracetamol and Dextropropoxyphene. If the swelling is tense then one or two injections of factor concentrate may be given to raise factor levels to 20–30%. As awareness of haemophilia is often lacking among primary-care physicians, attempts are sometimes made to aspirate the affected joints without factor cover and/or without appropriate aseptic precautions, leading to disastrous results (seen in three of 700 patients at our centre). Generally, joint aspiration is not needed for acute haemarthrosis unless the joint is very tense and threatening to rupture or where there is a suspicion of septic arthritis. Joint aspiration should not be attempted without proper replacement therapy. For pain relief, we find cyclooxygenase-2 inhibitors (rofecoxib, celecoxib) to be useful alternatives to paracetamol/dextropropoxyphene, and its additional anti-inflammatory effect may be of value. Many case reports of unusual complications associated with acute bleeding in haemophilia are available, including splenic rupture (Samaiya *et al.*, 2001), gas gangrene (Ghosh *et al.*, 1999), and cervical spinal cord haemorrhage (Ghosh *et al.*, 2001a; Ghosh, Shetty & Mohanty, 2001b). These cases were managed using the means available, with varying degrees of success.

Acute bleeding in osteofacial compartments may cause acute neurological problems, such as femoral nerve palsy, Volkmann's ischaemic contracture, etc. These need to be treated immediately, with generous factor replacement and fasciotomy where indicated. In developing countries, there is often a tendency to delay treatment, as factor concentrates may not be available in large quantities. Thus, treatment is often too little and too late (Figures 1 and 2). These patients often require prolonged physiotherapy, with various kinds of locally made casts, traction and support devices (Figure 3) and recovery is often incomplete. Some end up requiring



Figure 1. A neglected case of haemophilia pseudocyst in the thigh.



Figure 2. Radial nerve palsy due to bleeding in the arm.

surgical interventions, such as tenotomy, muscle/tendon transfer etc., which require large amounts of factor concentrate. A recent study from North India (Saraf, Singh & Singh, 2003) showed a 15% incidence of acute femoral/sciatic nerve palsy caused by acute bleeding, while in our centre, we found only two of 500 patients with these complications.

Life-threatening bleeding in haemophilia

Excluding road traffic accidents and major trauma, the most usual cause of life threatening bleeding in haemophilia is central nervous system (CNS) haemorrhage. In developed countries, CNS haemorrhage is a leading cause of death in haemophiliacs (Rizza, Spooner & Giangrande, 2001), accounting for almost 20% of non-infective deaths. Personal experience shows approximately 20–25% of severe haemophilia families in India has one or more siblings dying of cerebral haemorrhage. This fact is of major significance with respect to prenatal diagnosis of

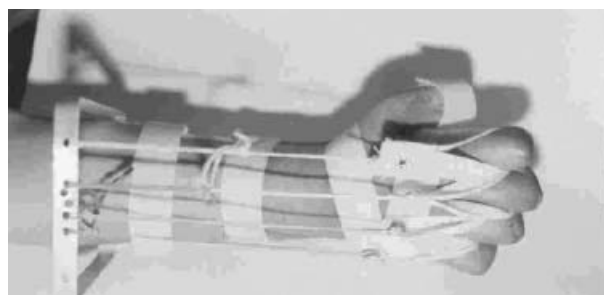


Figure 3. Locally made casts and traction devices in situ for a patient who developed Volkmann's ischaemic contracture because of a neglected forearm bleed.

haemophilia families by RFLP technique. In 9% of families, prenatal diagnosis was not possible because no there were no surviving index patients. It therefore makes sense to preserve the DNA of affected patients in Haemophilia Care Centres. As regards treatment, both factor concentrates, and cryoprecipitate are used in India, depending on their availability. Very few patients (<10%) need neurosurgical intervention for cerebral bleeding, most responding well to factor replacement therapy. However, it may be difficult to achieve 80–100% factor levels in these patients for 8–10 days. If factor concentrates can be given at the required dose for 3–4 days and then reduced to 30–40% levels for a further 8–9 days, then equally good results can be obtained. Many of our patients cannot afford factor concentrates for more than 72 h, and we have used simultaneous antifibrinolytic therapy with tranexamic acid/EACA for 3–4 weeks for CNS haemorrhage, with no mortality.

Consequences of repeated bleeding

Chronic haemophilic arthropathy is a well-recognized consequence of repeated bleeding into joints. Early initiation of prophylactic factor replacement prevents this disabling condition completely, although at a substantial cost. Doses of 3000–4000 IU factor concentrate/kg/year are required (Brown & Aledrot, 1998; Fischer *et al.*, 2002). Most joint bleeds are treated without factor concentrates (Dietrich, 1996). A significant proportion of patients (10–20%) develop disabling chronic synovitis (Ghosh *et al.*, 2003a,b; Ghosh, Jijina & Mohanty, 2003c). In the West, chronic synovitis is treated with physiotherapy for 4–6 weeks with intense factor-concentrate supplementation (Heijnen, 1995). In developing countries, chemical synoviorthesis using rifampicin (Fernandez-Palazzi, 1998) or radioactive synoviorthesis using ^{90}Yt colloid (Rodriguez Merchan, 2001) or ^{32}P colloid (Silva, Luck & Siegal, 2001) is gaining popularity, with good results in 60–80% of the patients. Chemical synoviorthesis with rifampicin requires six to eight injections into the affected joint, with factor-concentrate supplementation, while radioactive synoviorthesis requires only a single injection. In a recent study, we observed that severe haemophiliacs who co-inherit human leucocyte antigen (HLA) B-27 have a 32-fold increase in their risk of developing chronic synovitis (Ghosh *et al.*, 2003a,b; Ghosh, Jijina & Mohanty, 2003c). Thus severe haemophiliacs positive for HLA B-27 may require more intensive therapy or prophylactic therapy. Patients with chronic synovitis or chronic haemophilic arthropathy who develop fixed

deformities may be treated by a combination of therapeutic ultrasound or a dynamic dual-force surface traction system. The latter can be made cheaply from locally available materials (Kale, 1999; Kale *et al.*, 2000). Repeated joint bleeding in early life may sometimes lead to substantial lengthening of one limb, because of a variety of mechanisms.

- 1 Abnormal posture leads to more strain in some areas of the axial skeleton than others.
- 2 Abnormal transmission of forces caused by unequal limb length may lead to bleeding in relatively unaffected joints.
- 3 Non-use of muscles around a joint involved in repeated bleeding leads to periarticular muscular atrophy with loss of dynamic support, which predisposes to further bleeding.
- 4 Abnormal neuromuscular co-ordination leads to abnormal posture.

To correct these problems, physiotherapy may be used, including static and dynamic exercises (Ribbans, Giangrande & Beton, 1997), ultrasound therapy and proper designing of shoes (Heijnen, Hein & In Der Maur, 2000). Operative interference may sometimes be required. Various methods are available to improve neuromuscular co-ordination. The ancient Chinese method of 'Tai Chi Chuan' needs special mention in this regard (Danasantoso & Heijnen, 2001), as it has attracted the attention of several workers in the field. Chronic haemophilic synovitis also responds to short courses of corticosteroid therapy, in conjunction with physiotherapy and factor replacement therapy. A recent study (Corrigan *et al.*, 2003) showed that d-penicillamine may also be useful in this condition. When arthritis becomes chronic and interferes with daily activity, total knee replacement is often performed in the West. Osteotomy and arthrodesis may be a useful alternative in properly selected cases in developing countries (Wallny *et al.*, 2003).

One of the serious consequences of chronic bleeding into muscles and bones is the development of haemophilic pseudocysts or pseudotumours, with locally destructive effects on bones, muscles and nerves, causing chronic compressive neuropathy. This complication (Figure 1) is virtually unknown in countries, where factor concentrates are given prophylactically or are available on demand. In our centre, we encountered five patients with pseudocyst formation. Of these, two had pseudocysts in the psoas sheath and three in the thigh (1%). Reviews (Meyer & Hakami, 1985; Magallon *et al.*, 1994; Gupta *et al.*, 2001) suggest various therapeutic approaches:

- 1 Conservatively, with factor concentrate replacement therapy for months or years.
- 2 By surgical intervention, with generous factor-concentrate cover.
- 3 By radiotherapy.

Prolonged factor-concentrate therapy heals a very small proportion of cases (approximately 20%), confined mainly to those presenting early in the course of their disease (<6 months). Surgical treatment with factor-concentrate cover gives the highest response rate, while radiotherapy in the localized area also gives a good chance of preventing further development of this dreadful complication.

Haemophiliacs needing major surgical intervention

Surgical intervention may be required for complications of haemophilia or for other conditions.

Seemingly simple operations such as circumcision, can cause life-threatening bleeding in patients with severe haemophilia (Ghosh *et al.*, 1998; Kavakli & Nishi, 2001). A study from Nigeria showed that approximately 50% of circumcised haemophiliacs bled excessively following the procedure (Shittu & Shokunbi, 2001). In developing countries, surgical skill is more widely available than good haematologists or haematological laboratories. Thus many surgical procedures are performed without haemostatic assessment. Often, a patient or his family does not know that relatives died of a coagulation disorder, and even when a patient is known to have haemophilia, the surgeon is not told, for the fear he may not perform a much-needed operation. The results are often disastrous (Ghosh *et al.*, 1999). For circumcision and other types of cutaneous surgery, fibrin glue is being used increasingly with good results. Although commercially available, it can also be produced locally from cryoprecipitate, bovine thrombin and EACA (Ghosh *et al.*, 1998). With fibrin glue, the requirement for factor concentrate can be reduced drastically.

There are several reviews of the outcomes of surgery in patients with haemophilia (Aledort & Levine, 1977; Kasper *et al.*, 1985; Kitchens, 1986). There is disagreement regarding the amount of factor concentrate to be infused and the duration of treatment. Kasper *et al.* (1985) showed there was no significant difference in the frequency of bleeding complications between patients infused with doses ranging from 600 to 2500 IU/kg. In developing countries, it matters a great deal whether 600 or 2500 IU/kg will do the job. Several other studies have addressed this question (Srivastava *et al.*, 1998a,b), and very satisfactory haemostasis was reported using doses between 300 and 400 IU/kg in surgical procedures of

varying complexities. This was possible when factor concentrate saving measures such as antifibrinolytic therapy, local and general electrocautery were employed (Ghosh *et al.*, 1998, 2000a,b). Continuous infusion also minimizes the use of factor concentrate during operation (Martinowitz *et al.*, 1992; Varon & Martinowitz, 1998).

Inhibitor development in haemophiliacs

Approximately 15–35% of patients with severe haemophilia A in western countries develop inhibitors (Tizzano *et al.*, 1996; Vermylen, 1998). The prevalence of inhibitors in haemophilia A patients in developing countries has not been studied extensively. One study (Ghosh *et al.*, 2001a; Ghosh, Shetty & Mohanty, 2001b) reported an incidence of approximately 8% in a large group of haemophiliacs, similar to the frequency reported in haemophiliacs receiving intermediate-purity factor VIII concentrates in the West (Yee *et al.*, 1997). Inhibitor development in haemophiliacs has also been linked to race (Aledort & Dimichele, 1998), HLA phenotype (Oldenberg *et al.*, 1997), nature of mutation, and the type of factor concentrate used.

In developing countries, severe haemophilia patients are treated sparingly and this may explain the low prevalence of factor VIII inhibitors. Many of our haemophiliacs are exposed to substantial amounts of factor VIII concentrate for the first time when surgery is performed, leading to inhibitor development during the post-operative period (Ghosh *et al.*, 2002a,b).

When a haemophiliac develops high levels of inhibitor and subsequently suffers a bleeding complication, treatment becomes extremely difficult. In our centre, we have used high doses of anti-fibrinolytic agents (Ghosh *et al.*, 1998, 2000a,b) with or without FEIBA in these patients, with satisfying results. Bhave *et al.* (1995) successfully used low levels of FEIBA in a patient with inhibitor to secure surgical haemostasis.

Immunomodulation with regular replacement of factor VIII concentrate, with or without other drugs, are being used successfully in 50% of such patients. This treatment involves the use of 3000–5000 IU of factor VIII/kg per patient per year and is not feasible in haemophiliacs with inhibitors in developing countries.

Transfusion-transmitted diseases in haemophiliacs

No chapter on haemophilia management is complete without a reference to human immunodeficient virus (HIV) and viral hepatitis infection in haemophiliacs. Affluent western countries have largely controlled this

problem but in developing countries, up to 50% of haemophiliacs are affected by hepatitis C virus and 10% by HIV (Adewuy *et al.*, 1996; Evatt, 2002). Studies from India show a similar picture (Ghosh *et al.*, 2000a,b). It is believed that most hepatitis C virus infections in haemophiliacs are of genotype 1 and are resistant to ribavirin/interferon treatment (Dusheiko, 1998; Markis *et al.*, 2001).

World Federation of Haemophilia initiative for developing countries

The WFH (<http://www.wfh.org>) took several initiatives to improve the quality of haemophilia care in the developing countries. In the World Federation of Haemophilia Decade Plan, The Global Challenge (1992), the ultimate objective was to integrate the haemophilia care into the national health policies of different countries. Presently, the WFH is trying to improve haemophilia care in developing countries by:

1 The International Haemophilia Training Center Programme (IHTC), in which professionals from developing countries are trained in various aspects of haemophilia care at an advanced centres in the West. Recently, some IHTCs have been set up in the developing countries.

2 The Haemophilia Center Twinning Programme (Giangrande, Mariani & Black, 2003): in this programme, a haemophilia centre in a developing country is twinned with one in the developed country for the purposes of (i) providing medical advice, (ii) passing on knowledge and skills, (iii) donation of equipments, reagents and coagulation factors, (iv) working on special projects such as computerized patient registry, and (v) conducting research. The results have so far been very encouraging.

3 Official Journal of the World Federation of Haemophilia (*Haemophilia*): this international journal enables publication of challenges and solutions relating to treatment of haemophiliacs in developing countries, in addition to publishing basic scientific articles and the proceedings of various WFH meetings. This is an important repository for haemophilia research on a worldwide scale (Lee, 1998).

WFH has also inducted personnel from developing countries into their advisory committees, so as to improve haemophilia care all over the world. Detailed information may be accessed through its web page.

Conclusion

Eighty per cent of the haemophiliacs of the world live in under-privileged developing countries, and benefit from

only 20% of the worlds' total haemophilia care budget (Srivastava *et al.*, 1998a,b).

A large number of patients in these countries do not even know that they have haemophilia. When the diagnosis of haemophilia is made, factor concentrates are not available in sufficient quantities. Some countries, such as Malaysia and South Africa, have started producing freeze-dried and virus-inactivated cryoprecipitates for their patients, in a bid to become self-sufficient with regard to factor concentrates. In India, there is a small plasma fractionation centre at Mumbai. Similar plasma fractionation centres have been set up in Brazil, Cuba, Thailand and South Africa. Contract fractionation of locally collected plasma, as is practised in Malaysia, is also producing encouraging results. The high rate of HIV positivity in blood units collected in India and China is worrying. It is believed that for self-sufficiency with regard to factor VIII concentrate, the number of units produced per year in a country should equal the total population of that country. This should translate into 1000 million units of factor VIII concentrate and 200 million units of factor IX concentrate for a country like India. This is a formidable task, and help from the world community will be needed to achieve it. Improvement of the transfusion service will be beneficial not only to haemophiliacs but also to a large number of patients requiring red cells and other blood products.

Providing haemophilia care in developing countries is a challenge. Caregivers not only have to walk a tight rope regarding the amounts of factor concentrates needed for individual patients, but must also be conversant with factor-concentrate requirements for individual patients and factor-concentrate saving techniques and devices. Patient education is another great challenge, needing careful implementation in countries where literacy rates are still low. Some centres in developing countries provide prenatal diagnosis of haemophilia (Ghosh *et al.*, 2002a,b), but this is too restricted and needs to be made available more widely. Presently, this service is available in four centres in India. Over the last 7 years, we have offered prenatal diagnosis in 200 haemophilia families using a combination of RFLP techniques and demonstration of inversion of intron 22 of the factor VIII gene in some cases. In 9% of these families, RFLP could not be used because index cases were not available, nor was inversion of intron 22 demonstrable in the carrier mother. In these cases, we used cordocentesis at 16–17 weeks of gestation, enabling prenatal diagnosis in all patients (Shetty *et al.*, 2003). During the same period, carrier detection was performed in 397 families, 40 females (8% of carriers) having factor VIII or IX levels

<30%, putting them at risk for traumatic or operative bleeding. While prenatal diagnosis could not be undertaken in certain religious communities in some parts of the world, we have not faced such a problem in India. In fact, families have approached us spontaneously for prenatal diagnosis, irrespective of their religious background. There was only one misdiagnosis in the RFLP group in our series. Carrier detection generates some social problems in India, because at least 30% of marriages are still arranged by parents. Thus, disclosing the positive carrier status of a potential bride may jeopardize her marriage prospects, while non-disclosure may lead to marital disharmony, guilt feelings, etc. Thus, at our centre, we counsel at-risk families to perform carrier detection after marriage. This seems to work! Although the family has to pay \$150 for carrier detection and prenatal diagnosis by RFLP (regardless of the number of persons to be tested), they often have to spend much more, because of the distance they have to travel (sometimes up to 2000 km) and the costs of staying in the city for at least a day or two. Prenatal diagnosis in most developing in the world is still in its early stages, based mainly on RFLP techniques, where large numbers of family members are required for accurate diagnosis. This is slowly changing, and more sophisticated mutation detection techniques, including CSGE, DGGE, are coming into vogue. Fortunately, the World Federation of Haemophilia (WFH) is now looking more closely at haemophilia care of developing countries (Lee, 1998). An attempt is being made to provide factor concentrate by donation through the 'Operation Access' programme.

Haemophilia caregivers in developing countries still see many complications of haemophilia that are no longer seen in the developed countries. This provides a unique opportunity to study how efficiently these complications can be managed. Unfortunately, in many medical institutions in both the developing (Ghosh *et al.*, 2003a,b; Ghosh, Jijina & Mohanty, 2003c) and the developed world (Cleary, 2003), management of haemophiliacs is impeded by ignorance, administrative mismanagement, and poverty. It is clear that with effort and modest financial input, haemophiliacs in developing countries could be offered substantial relief. Rehabilitation of haemophiliacs is a major challenge and does not necessarily involve spending large sums of money on factor concentrates (Battistella, 1998). Many haemophiliacs in developing countries believe that the advent of gene therapy may relieve many of their woes, uncertainties and fears. Only time can confirm or refute that hope.

References

- Adeyemi J.O., Coutts A.M., Levy L. & Loyodo S.E. (1996) Haemophilia care in Zimbabwe. *Central African Journal of Medicine* **42**, 153–156.
- Aledort L.M. & Dimichele D.M. (1998) Inhibitors occur more frequently in African American and Latino haemophiliacs. *Haemophilia* **4**, 68–69.
- Aledort L.M. & Levine P.H. (1977) *Surgery in Haemophilia*. The National Haemophilia Foundation, USA, 1–8.
- Battistella L.R. (1998) Rehabilitation in haemophilia – options in the developing world. *Haemophilia* **4**, 486–490.
- Berntrop E., Boulyjenkov V., Brelter D., Chandy M., Jones P., Lee C., Lusher J., Mannucci P., Peak I. *et al.* (1995) Modern treatment of haemophilia. *Bulletin of the World Health Organization* **73**, 691–701.
- Bhave A., Srivastava A., Lee V., Daniel A.J., Dennison D., Sunderraj G.D. & Sundersanam A. (1995) Low dose activated factor IX complex concentrate (FEIBA) for post-operative haemostasis in a patient with high responding factor VIII inhibitor. *Haemophilia* **1**, 274–276.
- Brown S.A., Aledort L.M. and the Round Table Group (1998) Unsolved problems in haemophilia. *Haemophilia* **4**, 341–345.
- Chandy M. (1995) Management of haemophilia in developing countries with available resources. *Haemophilia* **1**, 44–48.
- Cleary P.D. (2003) A hospitalisation from hell: a patient's perspective on quality. *Annals of International Medicine* **138**, 33–39.
- Corrigan J.J. Jr., Damiano M.L., Leissinger C. & Wulf K. (2003) Treatment of chronic haemophilic synovitis in humans with d- penicillamine. *Haemophilia* **9**, 64–68.
- Danusantoso H. & Heijnen L. (2001) "Tai chi chuan" for people with haemophilia. *Haemophilia* **7**, 437–440.
- Dietrich S.L. (1996) The treatment of haemophilia bleeding problem with limited or no use of replacement therapy. *WFH Bulletin* **1**. World Federation of Haemophilia, Montreal, Geneva.
- Dusheiko G.M. (1998) Therapy for chronic hepatitis B and C infection in haemophilia. *Haemophilia* **4**, 577–586.
- Ehl S., Severin T. & Sutor A.H. (2000) DDAVP (desmopressin, 1 deaminocys-8D arginine–vasopressin) treatment in children with haemophilia B. *British Journal of Haematology* **111**, 1260–1262.
- Evatt B.L. (2002) Observations from global survey 2001 – an emerging database for progress. *Haemophilia* **8**, 153–156.
- Feng J., Drost J.B., Scaringe W.A., Lin Q. & Sommers S.S. (2002) Mutations in factor IX gene during past 150 years have relative rates similar to ancient mutations. *Human Mutation* **19**, 49–57.
- Fernandez-Palazzi F. (1998) Treatment of acute and chronic synovitis by non surgical means. *Haemophilia* **4**, 518–523.
- Fischer K., Astermark A., Van Der Born J.G., Ljung R., Berntrop E., Grobee D.E. & Van Den Berg H.M. (2002) Prophylactic treatment for haemophilia: comparison of an intermediate and high dose regimen. *Haemophilia* **8**, 753–760.
- Ghosh K., Jijina F., Pathare A.V. & Mohanty D. (1998) Surgery in haemophilia: experience from a centre in India. *Haemophilia* **4**, 94–97.

- Ghosh K., Jijina F., Pathare A.V. & Mohanty D. (1999) Gas gangrene in a patient with severe haemophilia A. *Haemophilia* **5**, 301–305.
- Ghosh K., Joshi S.H., Shetty S., Pawar A., Chipkar S., Pujari V., Madkaikar M., Pathare A.V., Jijina F. & Mohanty D. (2000a) Transfusion transmitted diseases in haemophilia from western India. *Indian Journal of Medical Research* **112**, 61–64.
- Ghosh K., Shetty S., Pathare A. & Mohanty D. (2000b) Epsilon Amino caproic acid inhibits the activity of factor VIII inhibitors in patients with severe haemophilia A in vivo and vitro. *Acta Haematologica* **103**, 67–72.
- Ghosh K., Shetty S., Kulkarni B., Nair S., Pawar A., Khare A., Baidur S. & Mohanty D. (2001a) Development of inhibitors in patients with haemophilia from India. *Haemophilia* **7**, 273–278.
- Ghosh K., Shetty S. & Mohanty D. (2001b) Haemorrhage in the upper cervical cord; an unusual manifestation in moderate haemophilia patients who ride motor bikes. *Haemophilia* **7**, 515–518.
- Ghosh K., Jijina F., Shetty S., Madkaikar M. & Mohanty D. (2002a) First time development of factor VIII inhibitors in haemophilia patients during postoperative period. *Haemophilia* **8**, 776–780.
- Ghosh K., Shetty S., Pawar A. & Mohanty D. (2002b) Carrier detection and prenatal diagnosis in haemophilia in India. Realities and challenges. *Haemophilia* **8**, 51–55.
- Ghosh K., Madkaikar M., Jijina F., Gandhi S., Shetty S. & Mohanty D. (2003a) Open heart surgery with mitral valve replacement – Ordeal of an undiagnosed haemophilia patient. *Clinical and Laboratory Haematology* **25**, 131–133.
- Ghosh K., Shankarkumar U., Shetty S. & Mohanty D. (2003b) Chronic synovitis and HLA – B27 in patients with severe haemophilia. *Lancet* **361**, 933–934.
- Ghosh K., Jijina F. & Mohanty D. (2003c) Haematuria and urolithiasis in patients with haemophilia. *European Journal of Haematology* **70**, 410–412.
- Giangrande P.L.F., Mariani G. & Black C. (2003) The WFH haemophilia center twinning programme: 10 years of growth, 1993–2003. *Haemophilia* **9**, 242–244.
- Gupta S., Mahapatra B.B., Ghai S., Seith A., Kashyap R., Sharma R. & Choudhry V.P. (2001) Haemophilic pseudotumour of the paranasal sinuses: management with radiotherapy and factor replacement therapy. *Haemophilia* **7**, 595–599.
- Haemophilia of Georgia USA. (2000) Protocols for treatment of haemophilia and Von Willebrand disease. *Haemophilia* **6**, 84–93.
- Heijnen L. (Ed.) (1995) *Recent Advances in Rehabilitation in Haemophilia*. Medical Education Network, Sussex.
- Heijnen L., Heim M., In Der Maur H. (2000). Manufactured shoes (shoes) and orthopaedic shoes. *Haemophilia* **6**, 4–6.
- Kale J. (1999) *Guide to Exercises for Haemophiliacs*, Haemophilia Society Mumbai (Chapter). Bhalani Publishing House, Mumbai.
- Kale J.S., Ghosh K., Mohanty D., Pathare A.V. & Jijina F. (2000) Use of dual force system to correct chronic knee deformities due to severe haemophilia. *Haemophilia* **6**, 177–180.
- Kasper C.K., Boylen A.L., Ewing N.P., Luck J.V., Dietrich S.L. (1985) Haematologic Management of haemophilia A for surgery. *Journal of the American Medical Association* **253**, 1279–1283.
- Kavakli K., Nishi G. (2001) Circumcision, hemophilia and being healthy in developing countries. *Pediatric Hematology and Oncology* **18**, 419–420.
- Kitchens C.S. (1986) Surgery in haemophilia and related disorders: a prospective study of 100 consecutive procedures. *Medicine (Baltimore)* **65**, 35–45.
- Lee C.A. (1998) World Federation of Haemophilia developing world programme. *Haemophilia* **4**, 59–63.
- Magallon M., Monteagudo J., Altisent C., Ibanez A., Rodriques-Perez A., Riba J., Tussell J. & Martin Villar J. (1994) Hemophilic pseudotumour: multicenter experience over a 25 year period. *American Journal of Hematology* **45**, 103–108.
- Mannuci P.M. (2000) Desmopressin (DDAVP) in the treatment of bleeding disorders the first twenty years. *Haemophilia* **6**, 60–67.
- Markis M., Berglin T., Dusheiko G., Giangrande P.L.F., Lee C.A., Ludlam C., Preston F.E., Watson H.G., Wilde J.T. & Winter M. (2001) Guide lines on diagnosis, management and prevention of hepatitis in haemophilia. *Haemophilia* **7**, 339–345.
- Martinowitz U., Schuklmann S., Gitel S., Horozowskitt, Heim K. & Vason D. (1992). Adjustment dose continuous infusion of factor VIII in patients with haemophilia. *British Journal of Haematology* **82**, 729–734.
- Mc Millan N., Belch J.J., Rolfe E.B., Forbes C.D. & Stuart J. (1982) Haemophilia and the kidney: assessment after 11 years of follow up. *British Medical Journal* **285**, 1609–1611.
- Meyer L. & Hakami N. (1985) Pseudotumour of haemophilia in the orbit: the role of radiotherapy in the management. *American Journal of Haematology* **19**, 99–102.
- Oldenberg J., Picard J.K., Schwab R., Brackmann H.H., Tuddenham E.G.D. & Simpson E. (1997) HLA genotype of patients with severe haemophilia A due to intron 22 inversion with and without inhibitors to factor VIII. *Thrombosis and Haemostasis* **77**, 238–242.
- Ribbans W.J., Giangrande P. & Beton K. (1997) Conservative treatment of haemarthrosis for prevention of haemophilic synovitis. *Clinical Orthopedics* **343**, 12–18.
- Rizza C.R. (1980) Inhibitor of fibrinolysis in the treatment of haemophilia. *Journal of Clinical Pathology* **14**, 50–54.
- Rizza C.R., Spooner R.J.D. & Giangrande P.L.F. (2001) Treatment of haemophilia in the United Kingdom: 1981–1996. *Haemophilia* **7**, 349–359.
- Rodriguez Merchan E.C. (2001) Methods to treat chronic haemophilic synovitis. *Haemophilia* **7**, 1–5.
- Samaiya A., Gupta S., Chumber S., Kashyap R., Dewanda N.K., Vashist S. & Choudhary V.P. (2001) Blunt abdominal trauma with delayed rupture of splenic haematoma in a haemophilic patient. *Haemophilia* **7**, 331–334.
- Saraf S.K., Singh O.P. & Singh V.P. (2003) Peripheral nerve complications in haemophilia. *JAPI* **51**, 167–169.
- Shetty S., Ghosh K., Anbhavne S. & Mohanty D. (2003) Requiem to prenatal diagnosis of haemophilia A & B using coagulation activity and antigen based assays: not yet! *European Journal of Haematology* **70**, 253–254.
- Shittu O.B. & Shokunbi W.A. (2001) Circumcision in haemophiliacs: the Nigerian experience. *Haemophilia* **7**, 532–536.
- Silva M., Luck J.V. Jr & Siegal M.E. (2001) 32p Chromic phosphate radio synovectomy for chronic haemophilic synovitis. *Haemophilia* **7**, 40–49.

- Srivastava A., Chuan Sumrit A., Chandy M., Duraiswamy G. & Karabus C. (1998a) Management of haemophilia in the developing world. *Haemophilia* **4**, 474–480.
- Srivastava A., Chandy M., Sunderrajan G.D., Lee V., Daniel A.J., Dennison D., Nair S.C., Mathews V., Anderson G., Nair A., Moses B.V. & Sundersanam A. (1998b) Low dose intermittent factor replacement for post operative haemostasis in haemophilia. *Haemophilia* **4**, 799–801.
- Tizzano E.F., Altisent C., Domenech M., Cornet Tussel J. & Baiger M. (1996) Inhibitor development in haemophilia A patients with inversion of intron 22 of the factor VIII gene. *Thrombosis and Haemostasis* **76**, 125–126.
- Varon D. & Martinowitz U. (1998) Continuous infusion therapy in haemophilia. *Haemophilia* **4**, 431–435.
- Vermeylen J. (1998) How do some haemophiliacs develop inhibitors? *Haemophilia* **4**, 538–542.
- Wallny T., Saker A., Hofman P., Brackman H.H., Nicolay C. & Kraft C.N. (2003) Long term follow up after osteotomy for haemophilic arthropathy of the knee. *Haemophilia* **9**, 69–75.
- Yee T.T., Williams M.D., Hill F.G., Lee C.A. & Pasik J. (1997) Absence of inhibitors in previously untreated patients with severe haemophilia A after exposure to a single intermediate purity factor VIII product. *Thrombosis and Haemostasis* **78**, 1027–1029.