bjh review

Modern management of haemophilic arthropathy

Leslie Raffini and Catherine Manno

Division of Hematology, Department of Pediatrics, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Summary

Currently available factor concentrates for treatment of patients with haemophilia are virally inactivated or are made by recombinant technology and their broad use in developed nations has resulted in the dramatic elimination of the treatment-related viral illnesses that decimated the haemophilia community in the late 20th century. The major morbidity experienced by patients with haemophilia today is joint disease, a result of repeated bleeding episodes into joint spaces. Although administration of factor concentrates to prevent bleeding has been demonstrated to prevent haemophilic joint disease when applied assiduously, repeated bleeding episodes induce synovitis that is irreversible and may progress despite subsequent prophylaxis. Surgical and nuclear medicine interventions are available to reduce the pain of haemophilic arthropathy and to reduce further bleeding episodes. Patients with high titre inhibitors are at great risk for the development of joint disease and present the greatest therapeutic challenges when joint surgery is needed.

Keywords: haemophilia, arthropathy, synovectomy, joint disease, arthrodesis.

Haemophilia, the most common inherited severe bleeding disorder, is an X-linked disorder that affects males of all ethnic groups. Haemophilia A (deficiency of factor VIII) occurs in approximately one in 5000 live male births and is 5–6 times more common than Haemophilia B (deficiency of factor IX) (Arun & Kessler, 2001) The severity of haemophilia is classified according to the amount of circulating functional clotting factor: patients with <1% have severe disease, those with 1–5% are moderate, and those with >5% are classified as mild. Patients with severe haemophilia experience frequent spontaneous bleeding episodes, in contrast to those with moderate and mild haemophilia in whom trauma or surgery is usually required to provoke haemorrhage. Although bleeding can occur at almost any site, haemarthrosis (intra-articular bleeding) is the most common clinical manifestation, and the ankles, knees and elbows are most frequently affected. The management of haemophilic arthropathy, which develops after repeated episodes of joint haemorrhage and accounts for the major morbidity in haemophilia, is reviewed here.

Correspondence: Dr Leslie Raffini, Division of Hematology, Fourth Floor, Wood Bldg., The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399, USA. E-mail: raffini@email.chop.edu

Factor replacement in haemophilia

Intravenous replacement of the deficient clotting factor is used to treat and prevent bleeding episodes in patients with haemophilia. Therapeutic options for haemophilia in developed countries have evolved significantly during the second half of the 20th century, resulting in tremendous improvement in the clinical course of this disorder. Careful screening of plasma donors combined with heat treatment and viral inactivation methods have resulted in much safer plasma-derived concentrates available since the late 1980's. The next innovation came in the early 1990's with the licensure of recombinant factor concentrates. Ongoing concern for the potential transmission of other infectious agents in plasma derived products, including variant Creutzfelt-Jacob disease, has prompted many to consider recombinant factors the product of choice for haemophilia treatment when available (Berntorp *et al*, 1995).

The development of inhibitors, which can occur after treatment with either high-purity, viral-inactivated plasma derived products or recombinant products, is the most significant treatment-related complication. Inhibitors develop in ~25–30% of patients with severe haemophilia, although a proportion of these are low titre, and may resolve over time (Scharrer *et al*, 1999). Patients with persistent high titre inhibitors demonstrate anamnesis following factor concentrate but may respond to immune tolerance regimens in which regular infusions (usually daily) of high doses of factor are administered in attempt to eradicate further inhibitor production. Those with persistent inhibitors who experience bleeding may be treated with bypassing agents, including activated prothrombin concentrates or recombinant factor VIIa, although the ability to prompt adequate haemostasis with these agents cannot always be ensured (Berntorp *et al*, 1995). As a result, patients with inhibitors experience bleeding episodes that are more difficult to treat and prevent, and subsequently are more likely to develop arthropathy (Soucie *et al*, 2004). The surgical management of arthropathy

in patients with haemophilia and high-titre inhibitors poses unique challenges that must be carefully considered on an individual basis.

Pathogenesis of haemophilic arthropathy

Early in an acute joint bleed, patients may report sensations of tingling and warmth, followed by pain, swelling and decreased motion (Furie *et al*, 1994). The pathogenesis of the progression from recurrent haemarthrosis to arthropathy is incompletely understood, but is characterised by inflammatory synovitis and cartilage destruction (Roosendaal & Lafeber, 2006). Haemosiderin deposition into synovial tissues induces proliferation of the synovium and neovascularisation of the sub-synovial layer, which results in an inflamed, villous, synovial tissue (Roosendaal & Lafeber, 2006). This friable and highly vascular synovium is more susceptible to further haemorrhage with minimal stress, which sets up a vicious cycle that is difficult to break (see Fig 1) (Roosendaal & Lafeber, 2006).

Iron appears to play a central role in the development of arthropathy in patients with haemophilia through the induction of genes involved in cellular proliferation and stimulation of inflammatory cytokines. *In vitro* studies evaluating the effect of iron on human synovial tissue demonstrate a dose-dependent increase in the expression of the proto-oncogene *c-myc* and synovial proliferation (Wen *et al*, 2002). This synovial proliferation could be blocked using ceramide, which induced apoptosis (Wen *et al*, 2002). Iron also induces expression of *mdm2*, a p53 tumour suppressor binding protein (Hakobyan *et al*, 2004). In addition to its effect on synovial proliferation, iron deposition also contributes to articular cartilage destruction, through stimulating the inflammatory cytokines interleukin-6, interleukin-1, and tumour necrosis factor, although the pathways involved here are unclear (Roosendaal *et al*, 1998).

Both *in vivo* and *in vitro* studies suggest blood may exert a more direct toxic effect on articular cartilage. *In vitro* studies reveal a marked inhibition of proteoglycan synthesis by whole blood (Roosendaal & Lafeber, 2006). Canine experiments demonstrate that exposure of the cartilage to blood for 4 d results in biochemical and histochemical changes in the cartilage matrix and chondrocyte metabolic activity (Roosendaal *et al*, 1999). Furthermore, these animal studies suggest that the articular cartilage of young animals is more susceptible to these changes than that of older animals (Hooiveld *et al*, 2003).

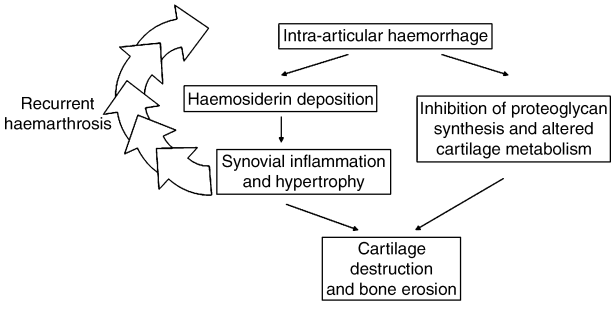

Fig 1. The pathogenesis of haemophilic arthropathy.

As chronic hypertrophic synovitis progresses, the synovium becomes palpable and the joint may remain permanently swollen (see Fig 2). The thickened synovium and cartilage degeneration lead to bone erosion that eventually results in advanced arthropathy, with joint stiffness, chronic pain and severely limited range of motion (ROM) with disability (Arun & Kessler, 2001). In the most severe cases, the bones become fused, resulting in a completely disabled and misshapen (swollen, distorted) joint (Arun & Kessler, 2001). Many patients experience polyarticular disease, and may develop severe arthropathy in one or both lower extremities, and/or one or both upper extremities, compounding their physical disability and adversely affecting their quality of life.

The number of bleeding episodes required to cause irreversible damage of the articular cartilage is not known, and is likely to vary from patient to patient. This progression is also influenced by the manner in which haemarthroses have been treated. Prompt, early factor replacement results in better outcomes than delayed or absence of therapy (Aledort *et al*, 1994).

Prophylaxis

Many patients with severe haemophilia receive regular prophylactic infusions of factor VIII or factor IX to prevent

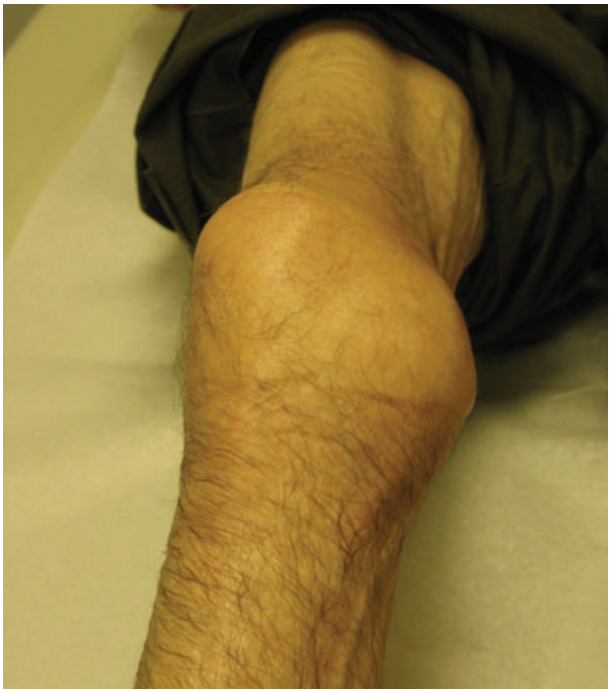

Fig 2. Chronic synovitis and joint deformity in the knee of an adult with severe haemophilia. This photograph shows the chronic synovitis and joint deformity in the knee of an adult with severe haemophilia. Note the muscle atrophy above the affected knee.

bleeding episodes. The epidemiology and natural history of haemophilic arthropathy has been greatly influenced by the availability of factor concentrates and the use of prophylaxis (Fischer *et al*, 2001). The goals of modern haemophilia management are to minimise joint disease and maximise quality of life. In many cases, this can be accomplished with early initiation of prophylaxis. The success of primary prophylaxis in reducing bleeding episodes compared with historical controls was first reported by Professor Nilsson in Sweden (Nilsson *et al*, 1976). However, despite this decrease in bleeding, prophylaxis started in school age boys who had already damaged joints did not prevent further deterioration of these joints (Pettersson *et al*, 1981). Subsequent initiation of prophylaxis at a much younger age (usually 1–2 years old) to boys with severe haemophilia resulted in the vast majority having normal musculoskeletal examinations with no evidence of joint disease by radiograph (Nilsson *et al*, 1992). These investigators concluded that effective prophylaxis at an early age could prevent haemophilic arthopathy (Nilsson *et al*, 1992). The results of these observational studies led to the 1995 World Health Organization and World Federation of Haemophilia (WFH) statement that the initiation of prophylaxis at an early age (1–2 years of age) is considered to be the optimal form of therapy for a child with severe haemophilia (Berntorp *et al*, 1995).

The optimal dosing of prophylaxis for prevention of joint disease has not been established and is likely to vary from patient to patient. There is significant variation in the bleeding phenotype in patients with severe haemophilia. Nearly 10% of patients with severe haemophilia rarely experience clinically apparent spontaneous bleeding, although the factors that modify this phenotype are not well characterised (Aledort *et al*, 1994; van Dijk *et al*, 2005). Most standard prophylaxis regimens are designed to keep factor trough levels of >1%. In patients with factor VIII deficiency, this is usually achieved with three infusions per week, compared with only two infusions for patients with haemophilia B, because of the longer plasma half-life of factor IX. Some haemophilia centres have reported success in dosing patients less frequently and escalating their therapy based on clinical bleeding patterns, rather that aiming for specific trough levels (Blanchette *et al*, 2003). Episodes of acute haemarthrosis usually begin when boys with severe haemophilia are between 1 and 2 years of age (Lusher, 1997). Once a patient has had several bleeding episodes into a single joint over a relatively short duration, that joint is referred to as a 'target' joint, and is more susceptible to further bleeding and damage.

Although joint preservation through early prophylaxis may be successful in preventing haemophilic arthropathy in many patients, it is not without substantial cost and effort. The financial burden of prophylaxis is prohibitive for the majority of patients with haemophilia in developing countries. Even if cost is not the primary issue, early prophylaxis may not be feasible or desirable for all patients, because of an absence of prior bleeding, poor venous access, or patient/family preference. Furthermore, despite early prophylaxis, some patients may still develop joint disease. This may be a result of bleeding episodes that were not recognised, reported, or treated in a timely matter, or may be related to participation in high impact contacts sports with repeated injury and trauma. In addition, patients who develop inhibitors and do not undergo successful immune tolerance are at ongoing risk for arthropathy because they may not achieve haemostasis as reliably following treatment with bypassing agents and options for prophylaxis are limited. Finally, delivery of adequate factor concentrate for prevention of haemarthrosis in young patients with severe haemophilia may not be possible without the placement of an indwelling central venous catheter. These devices are associated with infections in nearly one-third of patients who require them, a further limitation of the broad utilisation of primary prophylaxis (Journeycake *et al*, 2005). Therefore, despite the tremendous benefit in preventing joint disease offered by early prophylaxis, recurrent haemarthrosis with progression to chronic synovitis and haemophilic arthropathy still occurs in the haemophilia population.

Classification of haemophilic arthropathy

Several classifications systems have been developed to quantify and monitor the degree of haemophilic arthropathy based on clinical and radiological findings. The two most widely used systems based on conventional radiological findings are (i) the Petterson score, in which the joint disease is classified base on its stage of development (Pettersson *et al*, 1980) and (ii) the Arnold–Hilgartner scale, in which the joint is scored based on a summation of radiological changes (Arnold & Hilgartner, 1977). Recently, magnetic resonance imaging (MRI) has been used as a more sensitive imaging technique that can detect changes that are not visualised by conventional radiographs, and several scoring methods using MRI have been proposed (Nuss *et al*, 2000; Soler *et al*, 2002; Lundin *et al*, 2004). An international MRI expert subgroup of the International Prophylaxis Study Group (IPSG), under the auspices of the WFH has recently reviewed and revised these scales to develop the compatible MRI scoring system (Lundin *et al*, 2005). This scoring system has two components to assess both progressive and additive MRI changes. Standardisation of these methods for assessing haemophilic arthropathy is a necessary step to allow comparison of regimens aimed at preventing and treating joint disease. The clinical utility of these scoring methods has yet to be fully determined, although MRI is likely to be a valuable and sensitive tool for objective assessment of clinical studies that are designed to impact joint disease.

Physical examination and functional ability are critical components in the assessment of joint disease in patients with haemophilia. ROM has been the most utilised measurement for evaluating the effects of intervention on joint health. In 1985, the WFH developed the Physical Examination (PE) Scale, which evaluates ROM, joint deformity, swelling, crepitus, wasting and instability in the ankles, knees and elbows.

Over time, several other scoring systems have been introduced with the aims of increasing sensitivity, accounting for normal development and including assessments of gait and strength and pain (Manco-Johnson *et al*, 2000; Hill & Ljung, 2003). In an attempt to develop one scoring system that could find international acceptance, the IPSG has further modified existing tools to produce the Haemophilia Joint Health Score (HJHS) (Hilliard *et al*, 2006). Evaluation of the psychometric properties of the HJHS is ongoing, although the reliability appears to be quite good (Hilliard *et al*, 2006).

Management of haemophilic arthropathy

Treatment of an acute haemarthrosis requires early administration of factor replacement, analgesia and rest. The goal of factor administration is to allow for normal haemostasis (factor levels 30–50%) until the bleeding has stopped (Arun & Kessler, 2001). Joints should be splinted in the position of comfort and reassessed after 24 h (Buzzard, 1997).

Treatment recommendations for patients who develop chronic synovitis and arthropathy should be made after careful consideration of all potential options. Conservative options aimed at minimising bleeding and/or controlling pain should be considered prior to surgical intervention. Surgery should only be performed at well-established haemophilia centres that have orthopaedic expertise in patients with haemophilia. In addition, the feasibility and availability of both prolonged postoperative factor replacement and rehabilitation need to be established.

Physiotherapy

Physiotherapy, under the guidance of an experienced therapist, is an integral component of comprehensive haemophilia care and plays a role both in the prevention and treatment of joint disease. Encouraging patients at a young age to maintain healthy lifestyles with regular and appropriate exercise results in strong muscles that protect the joints (Buzzard, 1999). Regular exercise (30 min at least three times per week) in patients with existing joint disease may decrease or prevent the progression of haemophilic arthropathy (Harris & Boggio, 2006). Physiotherapy can be used acutely, after a haemarthrosis or surgery, as well as for patients with chronic synovitis or arthropathy. After a careful musculoskeletal assessment, treatment is individualised and often administered in conjunction with factor replacement. Goals of therapy include restoration or maintenance of ROM, muscle strengthening, prevention or treatment of articular contracture, pain management, increased exercise tolerance and improved balance, coordination and proprioception (Heijnen & Buzzard, 2005). There are a number of techniques utilised by the physiotherapist, including isometric and isotonic exercise regimens, splinting, orthotics, electrotherapy, therapeutic ultrasound and hydrotherapy (Buzzard, 1997, 1999; Heijnen *et al*, 1997; Watson, 2002; Heijnen & Buzzard, 2005).

Analgesia

Pain is an expected consequence of haemophilic arthropathy. There is limited data regarding analgesic use and other methods for coping with pain in patients with haemophilia. A survey of 68 patients with severe haemophilia demonstrated that over half had used over the counter analgesics in the previous month and one-third had used prescription analgesics, often containing opiates (Elander & Barry, 2003). Although narcotics may be effective, long-term use may lead to dependence. Non-steroidal anti-inflammatory drugs (NSAIDs) are often used to treat arthritic pain, and act by inhibiting cyclooxgenase (COX) enzymes resulting in both an analgesic and anti-inflammatory effect. This large class of drugs includes aspirin, traditional NSAIDS such as ibuprofen, and the newer selective COX-2 inhibitors. Traditional NSAIDS are used sparingly in patients with bleeding disorders because of their anti-platelet effect and the concern for increased bleeding. Two small clinical trials of NSAIDS (ibuprofen, benoxaprofen and salicylates) in patients with haemophilia have demonstrated efficacy without bleeding complications (Inwood *et al*, 1983; Steven *et al*, 1985). However, others have reported increased bruising and gastrointestinal bleeding (Daly & Scott, 1984; Cagnoni & Aledort, 1994). Recent studies have reported on the effective use of COX-2 inhibitors, which do not interfere with platelet function, to treat patients with haemophilia (Rattray *et al*, 2005, 2006; Tsoukas *et al*, 2006). A double-blind, placebo-controlled study demonstrated superior efficacy of etoricoxib compared with placebo to treat pain in patients with haemophilic arthropathy (Tsoukas *et al*, 2006). However, further evaluation of the safety and efficacy of these drugs in patients with haemophilia is needed, particularly because of the concerns of increased cardiovascular events associated with some of these drugs.

Synovectomy

Once a target joint has developed, it may be difficult to stop the cycle of repeated haemarthrosis with prophylactic clotting factor infusions (secondary prophylaxis) (Dunn *et al*, 2004). Patients who continue to bleed despite a trial of prophylaxis, and those in whom prophylaxis is not available or feasible, are candidates for interventions aimed at halting this cycle. Synovectomy, which entails excision or destruction of the friable synovium, is an approach that is frequently used to manage patients who experience recurrent haemarthrosis. This may be achieved by direct surgical excision during open or athroscopic synovectomy, or by injection of a radioactive or chemical agent that causes fibrosis or sclerosis of the synovium, also called synoviorthesis.

Patients with advanced arthritic changes, severely narrowed joint space, decreased ROM, and pain are less likely to benefit from synovectomy, and joint arthroplasty may be considered (see below) (Gilbert & Radomisli, 1997).

Open synovectomy

Open surgical synovectomy for the treatment of haemophilic synovitis was first reported by Storti *et al* (1969). Although this approach may be effective in decreasing subsequent haemarthroses, its main complication is the loss of motion that occurs after the procedure (Wiedel, 2002). This loss of motion, along with the relative invasiveness of the procedure, makes open synovectomy a rather undesirable approach given the alternatives discussed below.

Arthroscopic synovectomy

Arthoscopic techniques were developed in the 1970's and offered the advantages of a less invasive procedure and more rapid recovery than open procedures. Arthroscopic synovectomy for haemophilic arthropathy was first reported at the WFH Congress in 1983 (Kim *et al*, 1984; Wiedel, 1984). The arthroscopic technique offers clear improvements compared with open synovectomy, including decreased postoperative bleeding, shorter hospitalisation stays, fewer complications and improved ROM (Triantafyllou *et al*, 1992).

Arthroscopic synovectomy has been used most frequently in the knees, but there is increasing experience in the ankles, elbows and shoulders (Patti & Mayo, 1996; Wiedel, 2002; Dunn *et al*, 2004). Figure 3 shows an arthroscopic view of the inflamed synovium in a patient with haemophilia. Many studies have documented the effectiveness of this procedure in decreasing subsequent bleeding into that joint (reviewed in Dunn *et al*, 2004). Wiedel (1996) reported results of nine knee arthroscopic synovectomies after 10–15 years follow-up: five patients had no recurrent bleeding, two had no bleeding after a second procedure, one patient had occasional bleeds and in one the bleeding history was unknown. The ROM was unchanged in two, improved in three and worse in four, and radiographic evaluation of all the knees showed progression (Wiedel, 1996). Weidel concluded that arthroscopic synovectomy was effective in reducing recurrent haemarthrosis, and probably slowed, but did not prevent, haemophilic arthropathy. These findings are similar to those reported from other centres on the outcome of arthroscopic synovectomy in haemophilia (Triantafyllou *et al*, 1992; Eickhoff *et al*, 1997; Rodriguez-Merchan *et al*, 1997).

Fig 3. Arthroscopic view of the inflamed synovium in a patient with haemophilia. Note that the villi are large and haemosiden-laden. Reproduced with permission from Lippincott Williams & Wilkins (Dunn *et al*, 2004).

Some have suggested that young boys with haemophilia might not be good candidates for surgical synovectomy because they might not be very co-operative with the intensive postoperative physical therapy needed to restore ROM (Gilbert & Radomisli, 1997). However, the results of a large, single centre paediatric cohort study of 69 arthroscopic synovectomies in 44 boys who ranged in age from 4·3 to 18·4 years suggest this is not the case (Dunn *et al*, 2004). This study reported a 78% decrease in the median annual bleeding frequency (13·2 bleeds/year preoperative compared with 1·9 bleeds/year postoperative), with a median follow-up time of 6 years (Dunn *et al*, 2004). Furthermore, 97% of these patients experienced a reduction in their bleeding episodes. The ROM was stable or improved for the first year after surgery, but showed slow declines over time and radiographic scores also deteriorated (Dunn *et al*, 2004). Similar to earlier studies, these observations demonstrate that, despite the fairly dramatic reduction in bleeding, arthroscopic synovectomy was unable to halt progressive joint destruction. Normal preoperative ROM seemed most predictive of postoperative functional outcome (Dunn *et al*, 2004). Whether earlier intervention, before irreversible damage has occurred, would be able to halt this progression is not known.

Arthroscopic synovectomy appears to be generally well tolerated with relatively few complications. In the paediatric study reported above, there was only one complication (development of a pseudoaneurysm) in 69 procedures (1·4%) (Dunn *et al*, 2004). Others have reported early postoperative bleeding (Wiedel, 1996), two cases of an expanding portal haematoma (Heim *et al*, 1999), and the development of an arterial venous fistula (Cohen *et al*, 1992). Some patients have required a second procedure because of recurrent symptoms, although in some cases, these symptoms were related to arthritic changes rather than recurrent bleeding, and there was no evidence of synovitis at the time of the repeat surgery (Wiedel, 1996; Dunn *et al*, 2004).

Success of arthroscopic synovectomy in a patient with haemophilia requires considerable resources and a multidisciplinary approach. Critical components include a well equipped and experienced surgical team, the availability of adequate factor replacement with a carefully developed plan for intraoperative and extended postoperative haemostasis, and the ability to comply with requisite postoperative physical therapy.

Radionucleotide synovectomy

Radionucleotide synovectomy involves an intra-articular injection of a radionucleotide to cause sclerosis of the synovium.

Table I. Radionucleotide properties.

Isotope	Emission	Half-life (days)	Particle size (nm)	Soft-tissue penetration (mm)
^{198}Au	β, γ	2·7	20–300	1·2–3·6
^{32}P	β	14	500–2000	2·6–7·9
^{186}Re	β, γ	3·7	5–10	1·2–3·6
^{90}Y	β	2·7	1–1000	3·6–11

This procedure has been used extensively in patients with rheumatoid arthritis, a disorder characterised by synovial inflammation. The radionucleotide is complexed to a colloid to allow for homogenous distribution in the joint space, and the objective is to deliver a targeted dose of radiation to the local synovium, with little or no systemic effect. Radioactive agents used most frequently worldwide include yttrium-90 (^{90}Y), gold (^{198}Au), rhenium (^{186}Re) and phosphorous-32 (^{32}P). These agents vary with regard to size, half-life and emission properties- see Table I (Ingrand, 1973; Winston *et al*, 1973). The ideal agent should emit β-rays (which have a relatively shallow depth of penetration) and have a short half-life (Erken, 1991). The radionucleotide should be of a size that balances the risk of leakage, with a particle that is too small, with the risk of poor synovial distribution, with a particle that is too big (Erken, 1991). Given these considerations, there remains controversy as to which agent is optimal for radionucleotide synovectomy. Controlled studies have not been performed to determine the most effective isotope with the best safety profile.

Ahlberg (1971) was the first to report on the success of intra-articular ^{198}Au to decrease bleeding in patients with haemophilia. In a follow-up publication evaluating the radiological changes (Petterson score) in these patients, he noted that this procedure did not seem to affect the radiological progression of the joint disease (Ahlberg & Pettersson, 1979).

Rivard *et al* (1994) reported their results on 98 injections of ^{32}P in 48 patients with bleeding disorders from 1977 to 1992, with follow-up ranging from 1 to 15 years. Twelve of these patients had high titre inhibitors. Both pain and bleeding decreased in ~80% of patients. Twenty joints required a second injection, either because of recurrent synovitis (most often in patients with inhibitors) or an unusually thick synovial layer. ROM was reported as stable or improved in half of the patients, and continued to decrease in the other half, while radiographic changes progressed. Three patients who underwent radionucleotide synovectomy of the elbow experienced an intense inflammatory reaction characterised by pain and loss of motion that developed within hours of the procedure and lasted for 6 months.

One report of the long-term results of ^{90}Y injection into 34 elbow joints suggests caution (Heim *et al*, 2004). The authors noted that 60% of the elbows injected experienced a subsequent decrease in ROM, which, on average, was 30° loss of extension and 20° loss of flexion (Heim *et al*, 2004). This was felt to be an unacceptable morbidity, and the authors concluded that alternative isotopes should be considered for the elbow (Heim *et al*, 2004).

Potential complications of radionucleotide synovectomy include leakage of the isotope and a radiation effect to other tissues. Leakage is believed to be caused by drainage and accumulation of small radioactive particles in surrounding lymph nodes and reticuloendothelial system (Erken, 1991; Gratz *et al*, 1999). The amount of leakage that has been reported after injection ranges from little or no leakage in the majority of patients, to as high as 70% (Rivard *et al*, 1994; Siegel *et al*, 1994; Gedik *et al*, 2004). Joint immobilisation after the procedure is an important measure to minimise leakage (Gratz *et al*, 1999; de la Chapelle *et al*, 1972).

Several investigators have evaluated whether the radiation and subsequent leakage from this procedure results in any chromosomal damage in circulating lymphocytes (Fernandez-Palazzi *et al*, 1996; Fernandez-Palazzi, 1998; Falcon de Vargas & Fernandez-Palazzi, 2000). In the largest controlled study, conventional lymphocyte culture and chromosomal banding was performed in 79 patients with haemophilia and 110 age- and sex-matched controls at various times both prior to and after radionucleotide synovectomy with ^{198}Au, ^{186}Rh and ^{90}Y (Falcon de Vargas & Fernandez-Palazzi, 2000). Chromosomal structural changes (CSC) were considered non-specific when breakages were present, and premalignant when markers, triradial, dicentric and rings were found. No CSC were present in any of the healthy control subjects. Patients with haemophilia who did not undergo radionucleotide synoviorthesis had non-specific CSC in 0·79% of metaphases. One year after ^{198}Au synoviorthesis, premalignant CSC were found in 1·6% of the metaphases and non-specific CSC were present in 17·2%. After 2 years, the premalignant CSC were no longer present, and non-specific CSC were found in only 1·7% of the metaphases. Patients who underwent synoviorthesis with ^{186}Rh had non-specific CSC in 1·25% of metaphases 6 months after injection, but these were gone at 1 year. The authors concluded that while a low proportion of premalignant and non-specific CSC can be found after radionucleotide synovectomy, all of the premalignant changes were reversible, and non-specific changes may persist for up to 2 years, but were not associated with any adverse outcomes.

Recent reports have heightened the concern regarding the safety of radionucleotide synovectomy, particularly for young patients. There have been two paediatric patients in the United States who underwent synoviorthesis with ^{32}P (the only isotope currently approved by the U.S. Food and Drug Administration) and developed acute lymphocytic leukaemia in the year following the procedure (Dunn *et al*, 2005). To get a better idea of the total population of patients who had undergone this procedure, a survey of haemophilia treatment centres in the USA estimated that 563–577 patients had undergone synoviorthesis with ^{32}P since 1988 (Dunn *et al*, 2005). Although is it impossible to definitely establish cause and effect, these reports are worrisome, and should be part of

the informed consent process (Dunn *et al*, 2005). It is important to evaluate the risk–benefit ratio in each patient, and it is likely that radioactive synovectomy still offers significant benefit, particularly for patients with inhibitory antibodies, multiple affected joints, poor surgical candidates, or those in whom tight regulation of postoperative haemostasis and rehabilitation cannot be ensured.

Chemical synovectomy

Similar to radionucleotide synovectomy, other chemical agents, such as rifamycin, rifampicin and osmic acid, have been injected into the haemophilic joint to cause sclerosis with results comparable with other methods of synoviorthesis (Fernandez-Palazzi, 1998; Molho *et al*, 1999; Caviglia *et al*, 2001; Radossi *et al*, 2003). The best results are seen in joints with grade I and II arthropathy (Fernandez-Palazzi *et al*, 2000). One drawback of using these agents for synoviorthesis is that they may cause pain and require multiple injections (Fernandez-Palazzi *et al*, 2000). This approach may be more feasible than surgical or radionucleotide synovectomy particularly in countries with limited resources.

Steroid injections

Intra-articular injections of steroids have been used to transiently decrease pain and inflammation in patients with chronic synovitis, and may be useful as a palliative measure (Shupak *et al*, 1988; Fernandez-Palazzi, 1998). The use of these injections is well documented in the treatment of rheumatoid arthritis and osteoarthritis (Neustadt, 2006). Adverse effects on cartilage from repeated steroid injections, noted in animal studies, have not been observed in humans (Kalbhen *et al*, 1978; Raynauld *et al*, 2003).

Hyaluronic acid injections

Hyaluronic acid has become an increasingly common agent for intra-articular injection for patients with osteoarthritis. Hyaluronic acid is a natural occurring viscous substance that is a fundamental component of the cartilage matrix. Intra-articular injection of this substance can improve pain in patients with arthritis, although its mechanism of action in not well understood (Wallny *et al*, 2000). Improvements in pain or function after 3–5 injections in patients with haemophilic arthropathy have been reported in approximately 75% of patients (Wallny *et al*, 2000; Fernandez-Palazzi *et al*, 2002).

Joint arthroplasty

Patients with haemophilia who develop severe arthropathy may experience relentless pain, loss of motion and functional disability. If conservative management fails (analgesics, orthotics and physical therapy) these patients may benefit from total joint replacement. The knee is the most frequently replaced joint in haemophilia (Powell *et al*, 2005). Reports of total knee replacement (TKR) in patients with haemophilia using factor concentrates date back to the 1970's (Marmor, 1977). Over time, advances in orthopaedic surgery and postoperative care have improved the outcome of TKR (Legroux-Gerot *et al*, 2003). Pain relief can be achieved in the vast majority of patients who undergo TKR, but improvements in postoperative ROM are more variable (Small *et al*, 1983; Beeton *et al*, 2000; Legroux-Gerot *et al*, 2003). Factors which may influence the ROM outcome include soft tissue contracture, stage of joint deterioration, type of prothesis, and postoperative mobilisation (use of a continuous passive motion machine or manipulation under anaesthesia) (Beeton *et al*, 2000). Patients whose ROM does not increase may nonetheless experience improved functional mobility as a result of improvement in flexion contracture (Beeton *et al*, 2000).

However, despite these improvements in pain and functional mobility, TKR in haemophilia has been hampered by a high-complication rate. Complications include postoperative haemarthrosis, peroneal nerve palsy, wound infection, joint sepsis and prothestic loosening (Legroux-Gerot *et al*, 2003). The frequency of these complications varies, but infection has been the single biggest problem. Reports of TKR in the 1990's noted a higher incidence of postoperative infections, particularly in patients who were human immunodeficiency virus (HIV) positive. The infection rate after TKR in a normal population is about 1–2% (Bengtson & Knutson, 1991). The infection rate in patients with haemophilia and HIV was reported to be as high as 18–26%, and seemed to be influenced by the CD4 count (Ragni *et al*, 1995; Hicks *et al*, 2001). Others have not observed a higher rate of infection in HIV positive patients compared with HIV negative patients (Norian *et al*, 2002; Powell *et al*, 2005).

The long-term survival of joint replacement in haemophilia has been reported to be 90% at 5 years and 83% at 10 years (Norian *et al*, 2002; Silva & Luck, 2005). These outcomes are inferior to those observed in patients with osteoarthritis, in whom the 10–15 year prosthetic survival ranges from 90–95% (Ranawat *et al*, 1993; Rodriguez *et al*, 1996). Late infection, often occurring years after the procedure, is the most common reason for prosthetic failure in patients with haemophilia (Norian *et al*, 2002; Silva & Luck, 2005). The explanation for this high risk of late infection is not clear, but may be a consequence of frequent self-administration of factor and poor skin hygiene or technique resulting in haematogenous bacterial spread (Norian *et al*, 2002).

In the past, there has been reluctance to perform arthroplasty in younger adults because of the concern of the longevity of the prothesis. However, TKR in non-haemophilia patients younger than age 55 years has an 18-year survival rate of 94%. Haemophilic arthropathy develops at a younger age than osteoarthritis, as reflected by the average age of patients with haemophilia who have undergone TKR, which ranges from 21 to 40 years, although patients as young as 15 years have been reported (Thomason *et al*, 1999; Norian *et al*, 2002;

Legroux-Gerot *et al*, 2003; Sheth *et al*, 2004; Silva & Luck, 2005). The ultimate outcome and natural history of joint replacement in this younger population is not yet known.

Although the knee is by far the most frequently replaced joint in haemophilia, arthroplasty is also used for other joints with severe arthropathy. Hip replacement in patients with haemophilia may offer significant pain relief and improved function, albeit with a higher rate of complications that lead to revisions in 20–57% of patients, although recent reports are more encouraging (Luck & Kasper, 1989; Nelson *et al*, 1992; Kelley *et al*, 1995; Lofqvist *et al*, 1996; Habermann *et al*, 2006). Other joints have been successfully replaced in patients with haemophilia, including the ankle, shoulder and elbow, although these are confined to case reports and small series (reviewed in Beeton *et al*, 2000; Dalzell, 2004).

Arthrodesis

Patients who develop advanced haemophilic arthropathy of the ankle and severe pain may benefit from arthrodesis, a procedure in which the synovium is removed and the joint is fused to prevent further motion (Rodriguez-Merchan, 2006). There are limited reports on the outcome of this procedure in patients with haemophilia, although in one centre there were no recurrent haemarthroseis or infections over a 1–18-year follow-up in 34 fused ankles (Gamble *et al*, 1991; Rodriguez-Merchan, 2006). This approach, by its nature, reduces mobility but involves less extensive surgery and rehabilitation than joint replacement; it may be preferred for relief of pain in other joints for which joint replacement surgery is not routinely available.

Osteotomy

Corrective osteotomy may be performed in patients with haemophilic joint disease and axial deformities, particularly around the hip, knee and ankle. While this may not restore ROM, long-term results after osteotomy for haemophilic arthropathy of the knee showed improved pain in the majority of patients (Wallny *et al*, 2002, 2003). This may be an option for patients in whom joint replacement is not available or currently desirable.

Conclusion

In conclusion, the availability of safe factor concentrates administered prophylactically to paediatric patients with severe haemophilia has been demonstrated to prevent joint disease, and will undoubtedly postpone or eliminate the need for synovectomy or joint replacements in the most successful patients. Nonetheless, where factor concentrates are not available, or are not administered in a manner that prevents joint haemorrhage, haemophilic arthropathy will continue to require the co-ordinated efforts of haemophilia therapists, orthopaedic surgeons and physical therapists to optimise outcomes.

References

Ahlberg, A. (1971) Radioactive gold in the treatment of chronic synovial effusion in haemophilia. In: *Proceedings of the VII Congress World Federation of Haemophilia*, pp. 212–215. Excepta Medica, Amsterdam.

Ahlberg, A. & Pettersson, H. (1979) Synoviorthesis with radioactive gold in hemophiliacs. Clinical and radiological follow-up. *Acta Orthopaedica Scandinavica*, **50,** 513–517.

Aledort, L.M., Haschmeyer, R.H. & Pettersson, H. (1994) A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *Journal of Internal Medicine*, **236,** 391–399.

Arnold, W.D. & Hilgartner, M.W. (1977) Hemophilic arthropathy. Current concepts of pathogenesis and management. *The Journal of Bone and Joint Surgery*, **59,** 287–305.

Arun, B. & Kessler, C. (2001) *Inherited Bleeding Disorders: Haemostasis and Thrombosis*, 4th edn. Lippincott Williams and Wilkens, Philadelphia, PA.

Beeton, K., Rodriguez-Merchan, E.C. & Altree, J. (2000) Total joint arthroplasty in haemophilia. *Haemophilia*, **6,** 474–481.

Bengtson, S. & Knutson, K. (1991) The infected knee arthroplasty. A 6-year follow-up of 357 cases. *Acta Orthopaedica Scandinavica*, **62,** 301–311.

Berntorp, E., Boulyjenkov, V., Brettler, D., Chandy, M., Jones, P., Lee, C., Lusher, J., Mannucci, P., Peake, I., Rickard, K. & Seremetis, S. (1995) Modern treatment of haemophilia. *Bulletin of the World Health Organization*, **73,** 691–701.

Blanchette, V., Rivard, G.E., Israels, S.J., Robinson, S., Babyn, P.S., McLimont, M.J., Hilliard, P.E. & Feldman, B.M. (2003) Musculoskeletal results from the Canadian hemophilia dose-escalation prophylaxis trial. *Blood (ASH Annual Meeting Abstracts)*, **102,** p52a. Abstr. 171.

Buzzard, B.M. (1997) Physiotherapy for prevention and treatment of chronic hemophilic synovitis. *Clinical Orthopaedics and Related Research* (343), 42–46.

Buzzard, B.M. (1999) Physiotherapy for the prevention of articular contraction in haemophilia. *Haemophilia*, **5**(Suppl 1)**,** 10–15.

Cagnoni, P.J. & Aledort, L. (1994) Gastrointestinal bleeding in hemophilia as a complication of the use of over the counter nonsteroidal anti-inflammatory drugs. *American Journal of Hematology*, **47,** 336–337.

Caviglia, H.A., Fernandez-Palazzi, F., Galatro, G. & Perez-Bianco, R. (2001) Chemical synoviorthesis with rifampicin in haemophilia. *Haemophilia*, **7**(Suppl. 2)**,** 26–30.

de la Chapelle, A., Rekonen, A., Oka, M. & Ruotsi, A. (1972) Chromosome damage after intra-articular injections of radioactive yttrium. Effect of immobilization on the biological dose. *Annals of the Rheumatic Diseases*, **31,** 508–512.

Cohen, B., Griffiths, L. & Dandy, D.J. (1992) Arteriovenous fistula after arthroscopic synovectomy in a patient with haemophilia. *Arthroscopy*, **8,** 373–374.

Daly, H.M. & Scott, G.L. (1984) Extensive ecchymoses due to ibuprofen therapy in the management of haemophiliac arthropathy. *Clinical and Laboratory Haematology*, **6,** 85–87.

Dalzell, R. (2004) Shoulder hemiarthroplasty to manage haemophilic arthropathy: two case studies. *Haemophilia*, **10,** 649–654.

van Dijk, K., Fischer, K., van der Bom, J.G., Grobbee, D.E. & van den Berg, H.M. (2005) Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed. *Haemophilia*, **11,** 438–443.

Dunn, A.L., Busch, M.T., Wyly, J.B., Sullivan, K.M. & Abshire, T.C. (2004) Arthroscopic synovectomy for hemophilic joint disease in a paediatric population. *Journal of Pediatric Orthopedics*, **24,** 414–426.

Dunn, A.L., Manco-Johnson, M., Busch, M.T., Balark, K.L. & Abshire, T.C. (2005) Leukemia and P32 radionuclide synovectomy for hemophilic arthropathy. *Journal of Thrombosis and Haemostasis*, **3,** 1541–1542.

Eickhoff, H.H., Koch, W., Raderschadt, G. & Brackmann, H.H. (1997) Arthroscopy for chronic hemophilic synovitis of the knee. *Clinical Orthopaedics and Related Research*, (343), 58–62.

Elander, J. & Barry, T. (2003) Analgesic use and pain coping among patients with haemophilia. *Haemophilia*, **9,** 202–213.

Erken, E.H. (1991) Radiocolloids in the management of hemophilic arthropathy in children and adolescents. *Clinical Orthopaedics and Related Research*, (264), 129–135.

Falcon de Vargas, A. & Fernandez-Palazzi, F. (2000) Cytogenetic studies in patients with hemophilic hemarthrosis treated by 198Au, 186Rh, and 90Y radioactive synoviorthesis. *Journal of Pediatric Orthopaedics Part B*, **9,** 52–54.

Fernandez-Palazzi, F. (1998) Treatment of acute and chronic synovitis by non-surgical means. *Haemophilia*, **4,** 518–523.

Fernandez-Palazzi, F., Rivas, S., Cibeira, J.L., Dib, O. & Viso, R. (1996) Radioactive synoviorthesis in hemophilic hemarthrosis: materials, techniques, and dangers. *Clinical Orthopaedics and Related Research*, (328), 14–18.

Fernandez-Palazzi, F., Rivas, S., Viso, R., de Bosch, N.B., de Saez, A.R. & Boadas, A. (2000) Synovectomy with rifampicine in haemophilic haemarthrosis. *Haemophilia*, **6,** 562–565.

Fernandez-Palazzi, F., Viso, R., Boadas, A., Ruiz-Saez, A., Caviglia, H. & De Bosch, N.B. (2002) Intra-articular hyaluronic acid in the treatment of haemophilic chronic arthropathy. *Haemophilia*, **8,** 375–381.

Fischer, K., van der Bom, J.G., Mauser-Bunschoten, E.P., Roosendaal, G., Prejs, R., Grobbee, D.E. & van den Berg, H.M. (2001) Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia*, **7,** 446–452.

Furie, B., Limentani, S.A. & Rosenfield, C.G. (1994) A practical guide to the evaluation and treatment of hemophilia. *Blood*, **84,** 3–9.

Gamble, J.G., Bellah, J., Rinsky, L.A. & Glader, B. (1991) Arthropathy of the ankle in hemophilia. *The Journal of Bone and Joint Surgery*, **73,** 1008–1015.

Gedik, G.K., Ugur, O., Atilla, B. & Dundar, S. (2004) Is corticosteroid coinjection necessary for radiosynoviorthesis of patients with hemophilia? *Clinical Nuclear Medicine*, **29,** 538–541.

Gilbert, M.S. & Radomisli, T.E. (1997) Therapeutic options in the management of hemophilic synovitis. *Clinical Orthopaedics and Related Research*, (343), 88–92.

Gratz, S., Gobel, D., Behr, T.M., Herrmann, A. & Becker, W. (1999) Correlation between radiation dose, synovial thickness, and efficacy of radiosynoviorthesis. *The Journal of Rheumatology*, **26,** 1242–1249.

Habermann, B.E.C., Hovy, L., Zichnerr, L., Scharrer, I. & Kurth, A. (2006) Total hip replacement in patients with severe bleeding disorders: a 30 years single center experience. *International Orthopaedics* (epub).

Hakobyan, N., Kazarian, T., Jabbar, A.A., Jabbar, K.J. & Valentino, L.A. (2004) Pathobiology of hemophilic synovitis I: overexpression of mdm2 oncogene. *Blood*, **104,** 2060–2064.

Harris, S. & Boggio, L.N. (2006) Exercise may decrease further destruction in the adult haemophilic joint. *Haemophilia*, **12,** 237–240.

Heijnen, L. & Buzzard, B.B. (2005) The role of physical therapy and rehabilitation in the management of hemophilia in developing countries. *Seminars in Thrombosis and Hemostasis*, **31,** 513–517.

Heijnen, L., Roosendaal, G. & Heim, M. (1997) Orthotics and rehabilitation for chronic hemophilic synovitis of the ankle. An overview. *Clinical Orthopaedics and Related Research*, (343), 68–73.

Heim, M., Israeli, A., Varon, D., Chechic, A., Engelberg, S. & Martinowitz, U. (1999) Expanding portal haematomata as a complication of knee arthroscopies in persons with haemophilia. *Haemophilia*, **5,** 213–215.

Heim, M., Tiktinsky, R., Amit, Y. & Martinowitz, U. (2004) Yttrium synoviorthesis of the elbow joints in persons with haemophilia. *Haemophilia*, **10,** 590–592.

Hicks, J.L., Ribbans, W.J., Buzzard, B., Kelley, S.S., Toft, L., Torri, G., Wiedel, J.D. & York, J. (2001) Infected joint replacements in HIV-positive patients with haemophilia. *The Journal of Bone and Joint Surgery*, **83,** 1050–1054.

Hill, F.G. & Ljung, R. (2003) Third and fourth Workshops of the European Paediatric Network for Haemophilia Management. *Haemophilia*, **9,** 223–228.

Hilliard, P., Funk, S., Zourikian, N., Bergstrom, B.M., Bradley, C.S., McLimont, M., Manco-Johnson, M., Petrini, P., den Berg, M. & Feldman, B.M. (2006) Hemophilia joint health score reliability study. *Haemophilia*, **12,** 518–525.

Hooiveld, M., Roosendaal, G., Wenting, M., den Berg, M., Bijlsma, J. & Lafeber, F. (2003) Short-term exposure of cartilage to blood results in chondrocyte apoptosis. *American Journal of Pathology*, **162,** 943–951.

Ingrand, J. (1973) Characteristics of radio-isotopes for intra-articular therapy. *Annals of the Rheumatic Diseases*, **32**(Suppl. 6), 3–9.

Inwood, M.J., Killackey, B. & Startup, S.J. (1983) The use and safety of Ibuprofen in the hemophiliac. *Blood*, **61,** 709–711.

Journeycake, J., Brambilla, D. & Ragni, M. (2005) Central venous access device-related infections in hemophilia. *Blood (ASH Annual Meeting Abstracts)*, **106**: abstract 3216.

Kalbhen, D.A., Schauer, M. & Wentsche, B. (1978) [Animal experiment studies on the effect of intra-articular injections of antiphlogistic-antirheumatic agents on articular cartilage in vivo]. *Zeitschrift fur Rheumatologie*, **37,** 380–394.

Kelley, S.S., Lachiewicz, P.F., Gilbert, M.S., Bolander, M.E. & Jankiewicz, J.J. (1995) Hip arthroplasty in hemophilic arthropathy. *The Journal of Bone and Joint Surgery*, **77,** 828–834.

Kim, H.C., Klein, K., Hirsch, S., Seibold, J.R., Eisele, J. & Saidi, P. (1984) Arthroscopic synovectomy in the treatment of hemophilic synovitis. *Scandinavian Journal of Haematology*, **40,** 271–279.

Legroux-Gerot, I., Strouk, G., Parquet, A., Goodemand, J., Gougeon, F. & Duquesnoy, B. (2003) Total knee arthroplasty in hemophilic arthropathy. *Joint Bone Spine*, **70,** 22–32.

Lofqvist, T., Sanzen, L., Petersson, C. & Nilsson, I.M. (1996) Total hip replacement in patients with hemophilia. 13 hips in 11 patients followed for 1–16 years. *Acta Orthopaedica Scandinavica*, **67,** 321–324.

Luck, Jr, J.V. & Kasper, C.K. (1989) Surgical management of advanced hemophilic arthropathy. An overview of 20 years' experience. *Clinical Orthopaedics and Related Research*, (242), 60–82.

Lundin, B., Pettersson, H. & Ljung, R. (2004) A new magnetic resonance imaging scoring method for assessment of haemophilic arthropathy. *Haemophilia*, **10,** 383–389.

Lundin, B., Babyn, P., Doria, A.S., Kilcoyne, R., Ljung, R., Miller, S., Nuss, R., Rivard, G.E. & Pettersson, H. The International Prophylaxis Study Group. (2005) Compatible scales for progressive and additive MRI assessments of haemophilic arthropathy. *Haemophilia*, **11,** 109–115.

Lusher, J.M. (1997) Prophylaxis in children with hemophilia: is it the optimal treatment? *Thrombosis and Haemostasis*, **78,** 726–729.

Manco-Johnson, M.J., Nuss, R., Funk, S. & Murphy, J. (2000) Joint evaluation instruments for children and adults with haemophilia. *Haemophilia*, **6,** 649–657.

Marmor, L. (1977) Total knee replacement in hemophilia. *Clinical Orthopaedics and Related Research*, (125), 192–195.

Molho, P., Verrier, P., Stieltjes, N., Schacher, J.M., Ounnoughene, N., Vassilieff, D., Menkes, C. & Sultan, Y. (1999) A retrospective study on chemical and radioactive synovectomy in severe haemophilia patients with recurrent haemarthrosis. *Haemophilia*, **5,** 115–123.

Nelson, I.W., Sivamurugan, S., Latham, P.D., Matthews, J. & Bulstrode, C.J. (1992) Total hip arthroplasty for hemophilic arthropathy. *Clinical Orthopaedics and Related Research*, (276), 210–213.

Neustadt, D.H. (2006) Intra-articular injections for osteoarthritis of the knee. *Cleveland Clinic Journal of Medicine*, **73,** 897–898, 901–904, 906–911.

Nilsson, I.M., Hedner, U. & Ahlberg, A. (1976) Haemophilia prophylaxis in Sweden. *Acta Paediatrica Scandinavica*, **65,** 129–135.

Nilsson, I.M., Berntorp, E., Lofqvist, T. & Pettersson, H. (1992) Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *Journal of Internal Medicine*, **232,** 25–32.

Norian, J.M., Ries, M.D., Karp, S. & Hambleton, J. (2002) Total knee arthroplasty in hemophilic arthropathy. *The Journal of Bone and Joint Surgery*, **84-A,** 1138–1141.

Nuss, R., Kilcoyne, R.F., Geraghty, S., Shroyer, A.L., Rosky, J.W., Mawhinney, S., Wiedel, J. & Manco-Johnson, M. (2000) MRI findings in haemophilic joints treated with radiosynoviorthesis with development of an MRI scale of joint damage. *Haemophilia*, **6,** 162–169.

Patti, J.E. & Mayo, W.E. (1996) Arthroscopic synovectomy for recurrent hemarthrosis of the ankle in hemophilia. *Arthroscopy*, **12,** 652–656.

Pettersson, H., Ahlberg, A. & Nilsson, I.M. (1980) A radiologic classification of hemophilic arthropathy. *Clinical Orthopaedics and Related Research*, (149), 153–159.

Pettersson, H., Nilsson, I.M., Hedner, U., Norehn, K. & Ahlberg, A. (1981) Radiologic evaluation of prophylaxis in severe haemophilia. *Acta Paediatrica Scandinavica*, **70,** 565–570.

Powell, D.L., Whitener, C.J., Dye, C.E., Ballard, J.O., Shaffer, M.L. & Eyster, M.E. (2005) Knee and hip arthroplasty infection rates in persons with haemophilia: a 27 year single center experience during the HIV epidemic. *Haemophilia*, **11,** 233–239.

Radossi, P., Baggio, R., Petris, U., De Biasi, E., Risato, R., Davoli, P.G. & Tagariello, G. (2003) Intra-articular rifamycin in haemophilic arthropathy. *Haemophilia*, **9,** 60–63.

Ragni, M.V., Crossett, L.S. & Herndon, J.H. (1995) Postoperative infection following orthopaedic surgery in human immunodeficiency virus-infected hemophiliacs with CD4 counts <or = 200/mm3. *The Journal of Arthroplasty*, **10,** 716–721.

Ranawat, C.S., Flynn, Jr, W.F., Saddler, S., Hansraj, K.K. & Maynard, M.J. (1993) Long-term results of the total condylar knee arthroplasty. A 15-year survivorship study. *Clinical Orthopaedics and Related Research*, (286), 94–102.

Rattray, B., Nugent, D.J. & Young, G. (2005) Rofecoxib as adjunctive therapy for haemophilic arthropathy. *Haemophilia*, **11,** 240–244.

Rattray, B., Nugent, D.J. & Young, G. (2006) Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia. *Haemophilia*, **12,** 514–517.

Raynauld, J.P., Buckland-Wright, C., Ward, R., Choquette, D., Haraoui, B., Martel-Pelletier, J., Uthman, I., Khy, V., Tremblay, J.L., Bertrand, C. & Pelletier, J.P. (2003) Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis and Rheumatism*, **48,** 370–377.

Rivard, G.E., Girard, M., Belanger, R., Jutras, M., Guay, J.P. & Marton, D. (1994) Synoviorthesis with colloidal 32P chromic phosphate for the treatment of hemophilic arthropathy. *Journal of Bone and Joint Surgery*, **76,** 482–488.

Rodriguez, J.A., Saddler, S., Edelman, S. & Ranawat, C.S. (1996) Long-term results of total knee arthroplasty in class 3 and 4 rheumatoid arthritis. *The Journal of Arthroplasty*, **11,** 141–145.

Rodriguez-Merchan, E.C. (2006) The haemophilic ankle. *Haemophilia*, **12,** 337–344.

Rodriguez-Merchan, E.C., Magallon, M., Galindo, E. & Lopez-Cabarcos, C. (1997) Hemophilic synovitis of the knee and the elbow. *Clinical Orthopaedics and Related Research*, (343), 47–53.

Roosendaal, G. & Lafeber, F.P. (2006) Pathogenesis of haemophilic arthropathy. *Haemophilia*, **12,** 117–121.

Roosendaal, G., Vianen, M.E., Wenting, M.J., van Rinsum, A.C., van den Berg, H.M., Lafeber, F.P. & Bijlsma, J.W. (1998) Iron deposits and catabolic properties of synovial tissue from patients with haemophilia. *Journal of Bone and Joint Surgery*, **80,** 540–545.

Roosendaal, G., TeKoppele, J.M., Vianen, M.E., van den Berg, H.M., Lafeber, F.P. & Bijlsma, J.W. (1999) Blood-induced joint damage: a canine in vivo study. *Arthritis and Rheumatism*, **42,** 1033–1039.

Scharrer, I., Bray, G.L. & Neutzling, O. (1999) Incidence of inhibitors in haemophilia A patients – a review of recent studies of recombinant and plasma-derived factor VIII concentrates. *Haemophilia*, **5,** 145–154.

Sheth, D.S., Oldfield, D., Ambrose, C. & Clyburn, T. (2004) Total knee arthroplasty in hemophilic arthropathy. *The Journal of Arthroplasty*, **19,** 56–60.

Shupak, R., Teitel, J., Garvey, M.B. & Freedman, J. (1988) Intraarticular methylprednisolone therapy in hemophilic arthropathy. *American Journal of Hematology*, **27,** 26–29.

Siegel, H.J., Luck, J.V., Siegel, Jr, M.E., Quines, C. & Anderson, E. (1994) Hemarthrosis and synovitis associated with hemophilia: clinical use of P-32 chromic phosphate synoviorthesis for treatment. *Radiology*, **190,** 257–261.

Silva, M. & Luck, Jr, J.V. (2005) Long-term results of primary total knee replacement in patients with hemophilia. *Journal of Bone and Joint Surgery*, **87,** 85–91.

Small, M., Steven, M.M., Freeman, P.A., Lowe, G.D., Belch, J.J., Forbes, C.D. & Prentice, C.R. (1983) Total knee arthroplasty in haemophilic arthritis. *Journal of Bone and Joint Surgery*, **65,** 163–165.

Soler, R., Lopez-Fernandez, F., Rodriguez, E. & Marini, M. (2002) Hemophilic arthropathy. A scoring system for magnetic resonance imaging. *European Radiology*, **12,** 836–843.

Soucie, J.M., Cianfrini, C., Janco, R.L., Kulkarni, R., Hambleton, J., Evatt, B., Forsyth, A., Geraghty, S., Hoots, K., Abshire, T., Curtis, R., Forsberg, A., Huszti, H., Wagner, M. & White, II, G.C. (2004) Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. *Blood*, **103,** 2467–2473.

Steven, M.M., Small, M., Pinkerton, L., Madhok, R., Sturrock, R.D. & Forbes, C.D. (1985) Non-steroidal anti-inflammatory drugs in haemophilic arthritis. A clinical and laboratory study. *Haemostasis*, **15,** 204–209.

Storti, E., Traldi, A., Tosatti, E. & Davoli, P.G. (1969) Synovectomy, a new approach to haemophilic arthropathy. *Acta Haematologica*, **41,** 193–205.

Thomason, III, H.C., Wilson, F.C., Lachiewicz, P.F. & Kelley, S.S. (1999) Knee arthroplasty in hemophilic arthropathy. *Clinical Orthopaedics and Related Research*, (360), 169–173.

Triantafyllou, S.J., Hanks, G.A., Handal, J.A. & Greer, III, R.B. (1992) Open and arthroscopic synovectomy in hemophilic arthropathy of the knee. *Clinical Orthopaedics and Related Research*, (283), 196–204.

Tsoukas, C., Eyster, M.E., Shingo, S., Mukhopadhyay, S., Giallella, K.M., Curtis, S.P., Reicin, A.S. & Melian, A. (2006) Evaluation of the efficacy and safety of etoricoxib in the treatment of hemophilic arthropathy. *Blood*, **107,** 1785–1790.

Wallny, T., Brackmann, H.H., Semper, H., Schumpe, G., Effenberger, W., Hess, L. & Seuser, A. (2000) Intra-articular hyaluronic acid in the treatment of haemophilic arthropathy of the knee. Clinical, radiological and sonographical assessment. *Haemophilia*, **6,** 566–570.

Wallny, T., Brackmann, H.H., Hess, L., Seuser, A., Hofmann, P. & Kraft, C.N. (2002) Long-term follow-up after intertrochanteric varus osteotomy for haemophilic arthropathy of the hip. *Haemophilia*, **8,** 149–152.

Wallny, T., Saker, A., Hofmann, P., Brackmann, H.H., Nicolay, C. & Kraft, C.N. (2003) Long-term follow-up after osteotomy for haemophilic arthropathy of the knee. *Haemophilia*, **9,** 69–75.

Watson, T. (2002) Current concepts in electrotherapy. *Haemophilia*, **8,** 413–418.

Wen, F.Q., Jabbar, A.A., Chen, Y.X., Kazarian, T., Patel, D.A. & Valentino, L.A. (2002) c-myc proto-oncogene expression in hemophilic synovitis: in vitro studies of the effects of iron and ceramide. *Blood*, **100,** 912–916.

Wiedel, J.D. (1984) Arthroscopic synovectomy in hemophilic arthropathy of the knee. *Scandinavian Journal of Haematology*, **40,** 263–270.

Wiedel, J.D. (1996) Arthroscopic synovectomy of the knee in hemophilia: 10-to-15 year followup. *Clinical Orthopaedics and Related Research*, (378), 46–53.

Wiedel, J. (2002) Arthroscopic synovectomy: state of the art. *Haemophilia*, **8,** 372–374.

Winston, M.A., Bluestone, R., Cracchiolo, III, A. & Blahd, W.H. (1973) Radioisotope synovectomy with 32P-chromic phosphate-kinetic studies. *Journal of Nuclear Medicine*, **14,** 886–889.

