Haemophilia (2007), **13** (Suppl. 4), 1–16

Optimizing outcomes for patients with severe haemophilia A

S. W. PIPE* and L. A. VALENTINO†
**Department of Pediatrics, University of Michigan, Ann Arbor, MI; and †Departments of Pediatrics and Internal Medicine, Rush University Medical Center, Chicago, IL, USA*

Introduction

Haemophilia A is an inherited, sex-linked disorder in which coagulation factor VIII (FVIII) is deficient or absent [1]. The hallmark of the severe form of the disease, defined as plasma FVIII level of <1% of normal [2], is early, recurrent bleeding into soft tissues and joints [3]. Intra-articular bleeding (haemarthrosis) accounts for more than 90% of all serious bleeding events in patients with severe haemophilia, and 80% of these bleeds involve the knees, elbows and ankles [1]. An acute haemarthrosis is typified by rapid joint swelling that may be preceded by a prodrome of tingling, stiffness and pain (Fig. 1) [4,5]. Recurrent bleeding over time into the same joint (a target joint) results in progressive joint damage and the development of haemophilic arthropathy, characterized by synovial hypertrophy, cartilage damage, loss of joint space and bony changes (Fig. 2) [6,7]. Decreased use of a target joint leads to ongoing muscle atrophy, ankylosis, osteoporosis, bone cysts, and eventually, crippling arthritis by young adulthood [3,7].

The development of arthropathy is directly linked to the number of joint bleeding episodes [8,9]. In the landmark Orthopaedic Outcome Study, which enrolled 378 patients with severe haemophilia A, Aledort *et al.* reported the Pettersson radiologic scores increased 1 point for every 40 joint bleeds [8]. A subsequent evaluation by Fischer *et al.* of 117 severe haemophilia patients found that far fewer bleeds – just 13 – were necessary to cause a 1 point increase in the Pettersson score [9]. Yet even this lower number may be an overestimate. A major limitation to the use of plain film radiographs as a tool for assessing arthropathy is their ability to visualize only gross arthritic alterations [1]. When magnetic resonance imaging (MRI) was performed on children with haemophilia who had no obvious clinical signs of arthropathy, early changes in the soft tissues (e.g., synovium and cartilage) were demonstrated [1]. These MRI findings indicate that incipient joint damage may occur after very few bleeding episodes.

On-demand therapy (episodic factor replacement in response to acute bleeding events), while effective in controlling acute haemorrhage, cannot halt the ongoing joint destruction many patients with severe haemophilia A experience [10]. An epidemiologic survey conducted by the French Study Group of 116 haemophilia patients treated almost exclusively from birth with on-demand therapy found that at a mean age of 23 years, only 3.7% had normal joints by radiographic examination and 54.3% had undergone orthopaedic procedures [11]. Similarly dismal long-term outcomes were reported by Blanchette. Among patients with severe haemophilia managed in Canada with on-demand therapy, approximately 50% had evidence of joint disease by age 13 years; and by age 18, 24% of the 54 patients had undergone surgical synovectomy of at least 1 joint [12].

For children with severe haemophilia A and no evidence of inhibitors, the musculoskeletal complications that follow repeated joint bleeding can be effectively prevented with the early initiation of prophylaxis, the routine scheduled replacement of FVIII with the goal of maintaining FVIII trough

Abbreviations: ADL, activities of daily living; AVF, arteriovenous fistulae; BIW, two times weekly; CVAD, central venous access device; DDAVP, desmopressin acetate; FFC, fixed flexion contracture; FVIII, factor VIII; FVIII:C, factor VIII coagulant activity; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTC, haemophilia treatment center; ICH, intracranial haemorrhage; MRI, magnetic resonance imaging; NHF, National Hemophilia Foundation; QOD, every other day; QOL, quality of life; QW, once weekly; RCT, randomized controlled trial; TIW, 3 times weekly; WFH, World Federation of Hemophilia; WHO, World Health Organization

Correspondence: Leonard A. Valentino, MD, Associate Professor of Pediatrics, Director, Hemophilia and Thrombophilia Center, Rush University Medical Center, 1653 West Congress Parkway, Chicago, IL 60612-3833, USA. Tel.: 312 942 8114; fax: 312 942 8975; e-mail: lvalenino@rush.edu

This CME supplement is sponsored by Scienta Healthcare Education® and supported by an unrestricted grant from Baxter BioScience.

Accepted after revision 30 July 2007

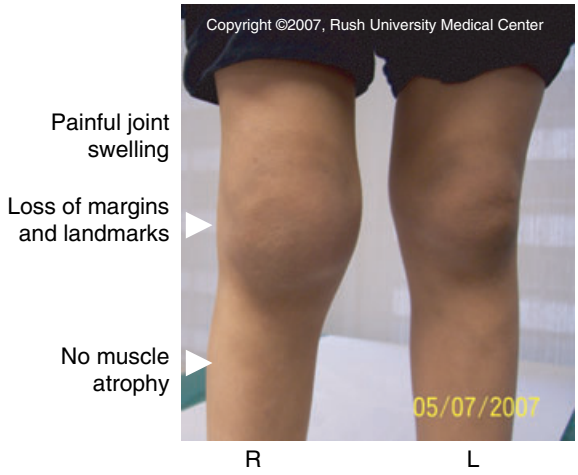

Fig. 1. Acute hemarthrosis. The right (R) knee is swollen, warm and painful to touch. Range of motion is limited. Palpation of the joint margin and patella is obscured. There is no muscle atrophy.

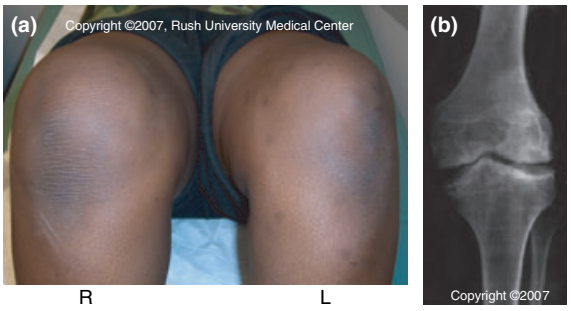

Fig. 2. Chronic synovitis and arthropathy. (a) Chronic synovitis of the right (R) knee is typified by a warm and swollen joint with reduced range of motion but no pain with palpation or motion. Palpation of the joint margins and patella are obscured by the spongy synovium, and muscle atrophy is present. (b) Radiograph of the knee showing narrowing of the joint space, erosions at the margins, sclerosis, osteoporosis, a widened intra-condylar notch and cyst formation.

levels above 1% [10,13–21]. Nonetheless, surveys of international practice patterns [22,23] and statistics from the Universal Data Collection Programme [24] indicate that the majority of patients with severe FVIII deficiency continue to receive on-demand therapy. In an effort to optimize outcomes in patients with severe haemophilia A through increasing the use of prophylaxis, a panel of clinicians from haemophilia treatment centres (HTCs) in North America convened in Miami, Florida, on January 27–28, 2007, to review the current state of knowledge about joint-protective therapeutic approaches and from this derive best treatment strategies. We hope that the information presented in this supplement, which summarizes our review of the literature and subsequent discussions and recommendations, will help physicians and their staffs develop protocols for the use of prophylaxis in children, adolescents and adults with severe haemophilia A.

We appreciate the opportunity to be guest editors of this CME supplement to *Haemophilia* and to work with our colleagues from the United States and Canada. The names and affiliations of the coauthors in alphabetical order:

Manuel Carcao
Hospital for Sick Children
Toronto, Ontario, Canada

Amy Dunn
Emory University School of Medicine
Atlanta, Georgia, USA

Ralph Gruppo
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio, USA

W. Keith Hoots
University of Texas Health Science Center
Houston, Texas, USA

Marilyn Manco-Johnson
University of Colorado Health Sciences Center
Denver, Colorado, USA

Christopher Walsh
Mount Sinai School of Medicine
New York, USA

Guy Young
Childrens Hospital of Los Angeles
Los Angeles, California, USA

Initiating prophylaxis in children

Data supporting prophylaxis

The rationale for prophylaxis is predicated on observations published by Swedish researchers more than 40 years ago. They reported that maintaining FVIII plasma levels between 1% and 3% of normal appeared to convert patients from a severe to a moderate haemophilia A phenotype, in which spontaneous bleeding events are less frequent and musculoskeletal complications are less likely to occur [25,26]. In the ensuing years, several observational studies demonstrated the efficacy of FVIII prophylaxis in preventing joint bleeding and the subsequent development of arthropathy, target joints and disability [8,13–20]. Moreover, the benefits of prophylaxis extended beyond joint protection and included preventing other serious or life-threatening haemorrhages, such as recurrent central nervous system bleeding following intracranial haemorrhage (ICH)

[16,27], and indirectly improving academic performance [28] and quality of life (QOL) [19,20]. Because of these advantages, prophylaxis is recommended as optimal therapy for patients with severe haemophilia A by the National Hemophilia Foundation (NHF) [29], the World Federation of Hemophilia (WFH) [30] and the World Health Organization (WHO) [31].

While the empiric benefits of prophylaxis have been clear for decades, a key piece of information was missing: results from a randomized controlled trial (RCT). Because of this deficit, a systematic review conducted by the Cochrane Collaboration concluded that there was insufficient evidence to determine the effectiveness of prophylaxis in decreasing the frequency of joint bleeding [32]. Fortunately, the deficiency of RCT data has been rectified. In August 2007, Manco-Johnson published the findings from the prospective, controlled US Joint Outcome Study [10]. This trial enrolled 65 children between 12 and 30 months of age with severe haemophilia A randomized to a prophylactic regimen of every-other-day FVIII infusions of 25 IU kg^{-1} (n = 32) or enhanced episodic therapy consisting of three or more FVIII infusions totalling at least 80 IU kg^{-1} to treat joint haemorrhages (n = 33). At the end of the 5-year follow-up period, joint bleeding was significantly lower in the prophylaxis group compared with the enhanced episodic therapy group: 0.47 bleeds annually vs. 4.9 bleeds annually respectively ($P < 0.001$). The favourable results from the first RCT of primary prophylaxis coupled with more than four decades of observational studies have now firmly established the efficacy of this treatment strategy.

Primary prophylaxis

Only a few joint bleeds may cause damage [33], and arthropathy, once established, does not reverse and may progress despite the use of prophylactic treatment [14]. Consequently, all children with severe haemophilia A ideally should be placed on primary prophylaxis. Primary prophylaxis is variably defined [34–36], but a commonly used definition developed by an international consensus panel describes it as long term, continual treatment started before the age of 2 years and prior to any clinically evident joint bleeding or started after the first joint haemorrhage, irrespective of age (Table 1) [35].

Whether primary prophylaxis should be started before the first joint haemorrhage or shortly thereafter remains a matter of debate. One argument for initiating treatment between 1 and 2 years of age and before the first bleeding event is that some children have developed joint disease despite no history or awareness of haemarthrosis [37]. This finding suggests that even subclinical joint bleeding may lead to slowly progressive arthropathy and underscores the need for early intervention. On the other hand, starting prophylaxis at a very young age is costly, can result in over treatment of a group of children who are not prone to haemarthroses despite low levels of endogenous FVIII, and often requires insertion of a central venous access device (CVAD) to administer factor [35]. Furthermore, patients on prophylaxis still experience joint bleeding [8,18,19], indicating that starting prophylaxis before the first bleeding episode can postpone haemarthrosis but does not entirely prevent it.

Marked variability in the severe haemophilia clinical phenotype has been described [8,38–41] and is well known to treating physicians. For patients with a milder phenotype, it may be possible to safely delay the initiation of primary prophylaxis until later in life [41]. Some HTCs allow a child to experience a few episodes of joint bleeding before embarking on a prophylactic regimen, as this gives the clinician an opportunity to observe the bleeding pattern [42] and also impress upon the parents the adverse impact of bleeding.

While the question of when to start primary prophylaxis remains unresolved, there is no debate

Table 1. Definitions of primary and secondary prophylaxis.

Type of prophylaxis	Definition
Primary prophylaxis determined by age [35]	Long-term continual* treatment started before age 2 years and prior to clinically evident joint bleeding
Primary prophylaxis determined by first bleeding episode [35]	Long-term continual* treatment started prior to the onset of joint damage (presumptively defined as not more than one joint haemorrhage), irrespective of age
Secondary prophylaxis [35,42]	Long-term continual* prophylaxis initiated after multiple joint bleeds and the onset of joint damage

*With the intent of treating 52 weeks per year up to adulthood and receiving treatment a minimum of 46 weeks per year.
Adapted with permission from Berntorp E, Astermark J, Bjorkman S *et al.* Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; 9(Suppl. 1): 1–4.

about the importance of initiating treatment after no more than a few joint haemorrhages. A study by Fischer *et al.* that followed 76 patients with severe haemophilia A for 20 years showed that the Pettersson score was 8% higher for every year prophylaxis was postponed after the first episode of haemarthrosis [43].

Recommendations for primary prophylaxis

Prophylaxis should be initiated in all patients with severe haemophilia A before 2 years of age and prior to clinically evident joint bleeding or after no more than a few joint haemorrhages (to establish the bleeding phenotype).

Secondary prophylaxis

Despite the clear advantages of primary prophylaxis, this treatment strategy remains underutilized [23,24]. However, a substantial segment of the haemophilia population can still benefit from prophylactic treatment when administered in the form of secondary prophylaxis, defined as long term, continuous prophylaxis initiated after multiple joint bleeds (Table 1) [35].

Secondary prophylaxis can reduce joint and other bleeding episodes; slow the progression of, although not reverse, existing joint damage; and permit participation in sports and other activities [44–48]. It also allows aggressive physical rehabilitation to be undertaken in children and adolescents with chronic joint damage [44]. The magnitude of the benefits of secondary prophylaxis depends on the number of previous bleeding episodes and the extent of pre-existing joint damage, which generally correlate with patient age at the start of prophylaxis [44]. The earlier the prophylactic regimen is started, the better the outcome. Nonetheless, the advantages of prophylaxis are seen regardless of the age at initiation [48]. In other words, it is never too late to start.

Although patients with severe haemophilia have the highest frequency of bleeding episodes, a subgroup of patients with moderate haemophilia, defined as a FVIII level of 1–5% of normal [2], also experience regular haemarthroses and develop target joints, arthropathy and impaired mobility while receiving on-demand therapy (Fig. 3) [24]. These individuals may also benefit from secondary prophylaxis.

Recommendations for secondary prophylaxis

1 In patients with severe haemophilia A in whom primary prophylaxis has been delayed, secondary prophylaxis should be initiated as soon as possible, even after the onset of joint damage (it is never too late to start).

2 Secondary prophylaxis should be considered in patients with moderate haemophilia A who experience frequent joint haemorrhages.

Prophylactic regimens

Three basic prophylactic regimens have been described that differ with regard to dose, dosing frequency and whether treatment is initiated on the basis of age or after joint bleeding has occurred (Table 2) [14,49,50].

Full-dose prophylaxis (Malmö regimen)

Prophylaxis for severe haemophilia A was first utilized in Malmö, Sweden, in 1958 [14]. Treatment has intensified over the years, and in the current regimen, FVIII is administered at a dose of 25–40 IU kg^{-1} three times weekly starting at age 1–2 years, irrespective of bleeding history [18]. The goal is to maintain FVIII coagulant activity (FVIII:C) above 1% of normal at all times. Pharmacokinetic measurements are used to guide dosing.

In 1992, Nilsson *et al.* described 25 years of experience with prophylaxis in 60 Swedish patients, aged 3–32 years, with severe haemophilia A or B [14]. Patients in the two youngest age groups, who received full-dose primary prophylaxis at a very early age, had better outcomes than the oldest group of patients, some of whom had joint damage when secondary prophylaxis was started, initially at lower doses. Specifically, boys aged 3–12 years (n = 15) experienced almost no bleeding episodes, had orthopaedic scores (Table 3) and radiologic scores (Table 4) of zero (0/0), and were able to lead normal lives. In comparison, patients aged 18–32 years (n = 25) had 0.5–16 joint haemorrhages annually, and only four had joint scores of 0/0. Nonetheless, patients who received any level of prophylaxis had better joint outcomes than patients in the on-demand therapy group.

In 1997, the Malmö group published follow-up data that showed that the youngest treatment groups (n = 15) still had not experienced any haemarthrosis, and their orthopaedic and radiologic joint scores remained 0/0 [18]. Despite treatment intensification, episodes of joint bleeding persisted in the oldest patient groups (n = 19). This finding confirms that prophylaxis can slow, but not halt, progressive arthropathy in patients with pre-existing joint disease.

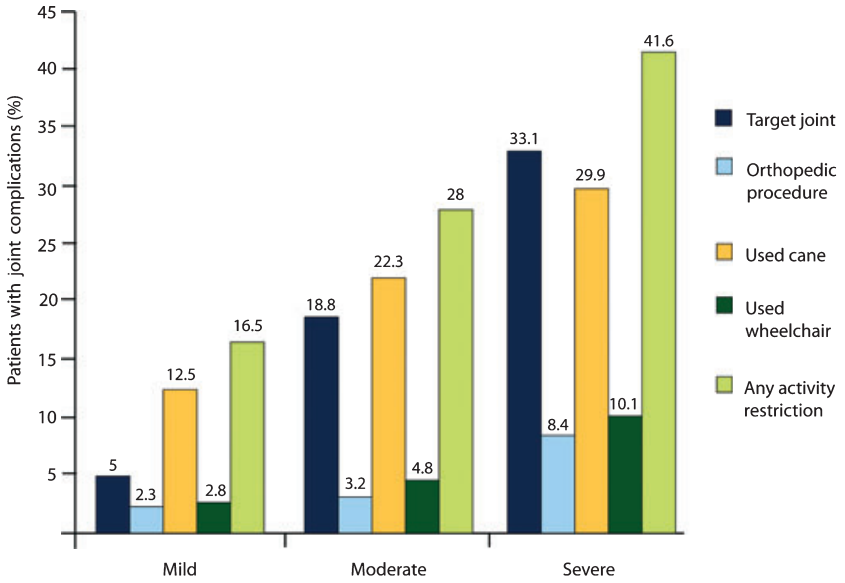

Fig. 3. Joint complications in patients ≥2 years by haemophilia severity [24].

Table 2. Regimens used for primary prophylaxis [14].

Regimen	FVIII dose (IU kg^{-1})	Frequency	Determinant of when prophylaxis is started
Full-dose (Malmö regimen)	24–40	TIW	Age
Intermediate-dose (Dutch regimen)	15–25	BIW or TIW	Bleeding pattern (usually after first joint haemorrhage)
Tailored-dose (Canadian regimen)	Step 1: 50	QW	Age
	Step 2: 30	BIW	
	Step 3: 25	QOD	
	5-IU kg^{-1} incremental increases if bleeding continues		

The Medical and Scientific Advisory Council [29] of the NHF recommends a slightly modified version of the Malmö regimen for prophylaxis: FVIII 25–50 IU kg^{-1} three times weekly or every other day, instituted before the onset of frequent bleeding.

Intermediate-dose prophylaxis (Dutch regimen)

In the Netherlands, prophylaxis is usually started after the occurrence of at least one episode of joint bleeding [49]. As in Sweden, dosing has been intensified over the years, and the current intermediate-dose prophylactic regimen for patients with haemophilia A is FVIII 15–25 IU kg^{-1} infused two or three times weekly. Dosing is adjusted in the event of spontaneous breakthrough bleeds, but FVIII trough levels are not considered when making the adjustments.

To determine the impact of different dosing regimens on long-term outcomes, Fischer *et al.* retrospectively compared 86 Dutch haemophilia patients treated with intermediate-dose prophylaxis beginning at a median age of 5 years with 42 Swedish haemophilia patients treated with full-dose prophylaxis beginning at a median age of 2 years [49]. After a median of 17 years of follow-up, the annual number of joint bleeds (adjusted for age) was 77% lower in patients treated with the high-dose regimen (median, 0.3/year vs. 3.3/year). The Pettersson score (Table 4) was also lower in the high-dose group (median, 0) vs. the intermediate dose group (median, 4), although the reduction in arthropathy as measured by the Pettersson score was not statistically significant ($P = 0.560$ or $P = 0.797$, depending on year of birth). No statistical differences in outcome, as measured by the Gilbert orthopaedic joint score promoted by the WFH (Table 3) or the physical domains of the SF-36 [51] (a multipurpose, short-form generic health-related QOL survey) emerged, and according to the investigators, prophylaxis enabled patients in both countries to lead normal lives, including participation in sports. Substantial

Table 3. Orthopaedic joint scoring system (Gilbert Score) [18,52].

	Score*			
Item	0	1	2	3
Chronic pain	No pain	Mild pain	Moderate pain Partial or occasional interference with occupation or ADL	Severe pain
	No functional deficit	Does not interfere with occupation or activities of daily living (ADL)	Use of non-narcotic medications	Interferes with occupation or ADL
	No analgesic use (except with acute haemarthrosis)	May require non-narcotic analgesic	May require occasional narcotic medications	Requires frequent use of non-narcotic and narcotic medications
Axial deformity				
Elbow	None	≤10°varus or valgus	>10°varus or valgus	—
Knee	No deformity (0°–7°valgus)	8–15°valgus or 0°–5°varus	>15°valgus or >5°varus	—
Ankle	No deformity	≤10°valgus or ≤5°varus	>10°valgus or >5°varus	—
Contracture				
Flexion	<15°fixed flexion contracture (FFC)	—	≥15°FFC	—
Equinus	<15°	—	≥15°	—
Joint physical findings				
Instability range of motion†	None	Slight (noted on examination but does not interfere with function or require bracing)	Severe (creates a functional deficit or requires bracing)	—
Pronation and supination†	0–10%	11–33%	33–100%	—
	0–33%	—	>33%	—
Chronic swelling	None	—	Present	—
Atrophy	None/minimal (<1 cm)	Present	—	—
Crepitus on motion	None	Present	—	—

*Sum of the elbows, knees and ankles = joint score; maximum possible score = 90.
†Expressed as percentage loss of full range of motion.

Table 4. Radiologic joint score (Pettersson score) [52].

Type of change	Finding	Score*
Osteoporosis	Absent	0
	Present	1
Enlarged epiphysis	Absent	0
	Present	1
Irregular subchondral surface	Absent	0
	Partially involved	1
	Totally involved	2
Narrowing of joint space	Absent	0
	Present; joint space >1 mm	1
	Present; joint space <1 mm	2
Subchondral cyst formation	Absent	0
	1 Cyst	1
	>1 Cyst	2
Erosion of joint margins	Absent	0
	Present	1
Gross incongruence of articulating bone ends	Absent	0
	Slight	1
	Pronounced	2
Joint deformity	Absent	0
	Slight	1
	Pronounced	2

*Maximum possible joint score = 13; maximum possible total joint score (sum of elbows, knees and ankles) = 78.

differences were noted in the cost of the two prophylactic regimens. Because prophylaxis was started earlier and administered in larger doses in the Swedish cohort, the consumption of clotting factor concentrate was twofold higher than in the intermediate-dose group.

Tailored-dose/dose-escalation prophylaxis (Canadian regimen)

The clinical manifestations of severe haemophilia A are variable [8,41], and there is considerable disparity in prophylactic dosing requirements due to interpatient differences, including the pharmacokinetics of FVIII:C [38,53,54]. Individualized dosing that is adjusted according to a patient's bleeding pattern offers an opportunity to provide adequate prophylactic coverage while reducing FVIII consumption [55].

A tailored-dose regimen developed by the Canadian Prophylaxis Study Group initiates FVIII prophylaxis at 50 IU kg^{-1} once weekly (step 1) [50]. The dose and frequency are increased to 30 IU kg^{-1} twice weekly if the patient develops target joint bleeding (≥3 bleeds into a single joint during a consecutive 3-month period), experiences excessive bleeding (defined by the investigators as ≥4 joint or soft tissue haemorrhages during a consecutive 3-month period), or has five or more haemorrhages into a single joint over any period of time (step 2). Dosing is further increased to 25 IU kg^{-1} every other day if any of the escalation criteria recur while on step 2 (step 3). Additional incremental increases of 5 IU kg^{-1} are prescribed if bleeding continues. This regimen was evaluated in 25 boys aged 1–2.5 years with severe haemophilia A, none of whom had a history of target joint bleeding [50]. After 5 years, 10 patients continued to receive once-weekly prophylaxis, eight patients had escalated to step 2 and received twice-weekly prophylaxis, and seven patients required full-dose alternate-day prophylaxis (having escalated from step 1 to 2 to 3). A total of 116 joint haemorrhages occurred during the study period, an average of 1.2 per person-year. Nine patients (36%) developed target joints within 3.5 years of starting prophylaxis, suggesting that the trade-off to this lower intensity regimen may be that some patients experienced frequent bleeding. However, dosing was escalated when this occurred, and no subject developed a second target joint. Furthermore, half of the patients have not required escalation, which has resulted in substantial savings on factor concentrate and, possibly, improved QOL compared with more intensive regimens. The ultimate impact of allowing patients to manifest some bleeding episodes before dosage escalation awaits long-term studies.

Recommendations for the prophylaxis dosing regimen

1 Optimal prophylaxis requires the administration of FVIII 25–40 IU kg^{-1} three times weekly or every other day, instituted before the onset of frequent bleeding.
2 In certain cases, individualized dosing regimens that provide adequate prophylactic coverage can be considered in an effort to reduce FVIII consumption, improve adherence and enhance the adoption of prophylaxis.

Outcome measures

FVIII trough level

Although *in vivo* pharmacokinetic measurements of FVIII are used in the Malmö regimen to ensure that trough levels exceed 1% of normal between prophylactic infusions [14,18], the correlation between FVIII levels and the incidence of joint bleeding is very weak [53]. A retrospective survey of medical records from the Malmö HTC over a 6-year period found that some patients with trough levels below

1% experienced no bleeding episodes, while others bled despite having trough levels exceeding 3%. Other pharmacokinetic parameters, such as FVIII recovery and half-life, have been used to detect the presence of non-neutralizing inhibitory antibodies [56]. Clinical outcome, not the maintenance of an arbitrary FVIII trough level, should determine whether dosing is sufficient and prophylaxis is effective.

Breakthrough bleeding

Spontaneous breakthrough bleeding may indicate that the prophylactic regimen is inadequate and requires adjustment. Breakthrough bleeding drives dose escalation in both the intermediate-dose and tailored-dose regimens [49,50]. However, the precise number of haemorrhages that is indicative of regimen failure and the need to intensify treatment is unknown.

Musculoskeletal assessment

The primary measure of the efficacy of prophylaxis is the assessment of musculoskeletal status by physical examination and plain film radiographs [12]. Two scoring systems are predominantly used. The orthopaedic joint score (Table 3), recommended by the Orthopaedic Advisory Committee of the WFH, uses a 15-point scale to evaluate each elbow, knee and ankle and has a maximum possible score of 90 [57]. The Pettersson radiologic score (Table 4) assesses each of these joints on a 13-point scale and has a maximum possible score of 78 [37]. The two assessments are generally performed in tandem, and a perfect score is rated as 0/0.

Limitations of the WFH orthopaedic joint scoring system are insensitivity to early haemophilic arthropathy and the use of tasks that may be beyond the developmental ability of young children to perform [12]. An expanded physical joint evaluation scale capable of detecting early structural or functional abnormalities has been developed specifically for young children with haemophilia [58] and is being studied in prospective, longitudinal clinical trials. Similarly, plain film radiographs, the standard tool for detecting and assessing structural joint damage associated with haemophilic arthropathy [35], are not sensitive to early joint damage [1]. As previously discussed, MRI allows evaluation of soft tissue changes that precede cartilage and bone destruction [59]. However, MRI is not cost-effective for routine clinical monitoring [35].

Health-related quality of life

Effective treatments have increased the life expectancy of patients with haemophilia. Consequently, improvement in health-related QOL has become one of the major concerns of haemophilia management [60]. Disease-specific measures of QOL for children with haemophilia are available for use in clinical studies [61] but are not typically used in clinical practice. Instead, QOL is assessed by asking questions about the patient's general well-being. Questioning is sometimes augmented with the SF-36 health survey, although this survey has not been validated for use in children. Because symptomatic haemophilic arthritis often appears years after the onset of joint bleeding, QOL measures determined in young adults are needed to realistically compare the outcomes of prophylactic regimens used in early childhood.

Recommendations for measuring prophylaxis outcomes

Objective assessments of musculoskeletal status and health-related QOL should be a part of any effort to evaluate outcomes in patients receiving prophylaxis.

Barriers to prophylaxis

Several barriers to the initiation and continuation of prophylaxis have been consistently identified in surveys of practice patterns and include venous access issues, cost and problems with adherence [22,23,62].

Venous access issues

Venous access issues are among the top reasons given for not administering prophylaxis or discontinuing treatment [22,23]. Venipuncture may be difficult for caregivers and patients [62], and CVADs, either fully implantable ports or external catheters [63], are often needed to facilitate prophylaxis administration to young children [14,33,50,64].

Infection is the major complication associated with CVADs used in haemophilia [65], and it is the most common cause for their removal [63]. In a meta-analysis of 48 studies that involved 2704 patients and 2973 CVADs, Valentino *et al.* found that 44% of patients and 40% of CVADs were affected by an infectious episode [63]. Thrombosis may also occur with CVAD use [63,66]. While this complication may be silent and clinically insignificant, patients may manifest severe and potentially life-threatening

symptoms, such as superior vena cava syndrome [67].

An escalating-dose prophylactic regimen is one strategy for minimizing the need for CVADs [41]. Petrini described a regimen that begins with once-weekly infusions very early in life to facilitate peripheral venous access and increases to full-dose prophylaxis by the time the child reaches 2 years [41,68]. When a CVAD is necessary, patient and family education is essential to minimize infectious risk and should be reinforced on a continuing basis [63]. Regular monitoring of the patient and CVAD by the haemophilia treatment team is also required [66].

Arteriovenous fistulae (AVF), the vascular access of choice for haemodialysis patients [69], are now being evaluated as an option for venous access in boys with haemophilia aged 1 year and older in an effort to avoid the complications of CVADs. A prospective study of 27 children with severe haemophilia found the AVF were regularly and successfully used at home by 26 patients (96%) for a median follow-up of 29 months [70]. Venous thrombosis occurred in one patient after 9 months, but symptoms spontaneously disappeared, and the AVF was used for an additional 9 months. McCarthy *et al.* also described the successful use of AVF in nine haemophilia patients, five of whom had a total of 21 failed CVADs before the creation of the AVF [71]. Adapting AVF to the requirements of children with haemophilia requires surgical expertise and long-term follow-up with ultrasonography and echocardiography. Once peripheral veins provide adequate vascular access, the AVF should be dismantled.

Cost

Prophylaxis allows haemophilia patients to lead functionally normal and productive lives, but at a high cost: FVIII consumption for patients treated with the full-dose Malmö regimen may exceed 8900 IU kg^{-1} annually [18]. Whether prophylaxis, as has been suggested, actually lowers overall healthcare costs by reducing the need for emergency room visits, hospitalization, orthopaedic interventions and other surgeries [8,16,19,72] is uncertain. An economic evaluation by Bohn *et al.* found that the savings fail to offset the expense of year-round prophylaxis [73]. A subsequent comparison of healthcare expenditures by Ullman and Hoots found that the yearly cost in US dollars for prophylaxis and on-demand therapy was similar [74]. Outpatient costs were greater for patients on prophylaxis, but inpatient costs were higher for those treated on-demand. However, when costs were adjusted for body mass, prophylaxis was two to threefold more expensive than on-demand therapy, confirming the findings of Bohn *et al.* that prophylaxis is the more costly intervention.

Intermediate-dose and tailored-dose regimens have the potential to appreciably reduce costs by providing therapeutic benefits similar to those of full-dose prophylaxis while using lower amounts of factor [49,50,75]. Not only would these regimens improve the cost-effectiveness of prophylaxis, but they may also make optimal therapy available to more patients with severe haemophilia [76].

Adherence

Poor adherence to the prophylactic regimen is a significant impediment to optimizing treatment [23]. A global survey of practice patterns identified denial; a lack of parental or family commitment; and the time-consuming nature of prophylaxis, which can interfere with other family needs and social obligations, as challenges to full adherence [23]. Teenage rebellion may also contribute to non-adherence, as evidenced by the fact that adherence is higher in younger patients whose infusions are administered by their parents than among adolescents who self-infuse. Yet the most significant obstacle to adherence was a lack of understanding of the potential benefits of prophylaxis. Conversely, knowledge of these benefits was cited as the primary facilitator of adherence in a survey of prophylaxis patients and their families [62]. Ongoing education and support provided by the haemophilia treatment team are key to encouraging patients and families to make the long-term commitment to a demanding treatment strategy [62,77–79].

Recommendations for overcoming barriers to prophylaxis

1. Consider an escalating-dose regimen when initiating prophylaxis to minimize the need for CVADs in young children.
2. AVF are an option for venous access in some children (e.g., those who have experienced repeated CVAD failure).
3. Intermediate- and tailored-dose regimens may reduce costs while providing therapeutic benefits similar to those of full-dose prophylaxis.
4. Provide patients and families with on-going education and support to facilitate their long-term commitment to prophylaxis.

Transitioning to adult care

Historical perspective

In June 1982, the first case of human immunodeficiency virus (HIV) was diagnosed in a US haemophilia patient who had no known risk factors [80]. HIV, transmitted by infusions of clotting factor concentrates, went on to ravage the haemophilia community (Fig. 4). Early in 1985, the availability of heat-treated FVIII products halted the clotting factor-related HIV epidemic [80], but by that time, more than 50% of haemophilia patients in the United States had been infected [81]. For many years thereafter, HIV and hepatitis C (Fig. 5)–not joint health–were the over-riding concerns of treaters, patients and families and the leading causes of death. Consequently, most adults with haemophilia alive today have never been treated with primary or secondary prophylaxis.

Difficulties in making the transition from paediatric to adult prophylaxis

Several factors are implicated in the decline in the use of prophylaxis in adulthood. First, while many larger HTCs treat both children and adults, some centres only have paediatric programmes [82]. Once a child reaches his late teens, his care may be transferred to an internist unfamiliar with prophylaxis or unaware of the importance of continuing the prophylactic regimen into adulthood. Lifestyle changes also contribute to lower rates of prophylaxis in adults. The demands of work, family and social activities may leave little time for regular infusions. Fatigue with the requirements of prophylaxis is another factor that may lead to treatment discontinuation, particularly for patients who started prophylaxis at a very young age. Finally, the high cost forces some patients to abandon prophylaxis. Patients who were covered under their parents' health insurance plans may not have their own insurance as adults. Furthermore, Medicaid benefits vary from state to state and may not include haemophilia prophylaxis after age 18.

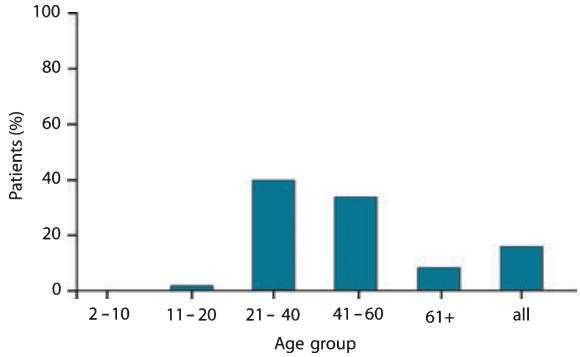

Fig. 4. Prevalence as of 2005 of human immunodeficiency virus infection among persons with haemophilia enrolled in UDC [24].

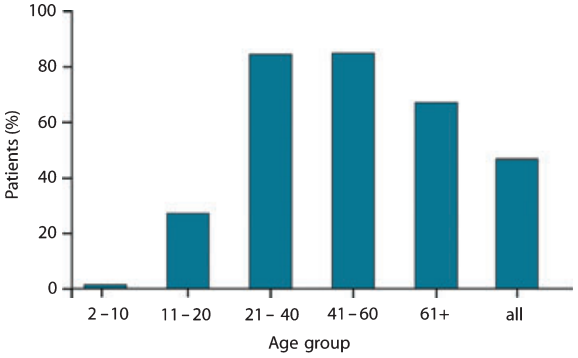

Fig. 5. Prevalence as of 2005 of hepatitis C virus infection among persons with haemophilia enrolled in UDC [24].

Should prophylaxis be stopped?

Given the difficulties in maintaining prophylactic regimens into adulthood, is it possible to stop prophylaxis at some point? The NHF [29], WFH [30], and WHO [31] recommend that prophylaxis be continued, possibly throughout life, as the risk of traumatic bleeding events persists in adults, the severity of haemophilia is practically the same as in childhood, and the benefits of prophylaxis are experienced by all age groups [76]. On the other hand, there may be some rationale for stopping treatment, or a least modifying the regimen. Adults are usually less physically active than children, so the likelihood of injury is lower. In addition, there is *in vivo* animal data to suggest that mature joint cartilage is less susceptible to blood-induced damage than is cartilage in younger joints [83].

Little clinical data exists on the impact of discontinuing prophylaxis in adulthood. van Dijk *et al.* reported on 80 patients with severe haemophilia born between 1970 and 1980 treated with prophylaxis in Denmark and the Netherlands [84]. The median age at the start of prophylaxis was 5.6 years (Denmark) and 6.0 years (the Netherlands), and the median follow-up period was 19 years. By the age of 26 years, 35% of the patients from both cohorts had changed to on-demand treatment, yet they experienced (on average) only three bleeds annually. Nearly 4 years after the patients discontinued prophylaxis, their joint status, assessed by clinical and

radiologic scores, appeared unaffected and outcomes were similar to those in patients who remained on prophylaxis.

A previous report by Fischer *et al.*, which described only the Dutch cohort, identified characteristics of the subgroup of patients who stopped prophylaxis [85]. They included a later start of prophylaxis, a lower weekly dose of FVIII, and reduced incidence of joint bleeding on prophylaxis, all of which suggested a milder bleeding pattern. Although those prognostic features failed to predict discontinuation of prophylaxis among the Danish patients described by van Dijk [84], the findings from both studies indicate that it may be possible to select candidates for permanent cessation of prophylaxis. However, prospective trials are needed to determine whether some patients can safely stop treatment and to determine the impact of such a change.

Other preventive infusion strategies

Primary or secondary prophylaxis is always the preferred treatment strategy for severe haemophilia A, especially for children. For older patients who are not on continuous prophylactic regimens, other preventive infusion strategies may prevent serious bleeding-related sequelae.

Limited prophylaxis

Limited prophylaxis, also referred to as intermittent or episodic prophylaxis, is defined as a short period of factor replacement to prevent bleeding in specific situations (Table 5). Surgery is the classic example of limited prophylaxis. Other situations where limited prophylaxis may be considered include prior to participating in sports or other strenuous activities; during travel, particularly if the patient will not have rapid access to high-quality medical care; and before special events, such as college final exams or a wedding.

There is minimal data on limited prophylaxis outside the surgical setting. In a UK pilot study, four adults with severe haemophilia A and arthropathy received factor sufficient to raise FVIII levels to 20% prior to each session of physical therapy [86]. Over a 2-year period, the patients experienced an 89% mean reduction in the number of bleeding episodes; general improvement in joint condition; improved QOL, as evidenced by increased activity and decreased pain and an overall reduction in annual FVIII usage.

The goal of limited prophylaxis is to completely prevent bleeding; to this end, aggressive dosing to achieve 100% correction may be required. For patients with severe haemophilia A, the panel recommended a dose of 50 IU kg^{-1} prior to the activity or event, with dosing repeated for multiple-day activities. Patients with mild haemophilia may also benefit from limited prophylaxis with desmopressin acetate, although the risks of hyponatremia and tachyphylaxis limit multiple-day dosing [87].

Short-term secondary prophylaxis to prevent recurrent bleeding following major haemorrhage, such as ICH or other traumatic injury, is another form of limited prophylaxis (Table 5). While the optimal dose and duration of therapy in this setting is unknown, several weeks–if not months–of treatment may be needed to prevent rebleeding into an injured area [88].

Intensive on-demand therapy

Most clinical trials have demonstrated that the vast majority of acute bleeding events in severe haemophilia can be managed with 1–2 on-demand infusions that achieve a target plasma correction of approximately 50% [89–91]. However, certain types of haemorrhages may require higher target plasma levels sustained over a longer duration of time. Intensive on-demand therapy refers to the administration of factor at higher-than-usual doses and frequency and for a longer-than-usual duration to achieve haemostatic FVIII levels during bleeding episodes (Table 5). Intensive on-demand therapy has been used for the management of ICH [92,93] and may also be appropriate for certain joint, muscle and other bleeding events in patients with severe haemophilia A who are not on prophylaxis [94].

Table 5. Definitions of other infusion strategies.

Type of infusion strategy	Definition
Limited prophylaxis	Short period of factor replacement to prevent bleeding in specific situations
Short-term secondary prophylaxis	Prophylaxis administered for a limited period to prevent recurrent bleeding following a major haemorrhage
Intensive on-demand therapy	Administration of factor at higher-than-usual doses, more frequent intervals, and for a longer-than-usual duration to achieve a haemostatic FVIII level during bleeding episodes in patients not on prophylaxis

Table 6. Summary of the consensus recommendations for FVIII prophylaxis.

Recommendations for primary prophylaxis
- Prophylaxis should be initiated in all patients with severe haemophilia A before 2 years of age and prior to clinically evident joint bleeding or after no more than a few joint haemorrhages (to establish the bleeding phenotype)

Recommendations for secondary prophylaxis
- In patients with severe haemophilia A in whom primary prophylaxis has been delayed, secondary prophylaxis should be initiated as soon as possible, even after the onset of joint damage. It is never too late to start
- Secondary prophylaxis should be considered in patients with moderate haemophilia A who experience frequent joint bleeds

Recommendations for the prophylaxis dosing regimen
- Optimal prophylaxis requires the administration of FVIII 25–50 IU kg^{-1} three times weekly or every other day instituted before the onset of frequent bleeding
- In certain cases, individualized dosing regimens that provide adequate prophylactic coverage can be considered in an effort to reduce FVIII consumption, improve adherence, and enhance the adoption of prophylaxis

Recommendations for measuring prophylaxis outcomes
- Objective assessments of musculoskeletal status and health-related QOL should be a part of any effort to evaluate outcomes in patients receiving prophylaxis

Recommendations for overcoming barriers to prophylaxis
- Consider an escalating-dose regimen when initiating prophylaxis to minimize the need for CVADs in young children
- AVF are an option for venous access in some children (e.g., those who have experienced repeated CVAD failure)
- Intermediate- and tailored-dose regimens may reduce costs while providing therapeutic benefits similar to those of full-dose prophylaxis
- Provide patients and families with on-going education and support to facilitate their long-term commitment to prophylaxis

Recommendations for other preventive infusion strategies
- Primary or secondary prophylaxis is always preferred for patients with severe haemophilia A
- Limited prophylaxis to prevent bleeding in specific situations may require 100% correction to completely prevent bleeding
- Weeks, if not months, of short-term prophylaxis may be needed in certain situations to prevent rebleeding
- Intensive on-demand therapy may be appropriate for the management of ICH and for certain joint, muscle, and other bleeding events in patients with severe haemophilia A who are not on prophylaxis

A variety of dosing regimens has been used for this type of on-demand therapy, some of which are more intensive than others [95]. In the US Joint Outcome Study, intensive on-demand therapy consisted of at least three FVIII infusions totalling at least 80 IU kg^{-1} [10]. While this study showed that on-demand therapy was inferior to prophylaxis, it was not designed to assess the efficacy of intensive vs. standard dosing.

The panel recommended that when intensive on-demand therapy is desirable, an 80%-100% correction of the FVIII level should be targeted, rather than the standard 50%-60% correction (Table 6). Subsequent doses aimed at a 50%-100% correction should be given for persistent symptoms (e.g. pain, swelling, decreased range of motion) and administered at least every 12 hours.

Recommendations for other preventive infusion strategies

1 Primary or secondary prophylaxis is always preferred for patients with severe haemophilia A.
2 Limited prophylaxis to prevent bleeding in specific situations may require 100% correction to completely prevent bleeding.
3 Weeks, if not months, of short-term prophylaxis may be needed in certain situations to prevent rebleeding.
4 Intensive on-demand therapy may be appropriate for the management of ICH and for certain joint, muscle, and other bleeding events in patients with severe haemophilia A who are not on prophylaxis.

Conclusion

The recurrent episodes of haemarthrosis that characterize severe haemophilia A result in progressive joint damage and eventually lead to significant disability and impaired QOL. Prevention of bleeding is the goal of modern therapy. Prophylaxis is the most effective strategy for optimizing outcomes in patients with severe haemophilia A. Primary prophylaxis can prevent the development of arthropathy, protect against other serious bleeding events, and allow patients to live full, active lives. Depending on when it is started, secondary prophylaxis may provide many of the same benefits as primary

prophylaxis, although it cannot reverse joint damage that has already occurred.

The full-dose Malmö and intermediate dose Dutch prophylactic regimens have been successfully used for decades. However, individualized prophylaxis that takes into consideration interpatient variability in bleeding patterns and FVIII pharmacokinetics can avoid overtreatment; reduce factor consumption; lower treatment costs; and possibly, minimize the need for CVADs. As a result, some of the barriers to prophylaxis utilization may be overcome.

Because of the life-long risk of joint and other bleeding events in patients with severe haemophilia A, prophylaxis should be continued ideally into adulthood to maintain the benefits achieved in childhood. However, difficulties in transitioning to adult care cause some patients to stop treatment. For these individuals, limited prophylaxis and aggressive on-demand therapy are alternative infusion strategies that may prevent bleeding episodes or reduce bleeding-related complications.

References

1 Pergantou H, Matsinos G, Papadopoulos A, Platokouki H, Aronis S. Comparative study of validity of clinical, X-ray and magnetic resonance imaging scores in evaluation and management of haemophilic arthropathy in children. *Haemophilia* 2006; **12**: 241–7.

2 White GC II, Rosendaal F, Aledort LM *et al.* Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IXof the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001; **85**: 560.

3 Carcao MD, Aledort L. Prophylactic factor replacement in hemophilia. *Blood Rev* 2004; **18**: 101–13.

4 Rodriguez-Merchan EC. Pathogenesis, early diagnosis, and prophylaxis for chronic hemophilic synovitis. *Clin Orthop Relat Res* 1997; **343**: 6–11.

5 Silva M, Luck JV Jr, Llinás A. Chronic hemophilic synovitis: the role of radiosynovectomy. Treatment of Hemophilia Monograph Series [No. 33]. Available at: http://www.wfh.org/2/docs/Publications/Musculoskeletal_Physiotherapy/TOH-33_English_Synovectomy.pdf. Accessed May 19, 2006.

6 DePalma AF. Hemophilic arthropathy. *Clin Orthop Relat Res* 1967; **52**: 145–65.

7 Arnold WD, Hilgartner MW. Hemophilic arthropathy. Current concepts of pathogenesis and management. *J Bone Joint Surg Am* 1977; **59**: 287–305.

8 Aledort LM, Haschmeyer RH, Pettersson H, and the Orthopaedic Outcome Study Group. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. *J Intern Med* 1994; **236**: 391–9.

9 Fischer K, van Hout BA, van der Bom JG, Grobbee DE, van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. *Acta Radiol* 2002; **43**: 528–32.

10 Manco-Johnson MJ, Abshire TC, Shapiro AD *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.

11 Molho P, Rolland N, Lebrun T *et al.* Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. The French Study Group secretariat.haemophiles@cch.ap-hop-paris.fr. *Haemophilia* 2000; **6**: 23–32.

12 Blanchette VS. Prophylaxis in hemophilia: a comprehensive prospective. *Hematologica* 2004; **89**(Suppl. 1): 29–35.

13 Fischer K, van der Bom JG, Mauser-Bunschoten EP *et al.* Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; **7**: 446–52.

14 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25–32.

15 van Creveld S. Prophylaxis of joint hemorrhages in hemophilia. *Acta Haematol* 1971; **45**: 120–7.

16 Panicker J, Warrier I, Thomas R, Lusher JM. The overall effectiveness of prophylaxis in severe haemophilia. *Haemophilia* 2003; **9**: 272–8.

17 van den Berg HM, Fischer K, Mauser-Bunschoten EP *et al.* Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *Br J Haematol* 2001; **112**: 561–5.

18 Lofqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients–a long-term follow-up. *J Intern Med* 1997; **241**: 395–400.

19 Liesner RJ, Khair K, Hann IM. The impact of prophylactic treatment on children with severe haemophilia. *Br J Haematol* 1996; **92**: 973–8.

20 Fischer K, van der Bom JG, Molho P *et al.* Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia* 2002; **8**: 745–52.

21 Brackmann HH, Eickhoff HJ, Oldenburg J, Hammerstein U. Long-term therapy and on-demand treatment of children and adolescents with severe haemophilia A: 12 years of experience. *Haemostasis* 1992; **22**: 251–8.

22 Butler RB, McClure W, Wulff K. Practice patterns in haemophilia A therapy–a survey of treatment centres in the United States. *Haemophilia* 2003; **9**: 549–54.

23 Geraghty S, Dunkley T, Harrington C *et al.* Practice patterns in haemophilia A therapy – global progress towards optimal care. *Haemophilia* 2006; **12**: 75–81.

24 Centers for Disease Control and Prevention. Report on the Universal Data Collection Program. 2005; **7**: 1–39. Available at www.cdc.gov/ncbddd/hbd/documents/UDC7(1).pdf. Accessed May 23, 2007.

25 Ahlberg A. Haemophilia in Sweden. VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B. *Acta Orthop Scand Suppl* 1965; **77**: 3–132.
26 Nilsson IM, Blomback M, Ramgren O. Haemophilia in Sweden VI. Treatment of haemophilia A with the human antihaemophilic factor preparation (fraction I–0). *Acta Med Scand Suppl* 1962; **379**: 61–110.
27 Antunes SV, Vicari P, Cavalheizro S, Bordin JO. Intracranial haemorrhage among a population of haemophilic patients in Brazil. *Haemophilia* 2003; **9**: 573–7.
28 Shapiro AD, Donfield SM, Lynn HS *et al*. Defining the impact of hemophilia: the Academic Achievement in Children with Hemophilia Study. *Pediatrics* 2001; **108**: E105.
29 National Hemophilia Foundation. *MASAC Recommendation Concerning Prophylaxis (Regular Administration of Clotting Factor Concentrate to Prevent Bleeding)*. Medical and Scientific Advisory Council (MASAC) Document no. 170. 2006.
30 Srivastava A, Giangrande P, Poon MC, Chua M, McCraw A, Wiedel J. Guidelines for the management of hemophilia. Available at http://www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Gudelines_Mng_Hemophilia.pdf. Accessed March 6, 2007.
31 Berntorp E, Boulyjenkov V, Brettler D *et al*. Modern treatment of haemophilia. *Bull World Health Organ* 1995; **73**: 691–701.
32 Stobart K, Iorio A, Wu JK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B (review). The Cochrane Collaboration. Available at http://www.thecochranelibray.com. Accessed February 25, 2007.
33 Kreuz W, Escuriola-Ettingshausen C, Funk M, Schmidt H, Kornhuber B. When should prophylactic treatment in patients with haemophilia A and B start?–The German experience. *Haemophilia* 1998; **4**: 413–7.
34 Ljung R. Second Workshop of the European Paediatric Network for Haemophilia Management, 17-19 September 1998 in Vitznau/Switzerland. *Haemophilia* 1999; **5**: 286–91.
35 Berntorp E, Astermark J, Bjorkman S *et al*. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; **9**(Suppl. 1): 1–4.
36 Ota S, McLimont M, Carcao MD *et al*. Definitions for haemophilia prophylaxis and its outcomes: the Canadian consensus study. *Haemophilia* 2007; **13**: 12–20.
37 Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res* 1980; **149**: 153–9.
38 Fijnvandraat K, Peters M, Ten Cate JW. Inter-individual variation in half-life of infused recombinant factor VIII is related to pre-infusion von Willebrand factor antigen levels. *Br J Haematol* 1995; **91**: 474–6.
39 van Dijk K, Fischer K, van der Bom JG, Grobbee DE, van den Berg HM. Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed. *Haemophilia* 2005; **11**: 438–43.
40 Barnes C, Lillicrap D, Pazmino-Canizares J *et al*. Pharmacokinetics of recombinant factor VIII (Kogenate-FS®) in children and causes of inter-patient pharmacokinetic variability. *Haemophilia* 2006; **12**(Suppl. 4): 40–49.
41 Astermark J, Petrini P, Tengborn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *Br J Haematol* 1999; **105**: 1109–13.
42 van den Berg HM, Dunn A, Fischer K, Blanchette VS. Prevention and treatment of musculoskeletal disease in the haemophilia population: role of prophylaxis and synovectomy. *Haemophilia* 2006; **12**(Suppl. 3): 159–68.
43 Fischer K, van der Bom JG, Mauser-Bunschoten EP *et al*. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. *Blood* 2002; **99**: 2337–41.
44 Valentino LA. Secondary prophylaxis therapy: what are the benefits, limitations and unknowns? *Haemophilia* 2004; **10**: 147–57.
45 Manco-Johnson MJ, Nuss R, Geraghty S, Funk S, Kilcoyne R. Results of secondary prophylaxis in children with severe hemophilia. *Am J Hematol* 1994; **47**: 113–7.
46 Liesner RJ. Prophylaxis in haemophilic children. *Blood Coagul Fibrinolysis* 1997; **8**(Suppl. 1): S7–10.
47 Yee TT, Beeton K, Griffioen A *et al*. Experience of prophylaxis treatment in children with severe haemophilia. *Haemophilia* 2002; **8**: 76–82.
48 Tagliaferri A, Rivolta GF, Rossetti G, Pattacini C, Gandini G, Franchini M. Experience of secondary prophylaxis in 20 adolescent and adult Italian hemophiliacs. *Thromb Haemost* 2006; **96**: 542–3.
49 Fischer K, Astermark J, van der Bom JG *et al*. Prophylactic treatment for severe haemophilia: comparison of an intermediate-dose to a high-dose regimen. *Haemophilia* 2002; **8**: 753–60.
50 Feldman BM, Pai M, Rivard GE *et al*. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost* 2006; **4**: 1228–36.
51 Ware JE. SF-35® health survey update. Available at http://www.sf-36.org/tools/sf36.shtml. Accessed February 8, 2007.
52 Gilbert MS. Prophylaxis: musculoskeletal evaluation. *Semin Hematol* 1993; **30**: 3–6.
53 Ahnstrom J, Berntorp E, Lindvall K, Bjorkman S. A 6-year follow-up of dosing, coagulation factor levels and bleedings in relation to joint status in the prophylactic treatment of haemophilia. *Haemophilia* 2004; **10**: 689–97.
54 Carlsson M, Berntorp E, Bjorkman S, Lindvall K. Pharmacokinetic dosing in prophylactic treatment of hemophilia A. *Eur J Haematol* 1993; **51**: 247–52.

55 Berntorp E. Pharmacoeconomics of factor dosing in the haemophilia population. *Haemophilia* 2006; **12**(Suppl. 4): 70–73.
56 Bjorkman S. Prophylactic dosing of factor VIII and factor IX from a clinical pharmacokinetic perspective. *Haemophilia* 2003; **9**(Suppl. 1): 101–8; discussion 9-10.
57 Pettersson H, Gilbert M. *Diagnostic Imaging in Hemophilia: Muscuskeletal and Other Hemorrhagic Complications* Berlin: Springer-Verlag, 1985: pp. 56–65.
58 Manco-Johnson MJ, Nuss R, Funk S, Murphy J. Joint evaluation instruments for children and adults with haemophilia. *Haemophilia* 2000; **6**: 649–57.
59 Kilcoyne RF, Nuss R. Radiological assessment of haemophilic arthropathy with emphasis on MRI findings. *Haemophilia* 2003; **9**(Suppl. 1): 57–63;discussion -4.
60 Scalone L, Mantovani LG, Mannucci PM, Gringeri A. Quality of life is associated to the orthopaedic status in haemophilic patients with inhibitors. *Haemophilia* 2006; **12**: 154–62.
61 Bradley CS, Bullinger M, McCusker PJ, Wakefield CD, Blanchette VS, Young NL. Comparing two measures of quality of life for children with haemophilia: the CHO-KLAT and the Haemo-QoL. *Haemophilia* 2006; **12**: 643–53.
62 Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia* 2001; **7**: 392–6.
63 Valentino LA, Ewenstein B, Navickis RJ, Wilkes MM. Central venous access devices in haemophilia. *Haemophilia* 2004; **10**: 134–46.
64 Blanchette VS, McCready M, Achonu C, Abdolell M, Rivard G, Manco-Johnson MJ. A survey of factor prophylaxis in boys with haemophilia followed in North American haemophilia treatment centres. *Haemophilia* 2003; **9**(Suppl. 1): 19–26.
65 Tarantino MD, Lail A, Donfield SM *et al.* Surveillance of infectious complications associated with central venous access devices in children with haemophilia. *Haemophilia* 2003; **9**: 588–92.
66 Ewenstein BM, Valentino LA, Journeycake JM *et al.* Consensus recommendations for use of central venous access devices in haemophilia. *Haemophilia* 2004; **10**: 629–48.
67 Carcao MD, Connolly BL, Chait P *et al.* Central venous catheter-related thrombosis presenting as superior vena cava syndrome in a haemophilic patient with inhibitors. *Haemophilia* 2003; **9**: 578–83.
68 Petrini P. How to start prophylaxis. *Haemophilia* 2003; **9**(Suppl. 1): 83–85;discussion 6-7.
69 National Institute of Diabetes and Digestive and Kidney Diseases. Vascular access for hemodialysis. NIH Publication No. 05-4554. January 2005. Available at kidney.niddk.nih.gov/kudiseases/pubs/pdf/vascularaccess.pdf. Accessed January 17, 2007.
70 Santagostino E, Gringeri A, Berardinelli L, Beretta C, Muca-Perja M, Mannucci PM. Long-term safety and feasibility of arteriovenous fistulae as vascular accesses in children with haemophilia: a prospective study. *Br J Haematol* 2003; **123**: 502–6.
71 McCarthy WJ, Valentino LA, Bonilla AS *et al.* Arteriovenous fistula for long-term venous access for boys with hemophilia. *J Vasc Surg* 2007; **45**: 986–90.
72 Steen Carlsson K, Hojgard S, Glomstein A *et al.* On-demand vs. prophylactic treatment for severe haemophilia in Norway and Sweden: differences in treatment characteristics and outcome. *Haemophilia* 2003; **9**: 555–66.
73 Bohn RL, Avorn J, Glynn RJ, Choodnovskiy I, Haschemeyer R, Aledort LM. Prophylactic use of factor VIII: an economic evaluation. *Thromb Haemost* 1998; **79**: 932–7.
74 Ullman M, Hoots WK. Assessing the costs for clinical care of patients with high-responding factor VIII and IX inhibitors. *Haemophilia* 2006; **12**(Suppl. 6): 74–80.
75 Fischer K, Van Den Berg M. Prophylaxis for severe haemophilia: clinical and economical issues. *Haemophilia* 2003; **9**: 376–81.
76 Astermark J. When to start and when to stop primary prophylaxis in patients with severe haemophilia. *Haemophilia* 2003; **9**(Suppl. 1): 32–6;discussion 7.
77 Chapman JR. Compliance: the patient, the doctor, and the medication? *Transplantation* 2004; **77**: 782–6.
78 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; **353**: 487–97.
79 Lindvall K, Colstrup L, Wollter IM *et al.* Compliance with treatment and understanding of own disease in patients with severe and moderate haemophilia. *Haemophilia* 2006; **12**: 47–51.
80 Evatt BL. The tragic history of AIDS in the hemophilia population, 1982-1984. *J Thromb Haemost* 2006; **4**: 2295–301.
81 Chorba TL, Holman RC, Clarke MJ, Evatt BL. Effects of HIV infection on age and cause of death for persons with hemophilia A in the United States. *Am J Hematol* 2001; **66**: 229–40.
82 Sieger L, Aledort L. Inhibitor challenges in the paediatric setting. *Haemophilia* 2006; **12**: 106–7.
83 Hooiveld MJ, Roosendaal G, Vianen ME, van den Berg HM, Bijlsma JW, Lafeber FP. Immature articular cartilage is more susceptible to blood-induced damage than mature articular cartilage: an in vivo animal study. *Arthritis Rheum* 2003; **48**: 396–403.
84 van Dijk K, Fischer K, van der Bom JG, Scheibel E, Ingerslev J, van den Berg HM. Can long-term prophylaxis for severe haemophilia be stopped in adulthood? Results from Denmark and the Netherlands. *Br J Haematol* 2005; **130**: 107–12.
85 Fischer K, van der Bom JG, Prejs R *et al.* Discontinuation of prophylactic therapy in severe haemophilia: incidence and effects on outcome. *Haemophilia* 2001; **7**: 544–50.
86 Loverin JA, Mensah P, Nokes TJC. Limited prophylaxis in adults with severe haemophilia: a pilot study. *Haemophilia* 2000; **6**: 275.

87 Ewenstein BM. Von Willebrand's disease. *Annu Rev Med* 1997; **48**: 525–42.
88 Luchtman-Jones L, Valentino LA, Manno C. Considerations in the evaluation of haemophilia patients for short-term prophylactic therapy: a paediatric and adult case study. *Haemophilia* 2006; **12**: 82–6.
89 Tarantino MD, Collins PW, Hay CR *et al.* Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. *Haemophilia* 2004; **10**: 428–37.
90 Abshire TC, Brackmann HH, Scharrer I *et al.* Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy–International Kogenate-FS Study Group. *Thromb Haemost* 2000; **83**: 811–6.
91 Lusher JM, Lee CA, Kessler CM, Bedrosian CL. The safety and efficacy of B-domain deleted recombinant factor VIII concentrate in patients with severe haemophilia A. *Haemophilia* 2003; **9**: 38–49.
92 Stieltjes N, Calvez T, Demiguel V *et al.* Intracranial haemorrhages in French haemophilia patients (1991-2001): clinical presentation, management and prognosis factors for death. *Haemophilia* 2005; **11**: 452–8.
93 Kulkarni R, Lusher J. Perinatal management of newborns with haemophilia. *Br J Haematol* 2001; **112**: 264–74.
94 Balkan C, Kavakli K, Karapinar D. Iliopsoas haemorrhage in patients with haemophilia: results from one centre. *Haemophilia* 2005; **11**: 463–7.
95 Bolton-Maggs PH, Stobart K, Smyth RL. Evidence-based treatment of haemophilia. *Haemophilia* 2004; **10**(Suppl. 4): 20–4.

