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“Hemophilia Clinical Consults: Hemophilic Arthropathy, Reduced Bone Density, and Preventive Strategies”

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Background

Bleeding into a joint (hemarthroses) is the most common clinical consequence of hemophilia.^{1,2} In nearly half of all children with severe hemophilia (baseline factor [F]VII or FIX activity <1%), the initial joint hemorrhage occurs during the first year of life,^{2,3} and 90% of children with severe disease experience at least one joint hemorrhage before the age of 4.5 years.^{2,4}

Hemarthrosis is the single most important risk factor for the development of hemophilic arthropathy.² Eighty percent of joint bleeding episodes involve the knees, elbows, and ankles, and patients often develop multiple target joints (the joints that are most commonly affected with repeated bleeding in an individual patient).² Approximately 50% of patients with hemophilia develop permanent changes in the target joint.⁵

Clinical Consequences of Hemarthroses

The presence of blood in a joint triggers an inflammatory process that results in joint swelling and decreased range of motion secondary to pain and spasm, iron staining of the articular cartilage, hypertrophy of the synovial membrane with reactive blood vessels, and macrophages containing

iron.^{2,6} Although blood rapidly clears from the joint space, the pathologic process continues, resulting in both radiographic and clinical changes. Progressive joint damage results in muscle atrophy, osteoporosis, cartilage degeneration with collapse of the joint space, and cyst formation.²

Roentgenographic Classification of Arthropathy

Five stages of arthropathy determined by clinical manifestations and radiographic abnormalities of bones and joints were proposed by Arnold and Hilgartner over 30 years ago. They are summarized in **Table 1** and described below.^{5,7}

Table 1. The Arnold-Hilgartner Classification of Hemophilic Arthropathy	
Stage	Findings
0	Normal joint
I	No skeletal abnormalities; soft-tissue swelling is present
II	Osteoporosis and overgrowth of the epiphysis; no cysts; no narrowing of the cartilage space
III	Early subchondral bone cysts; squaring of the patella; widened notch of the distal femur or humerus; preservation of the cartilage space
IV	Findings of stage III, but more advanced; narrowed cartilage space
V	Fibrous joint contracture; loss of the joint cartilage space; extensive enlargement of the epiphysis; substantial disorganization of the joint

Adapted from Kilcoyne PE, et al. Available at: <http://emedicine.medscape.com/article/401842-overview>. Updated March 21, 2008. Accessed February 18, 2011; and Arnold WD, et al. *J Bone Joint Surg Am.* 1977;59:297-305.

Stage I

In the first stage, there are no skeletal abnormalities visible on the x-rays, but there is soft-tissue swelling secondary to bleeding into the tissues surrounding the joint.⁷

Stage II

Osteoporosis, particularly in the epiphyses, occurs in Stage II, as does overgrowth of the epiphyses, especially in an affected knee or elbow. Joint integrity is maintained, however, with no narrowing of the cartilage space and no bone cysts.²

Stage III

In the third stage, disorganization of the joint is evident on the x-ray, but there is no significant narrowing of the cartilage space (**Figure 1**).² Subchondral cysts, which occasionally communicate with the joint space, are visible, as is so-called squaring of the patella, which presumably reflects an alteration in its structure due to hyperemia. The synovium may be opacified with hemosiderin deposits. The intercondylar notch of the knee and the trochlear notch of the ulna are usually widened. At this stage, the radiographic findings document that the articular cartilage is preserved. This is the final stage at which hemophilic arthropathy may be reversible with treatment.²



Figure 1

Stage III hemophilic arthropathy. The joint changes include so-called patellar squaring, subchondral cysts, and minor irregularities of the joint surfaces, but the cartilage space is preserved. Posted with permission from Arnold WD, et al. *J Bone Joint Surg Am.* 1977;59:287-305. <http://www.jbjs.org>.

Stage IV

The fourth stage is characterized by narrowing of the joint space and cartilage destruction. The changes that first become apparent in Stage III are now more striking.²

Stage V

The end stage is defined by fibrous joint contracture, loss of joint space, extensive enlargement of the epiphyses, and substantial disorganization of the joint structures. There is marked restriction of joint motion, and bleeding episodes may be less frequent. Pathologically, the synovium has been altered so that little or no recognizable synovial tissue remains and the articular cartilage is absent.²

Pathophysiology of Hemophilic Arthropathy

Although the pathogenesis of hemophilic arthropathy is not fully understood, it appears to have similarities with the degenerative joint damage that occurs in osteoarthritis and the inflammatory processes associated with rheumatoid arthritis (RA).^{1,2,7} The early synovial reaction to bleeding in the joint closely resembles RA. Iron deposition in phagocytic cells, synovial hypertrophy, focal aggregations of perivascular inflammatory cells, and early fibrosis of subsynovial tissues all take place. The hypervascularity of the synovium leads to chronic bleeding and the formation of clots on the synovial surface. With organization of the clots and the development of intrasynovial fibrous adhesions, thickening of the synovium occurs with loss of the cartilage space. Pannus formation similar to that in rheumatoid joints is also present but to a lesser degree.²

The cartilage degeneration and joint destruction that occur in the later stages of hemophilic arthropathy resemble osteoarthritis and RA. Osteochondral lesions begin to form, which may be the result of toxic or chemical events, since little or no hemorrhage occurs in the bone.²

Preventive Strategies

Today, patients with severe hemophilia may be managed in one of two ways: prevention (prophylactic therapy) or treatment when bleeding occurs (on-demand or episodic therapy). Large retrospective,

nonrandomized studies of patients followed over 4 decades show that factor prophylaxis initiated at an early age before the onset of recurrent bleeding reduces the incidence of hemophilic arthropathy, the main cause of morbidity and diminished quality of life in patients with severe hemophilia.^{6,8} Preventing or reducing the clinical impact of hemophilic arthropathy by early (primary) prophylaxis allows children with hemophilia to lead normal lives and experience normal psychosocial development (**Figure 2**).^{6,8} This includes the possibility of regular school attendance and engaging in physical and social activities. Overall, data thus far suggest that patients with severe hemophilia on prophylaxis and their families have a better quality of life than patients who receive on-demand treatment.⁸

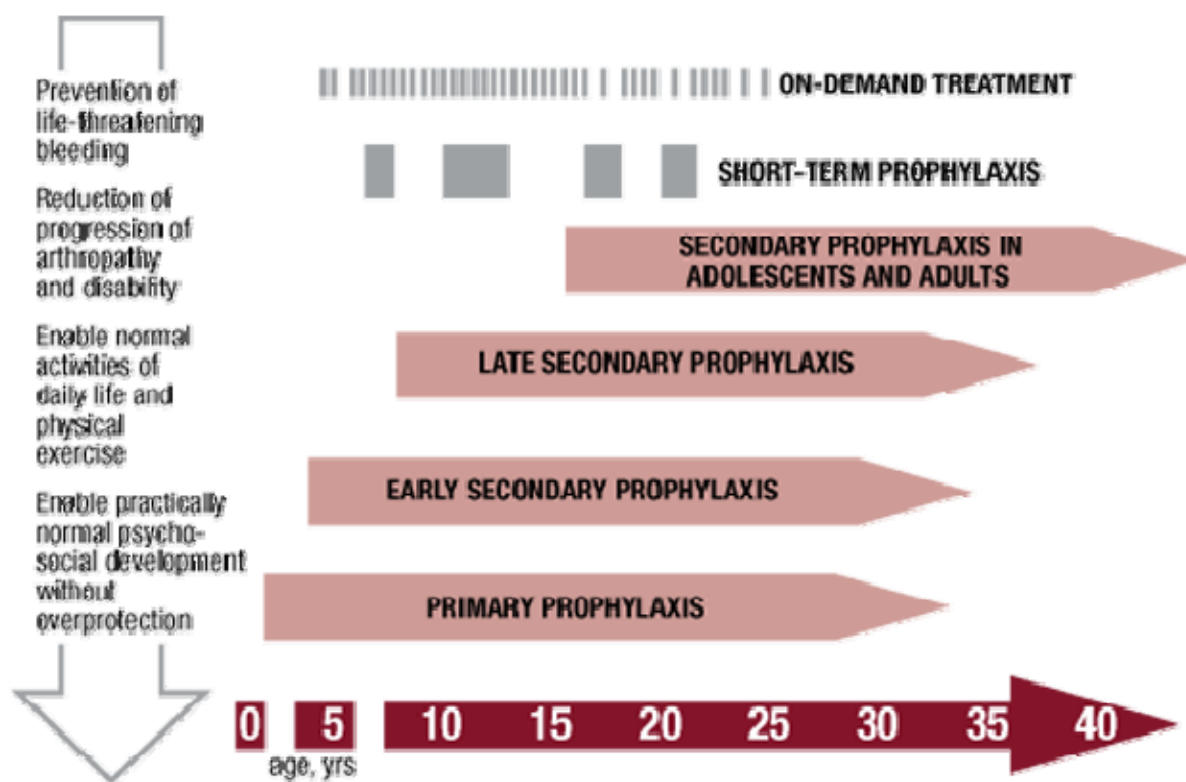


Figure 2

Choices of treatment regimens in hemophilia patients by age and impact on clinical and psychosocial outcomes. Posted with permission from Coppola A, et al. *Blood Transfus.* 2008;6(suppl 2):S4-S11.

Definitions of Prophylaxis

According to the current definitions, primary prophylaxis is intended as regular, continuous long-term treatment started before the patient is 2 years old and/or after no more than one joint hemorrhage, whereas secondary prophylaxis includes all long-term regular treatments not fulfilling these criteria (**Table 2**).⁸ Given its benefits, prophylaxis is recommended as the first choice of treatment for severe

hemophilia by the World Health Organization (WHO) and the World Federation of Hemophilia (WFH). Recently, the Medical and Scientific Advisory Council of the US National Hemophilia Foundation (MASAC) recommended prophylaxis as the standard of care for patients of all ages with severe hemophilia.²

Regimen	Definition
Primary prophylaxis	Long-term continuous (at least 46 weeks/year)** treatment started
by age	before the age of 2 years and prior to any clinically evident joint bleeding
by first bleed	after no more than one joint bleed and before the age of 2 years
Secondary prophylaxis	Long-term continuous (at least 46 weeks/year)** treatment not fulfilling the criteria for primary prophylaxis
Short-term prophylaxis	Short-term regular treatment to prevent bleeding
On-demand therapy	Treatment given when bleeding occurs

*Consensus Perspectives on Prophylactic Therapy for Hemophilia, London 20-21 September 2002, updated by the European Paediatric Network for Hemophilia Management in 2006.

**With the aim of treating 52 weeks/year up to adulthood.

Reprinted with permission from Coppola A, et al. *Blood Transfus*. 2008;6(suppl 2):S4-S11.

Some of the earliest evidence in support of prophylaxis in patients with severe hemophilia came from Sweden, where researchers observed that prophylaxis reduced bleeding and prevented severe joint damage if initiated at an early age.⁶ In an account of 25 years' experience with prophylactic therapy, this group reported that boys with severe hemophilia who began prophylactic treatment with clotting factors between 1 and 2 years of age all had normal joints and were able to lead normal lives.¹⁰ In contrast, studies suggest that initiation of prophylactic treatment later in life may slow the progression of joint damage but does not reverse it. Pettersson scores, a radiologic measure of arthropathy, increase 8% for every year that prophylaxis is delayed after the initial joint hemorrhage.⁴

Additional retrospective studies and anecdotal reports supported the importance of early prophylactic therapy in preventing arthropathy.⁸ However, only in the past few years have prospective, randomized clinical trials provided evidence of the positive impact of prophylactic therapy in patients with severe hemophilia.^{11,12}

Results of the Joint Outcome Study (JOS), a multicenter, randomized, open-label trial conducted in the United States by Manco-Johnson and colleagues, were published in 2007. In this study, the outcomes of patients given prophylactic FVIII infusions on alternate days were compared with those of patients treated with an intensive replacement regimen initiated at the time of a hemarthrosis (on-demand or episodic therapy). The primary outcome was the proportion of children with normal joint structure in 6 index joints (bilateral ankles, knees, and elbows) at 6 years of age. Joint assessments by magnetic resonance imaging (MRI) indicated that all 6 joints were normal in 93% of the children in the prophylaxis group, compared to 55% of children in the episodic therapy group ($P=.002$).¹¹

The recently published European-based ESPRIT study confirmed the feasibility and efficacy of prophylaxis in the prevention of hemarthroses and arthropathy.¹² Forty children with severe hemophilia A and a median age of 4 years were randomized to receive prophylaxis or on-demand therapy. Compared to patients who received on-demand therapy, children on prophylaxis had fewer bleeding episodes in general (0.52 vs 1.08 event/patient/month; $P<.01$) and fewer hemarthroses (0.2 vs 0.53; $P<.01$). Radiographic evaluation disclosed hemophilic arthropathy in 29% of patients on prophylaxis compared to 74% of on-demand patients ($P<.05$).

Benefits of Secondary Prophylaxis

The clinical benefits of secondary prophylaxis have been less extensively studied, especially in adolescents and adults. Tagliaferri et al conducted a survey among members of the Italian Association of Haemophilia Centres (AICE) to assess the effects of secondary prophylaxis started in adolescent and adult hemophiliacs. This retrospective survey collected data on 84 patients with severe hemophilia who switched from on-demand treatment to prophylaxis in adolescence ($n=30$) or adulthood ($n=54$). The switching of the patients to secondary prophylaxis significantly reduced the mean number of total and joint hemorrhages (35.8 vs 4.2 and 32.4 vs 3.3; $P<.01$, respectively) and the days of work/school lost (34.6 vs 3.0, $P<.01$). Furthermore, although adolescent/adult hemophiliacs received about 39% more factor concentrate, with consequently higher costs, during secondary prophylaxis than during on-demand treatment, these higher costs were offset by marked clinical benefits with improved quality of life.¹³

Additional Benefits of Prophylaxis

Recent data suggest new potential benefits of early initiation of prophylaxis in hemophilic children. A protective effect against the development of inhibitors has been shown in a case-control Italian study by Santagostino et al with a 70% reduction of inhibitor risk in children starting prophylaxis at a median age of 35 months.^{8,14} The CANAL study confirmed the protective effects of prophylaxis. In this larger

multinational study, early regular prophylaxis (started at a median age of 20 months) was an independent negative predictor associated with a 60% lower risk of inhibitor development than on-demand treatment.¹⁵

What percentage of your patients with severe hemophilia currently receive prophylaxis?

- 10%
- 25%
- 50%
- >50%

VOTE

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Prophylaxis Underused

As noted earlier, leading medical and scientific organizations all support the use of prophylaxis in patients with severe hemophilia A or B (NHF, WHO, MASAC). Nevertheless, Berntorp reports that in a survey from 147 centers worldwide, the majority (54%) of patients with severe hemophilia A continue to be treated with on-demand therapy, and only 19% receive primary prophylaxis.⁶ In the United States, only 54% of patients with severe hemophilia A and 44% of patients with severe hemophilia B receive some form of prophylactic therapy.¹⁶

What is the most significant barrier to greater use of prophylaxis in your patients with severe hemophilia?

- Cost and availability of clotting factor
- Difficulties associated with venous access
- Patient/caregiver acceptance of long-term treatment
- Adherence

VOTE

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Barriers to Prophylaxis

Some of the barriers that influence the adoption of and adherence to prophylaxis include the cost and availability of clotting factors; complications associated with venous access devices, including infections and thrombosis; the need for therapy as perceived by the patient; and the time required for prophylactic infusions. Among patients with excellent compliance, the time required for prophylaxis was considered the most significant barrier to adherence.⁶ The issues of availability and, in particular, the costs of clotting factor concentrates remain the main barriers to the diffusion of prophylaxis, since these costs are prohibitive particularly for developing countries.⁸

Case Report: Patient Overview

Dosing of the Bypassing Agents

John S. is an 18-year-old African American who presented to our office in 2003 at age 10 with a history of severe hemophilia, right hip pain, and bilateral knee bleeding. A scalp hematoma at birth led to the diagnosis of severe hemophilia A (<1% factor VIII activity), which required a 2-week stay in the NICU for monitoring and management. His mother is a carrier, but there is no other family history of hemophilia. The patient suffered an intracranial hemorrhage shortly after birth that was managed with factor replacement. Inhibitor development was detected at age 2 (titers of 7-221 BU).

Both of John's parents have histories of psychiatric illness, which has complicated the optimal management of his condition. John received no immune tolerance induction therapy (ITI) as a child, and his bleeding was managed on an emergency basis with on-demand therapy. He currently lives with his family and, due to mobility issues and complications related to severe arthropathy, John is obtaining his high school diploma online.

John takes allergy and asthma medications for cat and mold allergies as well as calcium and vitamin D supplements. Acetaminophen and acetaminophen-codeine are available PRN for pain management (**Table 3**).

Table 3. Current Medications

Medication	Dosage
Antihemophilic factor/von Willebrand factor complex (human)	2000 U QOD
rFVIIa	10 mg PRN for daily breakthrough bleeds
Montelukast	10 mg PO daily
Loratadine	10 mg PO daily
Ferrous sulfate	325 mg PO BID
Calcium supplement + vitamin D	600 mg PO BID
Vitamin D	50,000 mcg once a month
Fluticasone propionate and salmeterol	1 puff (230-21 mcg) every 12 hours
Levalbuterol	PRN
Acetaminophen-codeine/acetaminophen	PRN

Preventing Arthropathy in Inhibitor Patients

The development of neutralizing antibodies (inhibitors) against replacement clotting factor is currently considered the most serious complication of hemophilia treatment. Inhibitors may develop in approximately 30% of people with severe or moderately severe hemophilia A and 1% to 6% of people with hemophilia B.¹⁷ A number of genetic and environmental risk factors have been identified, including duration of exposure to clotting factor, ethnicity, and type of gene mutation. The presence of inhibitors

is associated with increased all-cause mortality and morbidity in both severe and mild/moderate hemophilia.^{17,18}

Pediatric patients with hemophilia and inhibitors are at particular risk of recurrent hemarthroses.¹⁹ All patients with inhibitors, and children in particular, face the threat of severe bleeding complications such as limb- or life-threatening bleeds, and are at risk of developing target joints and progressive arthropathy that may lead to permanent disability. Management of these patients should seek to avoid joint damage and support the child's full social and physical development.¹⁹

When a child develops inhibitors, the key aims of management are similar to those for any pediatric hemophilia patient. Management aims to treat acute bleeding episodes promptly, manage complications, prevent recurrent bleeds, and conserve or restore joint function. The overall goal is to support a child's healthy development favoring full integration into a normal social life. To achieve this, inhibitor patients should have access to the same treatment options as noninhibitor patients. Treatment options for children with hemophilia and inhibitors include on-demand therapy with bypassing agents, recombinant activated factor VII (rFVIIa), or plasma-derived activated prothrombin complex concentrate (aPCC).^{17,20}

According to recent expert panel recommendations, systematic approaches are needed for early diagnosis of joint and muscle bleeds in inhibitor patients, which could facilitate rapid treatment. The expert panels suggested exploring new diagnostic techniques used in osteoarthritis to enable earlier diagnosis of hemophilic arthropathy. Overall, the panel concluded that greater emphasis should be placed on education and the patients' psychological needs to enable inhibitor patients to cope more effectively with their disease.²¹

Case Report Part 2: Hemophilic Arthropathy

When John presented to our office in 2003, he had already developed hemophilic arthropathy of both knees. An arthroscopic synovectomy of the right knee was performed in April 2004 and managed with rFVIIa bolus (90 mcg/kg) followed by a continuous infusion (50 mcg/kg/hr) of FEIBA (**Table 4**). In 2007, the patient underwent a left knee arthroscopic synovectomy that was managed with rFVIIa (6000 mcg/kg) followed by a continuous infusion (50 mcg/kg/hr) of FEIBA.

Table 4. Surgical History

- Right knee arthroscopic synovectomy
– rFVIIa bolus (90 mcg/kg) followed by a continuous FEIBA infusion (50 mcg/kg/hr)
- Left knee arthroscopic synovectomy
– rFVIIa (6000 mcg/kg) followed by a continuous FEIBA infusion (50 mcg/kg/hr)
- AVF creation (right brachial artery to cephalic vein; 8-21-08)
- CVAD removal (8-14-08)

On August 1, 2008, John developed septic arthritis caused by *Staphylococcus aureus* infection in his left sacroiliac joint. A CVAD infection with bacteremia developed the next day. The CVAD was removed on August 14 and replaced with an AVF (right brachial artery to cephalic vein) 1 week later.

Arthropathy continued to progress. MRI of the right and left ankles without contrast was performed on February 22, 2010. The right ankle demonstrated mild joint space narrowing with no evidence of joint effusion or bony erosions. MRI of the left ankle revealed moderate left tibiotalar joint effusion with evidence of hemosiderin deposits, and a 12-mm pseudotumor was observed within the tibial epiphysis.

Based on the progression of the arthropathy, the decision was made in September 2010 to begin ITI therapy with antihemophilic factor/von Willebrand factor complex (human) 2000 U QOD and rFVIIa 10 mg PRN for breakthrough bleeds.

Which of the following is the most important barrier to the optimal management of hemophilia patients with inhibitors?

- Time required to do infusions
- Lack of cooperation of the child receiving infusions
- High cost of treatment
- Variable efficacy of each bypassing agent

VOTE

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What treatment strategy do you most frequently employ for your inhibitor patients?

- Inhibitor eradication
- On-demand therapy with bypassing agents
- Sequential use of bypassing agents
- Prophylaxis with bypassing agents

VOTE

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Other Musculoskeletal Complications in Hemophilia

In addition to arthropathy and progressive joint destruction, severe hemophilia has been associated with other bone disorders, most notably osteopenia, reduced bone mineral density (BMD), and the development of osteoporosis.^{2,22-24} Individuals with severe hemophilia A and B may be at risk for osteoporosis because of reduced weight-bearing exercise and hepatitis C infection, although studies have not confirmed the association between osteoporosis and hepatitis C in hemophilia.^{7,22,24}

Numerous investigations indicate that individuals with severe hemophilia have reduced BMD, which, left untreated, can progress to osteoporosis.² Patients at highest risk are those with signs of hemophilic arthropathy.²⁴ Reduced BMD may be a result of limited weight-bearing exercise as well as increased osteoclast activity following recurrent joint bleeds.^{2,7,22,23}

Management Options for Reduced BMD

Swedish studies showed factor prophylaxis in noninhibitor patients improved outcomes and may preserve normal BMD in severe hemophilia.²⁴ Use of factor prophylaxis in early childhood may thus allow more regular physical activities and weight-bearing exercise to preserve BMD and prevent osteoporosis.²⁴ Finally, because osteoporosis may complicate the future treatment of patients with hemophilia, BMD screening of pediatric hemophilia patients is recommended.^{22,23}

Case Report: Osteoporosis Screening

The patient underwent routine evaluation for osteopenia and osteoporosis in April 2009. DEXA bone densitometry of the A.P. spine (Total L1-L4) revealed a T score of -3.4 and a Z score of -.1. The scores were compatible with a classification of osteoporosis with high fracture risk.

Laboratory evaluation demonstrated an intact PTH; magnesium, calcium, and thyroid hormones within normal limits; and phosphorous and vitamin D were low-normal (**Table 5**). Daily calcium supplements and monthly vitamin D injections were prescribed.

Table 5. Osteoporosis Workup: Laboratory Data	
Vitamin D 25-OH Total	30 (30-100) ng/mL Final
Intact PTH	35.3 (22.0-60.0 pg/mL) Final
Calcium	9.4 (8.7-10.7 mg/dL) Final
Ion Ca Circ Dialysis	1.25 H (0.25-0.40 mmol/L) Final
Magnesium	2.2 (1.6-2.7) mg/dL Final
TSH	1.067 (0.350-4.940) μ IU/mL Final
Thyroxine	10.5 (4.9-11.7) mcg/dL Final
Phosphorus	4.6 (2.5-4.6) md/dL Final

Follow-up bone densitometry of the A.P. spine (Total L1-L4) was performed 13 months later, in May 2010. At that time, the T score was -3.0 and the Z score was -2.1. Although BMD had increased from the previous examination, these findings are compatible with a WHO classification of osteoporosis.

Densitometry of the left proximal femur (total) revealed a T score of -2.4 and a Z score of 1.9, demonstrating an increase in BMD from previous examination but also compatible with a WHO classification of osteopenia.

Conclusions

Arthropathy is a clinical hallmark of repeated joint bleeding in patients with hemophilia and a leading cause of pain, disability, and diminished quality of life. Although the exact pathogenesis of arthropathy is not known, data from RA and osteoarthritis may expand our knowledge of this complication of hemophilia, enabling us to develop better treatments and strategies for this disabling condition.

At present, management strategies for hemophilic arthropathy should focus on preventing the musculoskeletal complications of recurrent joint bleeding. Starting prophylaxis earlier in life and after very few joint hemorrhages has been associated with better joint outcomes and is now considered the standard of care.⁸ In addition, BMD screening of young hemophilia patients is also recommended to prevent the development of osteoporosis.²³ Finally, rapid diagnosis of joint bleeding, along with the use of bypassing agents and increased patient education, can help reduce the risk of long-term complications in inhibitor patients and improve their quality of life.¹⁷

Listen to Angela Forsyth, PT, DPT, and Nick Zourikian, PT, discuss the
“Pathophysiology of Joint Bleeding and Synovitis: The Impact on Joint Health”

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Listen to noted hemophilia experts James V. Luck, Jr, MD, and Mauricio Silva, MD,
discuss the *“Safe Use of Radiosynovectomy for Chronic Hemophilic Synovitis.”*

[Enter Program](#)

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