1 Haemophilia A and Haemophilia B

Complications of Treatment

Haemophilia and Immune Tolerance Therapy

Question/ Case	A 2.5-year-old boy has severe haemophilia A diagnosed at 11 months of age and no family history. An inhibitor was detected at 22 months after 25 exposures to FVIII lacking the B domain, Refacto™. The inhibitor titre never rose above 17 BU. The genetic defect was due to a large FVIII deletion of exons 7–10. He was started on low-dose immune tolerance for 8 months with no response. Should we consider change of regimen or any additional therapies? He receives 25 U/kg per infusion three times a week and bleeds are treated with rVIIa. The inhibitor titres have been 5.1, 5.1, 11.6, 10, 17.5, 17.5, and 18 BU.

Response from **Keith Hoots, MD**
Gulf States Hemophilia & Thrombosis Center, University of Texas Houston Health, Houston, Texas, USA

This is, unfortunately, not a unique situation since 25–30% of attempts at immune tolerance induction (ITI) fail. This may be even higher for patients with large deletions, although data are still not sufficient to firmly draw that conclusion. At this stage of ITI after approximately 8 months of poor response, I typically consider altering the regimen by escalating the dosage and frequency when a low-dose regimen has been employed. You did not say whether the inhibitor has stayed at a plateau around 20 BU or if there has been a significant anamnesis that leaves the child with a much higher titre now. The latter scenario may lessen the likelihood of successful ITI even after increasing the dose and the frequency. Also, I would recommend a high-dose regimen for immune tolerance, that is 100–200 U/kg FVIII per dose daily. There is some suggestion in the literature that an intermediate-purity product may be successful when ultra-high-purity products have failed to induce IT; this is still far from proven but it is an option to offer the

parents. If they prefer to continue the recombinant route, I still think there is a real, as-yet-undefined possibility that a high-dose regimen could work – even after initial ITI failure. I do not think that immune suppression therapy should be a component of the ITI at this stage of the process.

The Haemophilic Ankle: An Update

Question	What is the latest information regarding the treatment of the haemophilic arthropathy in the ankle?

Response from **E. Carlos Rodriguez-Merchan, MD, PhD**
La Paz University Hospital; and Autonoma University, Madrid, Spain

Introduction

It is well known that in haemophilia the ankles tend to bleed beginning at an early age of 2–5 years. The synovium is only able to reabsorb a small amount of intra-articular blood; if the amount of blood is excessive, the synovium will hypertrophy as a compensating mechanism, so that eventually the affected joint will show an increase in size of the synovium, leading to hypertrophic chronic haemophilic synovitis. The hypertrophic synovium is very richly vascularized, so that small injuries will easily make the joint rebleed. The final result will be the vicious cycle of haemarthrosis–synovitis–haemarthrosis, which eventually will result in haemophilic arthropathy (Figure 1.1a and b).

Pathogenesis of Synovitis and Cartilage Damage in Haemophilia: Experimental Studies

There are three articles on the pathogenesis of synovitis and cartilage alterations in haemophilic joints. In the first article, Hooiveld *et al.* investigated the effect of a limited number of joint bleedings, combined with loading of the affected joint, in the development of progressive degenerative joint damage [1]. They concluded that experimental joint bleedings, when combined with loading (weight bearing) of the involved joint, result in features of progressive degenerative joint damage, whereas similar joint haemorrhages without joint loading do not. The authors suggest that this might reflect a possible mechanism of joint damage in haemophilia. In two other articles, haemophilic arthropathy was studied in animal models [2,3]. Despite these three

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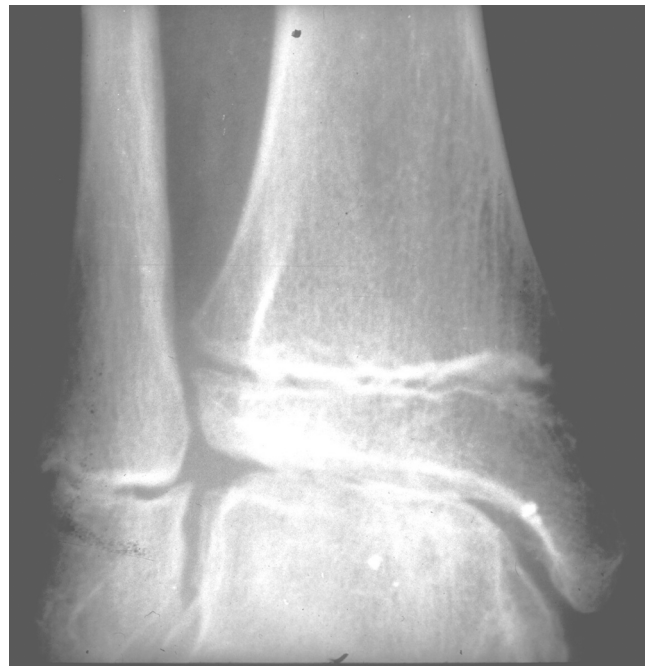

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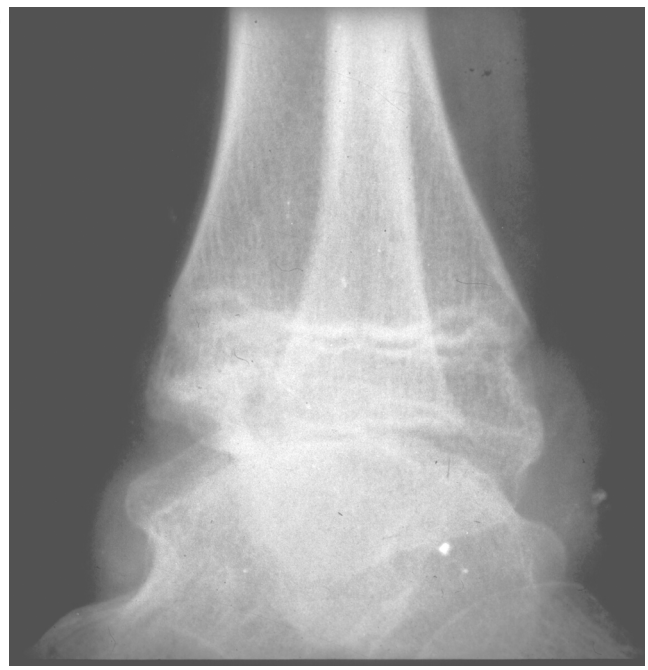


Figure 1.1 Haemophilic arthropathy of the ankle in a young boy: (a) A/P view and (b) lateral view.

interesting articles, the pathogenesis of haemophilic arthropathy is poorly understood.

The best way to protect against haemophilic arthropathy (cartilage damage) is primary prophylaxis beginning at a very early age. Starting prophylaxis gradually with once-weekly injections has the presumed advantage of avoiding use of a central venous access device, such as a PortaCath, which is often necessary for frequent injections in very young boys. The decision to institute early full prophylaxis by means of a port has to be balanced against the child's bleeding tendency, the family's social situation, and the experience of the specific haemophilia centre. The reported complication rates for infection and thrombosis have varied considerably from centre to centre. Risk of infection can be reduced by repeated education of patients and staff, effective surveillance routines, and limitations on the number of individuals allowed to use the device. In discussing options for early therapy, the risks and benefits should be thoroughly discussed with the parents. For children with inhibitors needing daily infusions for immune tolerance induction, a central venous line is often unavoidable and is associated with an increased incidence of infections.

From a practical point of view, radioactive synoviorthesis, together with primary prophylaxis to avoid joint bleeding, can help halt haemophilic synovitis. Ideally, however, synoviorthesis should be performed before the articular cartilage has eroded. Radioactive synoviorthesis is a relatively simple, virtually painless, and inexpensive treatment for chronic haemophilic synovitis, even in patients with inhibitors, and is the best choice for patients with persistent synovitis.

Synoviorthesis

Radiation synovectomy consists of destruction of synovial tissue by intra-articular injection of a radioactive agent. Radioactive substances have been used for the treatment of chronic haemophilic synovitis for many years (Figures 1.2 and 1.3). Radiation causes fibrosis within the subsynovial connective tissue of the joint capsule and synovium. It also affects the complex vascular system, in that some vessels become obstructed; however, articular cartilage is not affected by radiation.

The indication for medical synovectomy is chronic haemophilic synovitis causing recurrent haemarthroses, unresponsive to treatment. Synoviorthesis is the intra-articular injection of a certain material to diminish the degree of synovial hypertrophy, and decrease the number

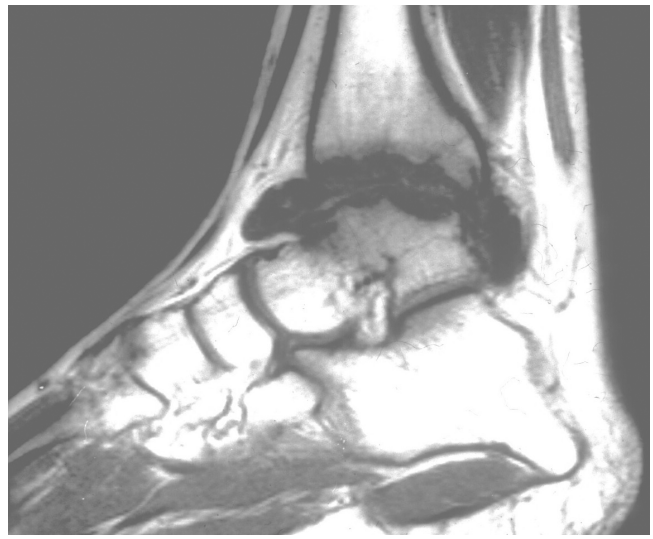


Figure 1.2 Lateral view of an MRI of the ankle showing an intense degree of haemophilic synovitis. Radiosynoviorthesis should then be indicated early.

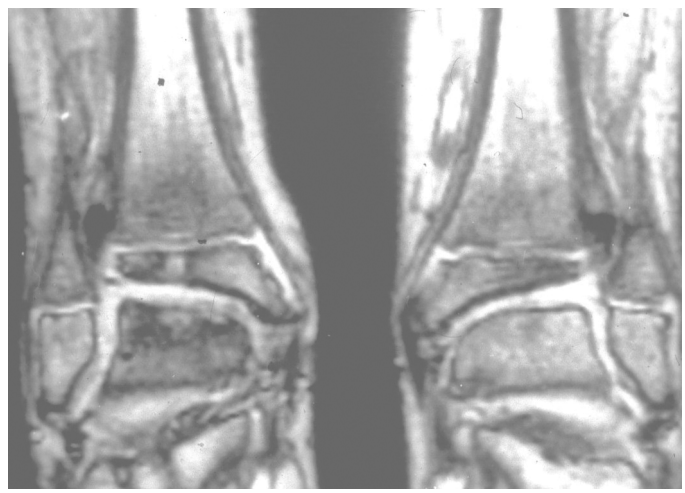


Figure 1.3 MRI anteroposterior views of the two ankles of the same child. On the left (right ankle) the distal tibial physis and the talus are severely affected in comparison with the same structures of the left ankle. Although radiosynoviorthesis could be indicated in both ankles, it will be much better in the left ankle.

and frequency of haemarthroses. There are two basic types of synoviortheses: chemical synoviorthesis and radiation synoviorthesis. On average, the efficacy of the procedure ranges from 76% to 80% and can be performed at any age. The procedure slows the cartilaginous damage, which intra-articular blood tends to produce in the long term.

Synoviorthesis can be repeated up to 3 times at 3-month intervals if radioactive materials are used (yttrium-90, phosphorus-32, and rhenium-186), or weekly up to 10–15 times if rifampicin (chemical synovectomy) is used. After 30 years of using radiation synovectomy worldwide, no damage has been reported in relation to the radioactive materials. Radiation synovectomy is currently the preferred procedure when radioactive materials are available; however, rifampicin is an effective alternative method if radioactive materials are not available. Several joints can be injected in a single session, but it is best to limit injections to two joints at the same time.

There are two interesting articles that focus on the treatment of chronic haemophilic synovitis. Corrigan *et al.* have used oral D-penicillamine for the treatment of 16 patients [4]. The drug was given as a single dose in the morning before breakfast. The dose was 5–10 mg/kg body weight, not to exceed 10 mg/kg in children or 750 mg/day in adults. The duration of treatment was 2 months to 1 year (median 3 months). Ten patients had an unequivocal response, three had a reduction in palpable synovium, and three had no response. Minor reversible drug side effects occurred in two patients (proteinuria in one and a rash in the second).

Radossi *et al.* have used intra-articular injections of rifamycin [5]. Among a large cohort of nearly 500 patients, they treated 28 patients during a 2-year period. The patients followed an on-demand replacement therapy programme and developed single or multiple joint chronic synovitis. The indications for synoviorthesis were symptoms of chronic synovitis referred by patients reported in a questionnaire. In Radossi's series there were five patients with inhibitors to factor VIII [5]. Their average age was 34 years. Rifamycin (250 mg) was diluted in 10 ml of saline solution and 1–5 ml was then injected into the joint. The follow-up ranged from 6 to 24 months. Thirty-five joints were treated with 169 infiltrations in total. Rifamycin was injected once a week for 5 weeks, that is the patient had to come to hospital at weekly intervals. Twenty-four procedures were considered effective in 19 patients according to the evaluation scale, while six

treatments were considered fair to poor. Five patients (six joints) with anti-factor VIII inhibitors were treated. In four joints the results were good, while in the two remaining joints the results were poor.

There are two main limitations for the use of antibiotics in synoviorthesis: the procedure is painful, and it should be repeated weekly for many weeks to be effective. In fact, Radossi's schedule included injection of rifamycin into the joints once a week for 5 weeks [5]. However, the authors make no mention of the pain associated with the injections. They also state that rifamycin may be indicated when radiosynoviorthesis is not available, contraindicated for medical reasons, or not accepted by patients. To the best of my knowledge, I do not know of any medical contraindications to radiosynoviorthesis, or why patients should reject such an efficient and safe procedure. The Italian authors state that, to date, they cannot say if their programme is able to delay long-term functional impairment because of the lack of a longer follow-up. However, according to their preliminary experience, they consider that rifamycin synoviorthesis appears to be effective in reducing joint pain and improving the range of motion.

The study of Corrigan *et al*. who used D-penicillamine has two main limitations: the small number of patients, and the lack of use of ultrasound and/or magnetic resonance imaging (MRI) for diagnostic purposes. It is also important to emphasize two potential side effects of D-penicillamine: aplastic anaemia and renal disease. To minimize the possibility of side effects, Corrigan and co-workers have suggested that the drug be used on a short-term basis (i.e. 3–6 months) and the amount restricted (see reference for dosing) [4].

I agree with the authors' statement that synoviorthesis (radiosynovectomy) using intra-articular yttrium-90 or phosphorus-32 has been reported to be effective. However, I disagree with the authors' comment that this is an invasive procedure whose long-term safety has not been established. In fact, the long-term safety has been established after 30 years of using radiation synovectomy worldwide, with no damage reported in relation to the radioactive materials [2].

It is important to emphasize that controversy exists regarding which type of synoviorthesis is better. Most authors in developed countries use radiosynoviorthesis (yttrium-90 and phosphorus-32), while others utilize chemical synoviorthesis mainly because of the lack of availability of radioactive materials. My view is that further studies with an adequate number of patients and an appropriate follow-up are needed to confirm the efficacy of oral penicillamine and rifamycin synoviorthesis for chronic haemophilic synovitis. In other words, the aforementioned

articles are preliminary studies requiring confirmation. Meanwhile, the general recommendation is to use yttrium-90 or phosphorus-32 synoviorthesis, because these agents have proved to be efficient for the treatment of chronic haemophilic synovitis, even in patients with inhibitors. Moreover, no complications related to the use of radioactive materials have been reported after 30 years of being used worldwide.

Editors' Note

In 2005 after the initial publication of this monograph, a report of pain of patients treated with P32 radioactive synovectomies was published. These 2 boys developed ALL, one T-cell ALL & one precursor B-cell ALL, within one year of radioactive synovectomy. Dunn AL, *et al*., *J Thromb Haemost* 2005;3: 1541–2.

Haemophilic Arthropathy of the Ankle and Subtalar Joints

Chang *et al*. have made an analysis of podiatric surgery in haemophilic arthropathy of the ankle and subtalar joints [6]. This condition often results in severe pain and physical limitations. Conservative treatment (splints, braces, wedge insoles, and calipers) should always be attempted prior to surgery. The most common surgical approaches are synovectomy, joint debridement, arthroplasty, and arthrodesis. Finally, the authors describe an interesting case of avascular necrosis of the talus, ankle/joint degeneration with periarticular osseous fragmentation, a cyst in the medial aspect of the talar dome, and a fracture of the os trigonum with resultant hypertrophy of soft tissues.

The most common deformities affecting the ankle and subtalar joints are fixed plantar flexion due to degeneration of the anterior part of the ankle, varus hindfoot due to malalignment of the subtalar joint, and valgus rotation of the ankle due to differential overgrowth of the distal tibial epiphysis during adolescence or progressive arthropathy during maturity. The process always starts with a single or a recurrent haemarthrosis, which is extremely painful, and results in an equinus or a plantar flexion position of the ankle. This deformity, initially correctable, eventually becomes fixed.

Probably the first treatment to be considered for recurrent ankle haemarthroses is radiosynoviorthesis. Another common procedure to prevent fixed equinus deformity is lengthening the Achilles tendon.

Sometimes a large osteophyte develops on the anterior part of the ankle, which can cause severe pain. Surgical removal of the osteophyte (queilectomy) is sometimes indicated. When the ankle joint shows an important degree of malalignment, a supramalleolar valgus or varus osteotomy is indicated.

In advanced haemophilic arthropathy, an ankle arthrodesis or arthroplasty should be considered. The main indications for these are intractable pain not relieved by alternative treatments and severe deformity. Regular prophylactic transfusions of clotting factor may prevent recurrent bleeds and further development of haemarthrosis. Ankle arthrodesis has been associated with better long-term results than ankle arthroplasty (rarely performed in haemophilia today).

[For more detailed description of ankle haemarthropathy, the reader is referred to the original submission by Dr Rodriguez-Merchan, www.haemostasis-forum.org.]

Rehabilitation

The importance of preoperative and postoperative rehabilitation of the ankle joint in haemophilia must be emphasized. Children must utilize the resources available and seek early consultation with their centre's rehabilitation physician and physiotherapist. Using the techniques

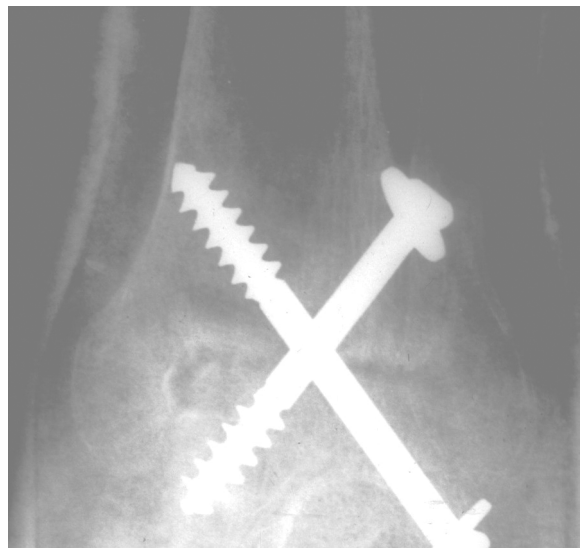


Figure 1.4 Ankle arthrodesis with two crossed screws in a haemophilia patient with severe haemophilic arthropathy of the ankle.

available, rehabilitation has been shown to speed recovery, reduce pain, and prevent contractures. Physiotherapy is important to ankle rehabilitation of patients following surgical procedures, and the physical therapist must work closely with the orthopaedic surgeon.

Conclusions

Radiation synoviorthesis is a very effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage. It can also be used in patients with inhibitors with minimal risk of complications.

Radioactive synoviorthesis is the best choice for patients with persistent synovitis. Personal experience and the general recommendation among orthopaedic surgeons and haematologists are that when three early consecutive synoviortheses (repeated every 3 months) fail to halt synovitis, a surgical synovectomy (open or by arthroscopic) should be immediately considered. For advanced haemophilic arthropathy of the ankle, the best solution is an ankle arthrodesis (Figure 1.4) [7].

References

1 Hooiveld MJ, Roosendaal G, Jacobs KM, Vianen ME, van den Berg HM, Bijlsma JW, *et al*. Initiation of degenerative joint damage by experimental bleeding combined with loading of the joint: a possible mechanism of hemophilic arthropathy. *Arthritis Rheum* 2004;50(6):2024–31.

2 Hakobyan N, Kazarian T, Jabbar AA, Jabbar KJ, Valentino LA. Pathobiology of hemophilic synovitis I: overexpression of mdm2 oncogene. *Blood* 2004;104(7): 2060–4.

3 Valentino LA, Hakobyan N, Kazarian T, Jabbar KJ, Jabbar AA. Experimental haemophilic synovitis: rationale and development of a murine model of human factor VIII deficiency. *Haemophilia* 2004;10(3):280–7.

4 Corrigan Jr JJ, Damiano ML, Leissinger C, Wulff K. Treatment of chronic haemophilic synovitis in humans with D-penicillamine. *Haemophilia* 2003;9(1): 64–8.

5 Radossi P, Baggio R, Petris U, De Biasi E, Risato R, Davoli PG, *et al*. Intra-articular rifamycin in haemophilic arthropathy. *Haemophilia* 2003;9(1):60–3.

6 Chang TJ, Mohamed S, Hambleton J. Hemophilic arthropathy: considerations in management. *J Am Podiatr Med Assoc* 2001;91(8):406–14.

7 Rodriguez-Merchan E. *The Haemophilic Joints: New Perspectives*. Oxford: Blackwell, 2003.

The Haemophilic Knee: An Update

Question	What is the latest information on the treatment of haemophilic arthropathy in the knee?

Response from **E. Carlos Rodriguez-Merchan, MD, PhD**
La Paz University Hospital; and Autonoma University, Madrid, Spain

Figure 1.5 shows hypertrophic haemophilic synovitis in the knee. Synovectomy of the knee is similar to that in the ankle (see The Haemophilic Ankle: An Update).

Surgical synovectomy may be done through an open technique or by arthroscopic means. At the knee, arthroscopic synovectomy is preferred and the open procedure is reserved for when the arthroscopic technique fails to control the synovitis. Open synovectomy should be performed through a medial parapatellar approach, and a synovectomy as complete as possible should be carried out (Figure 1.6).

Arthroscopic synovectomy should be done through three portals (anterolateral, anteromedial, and lateral or medial suprapatellar

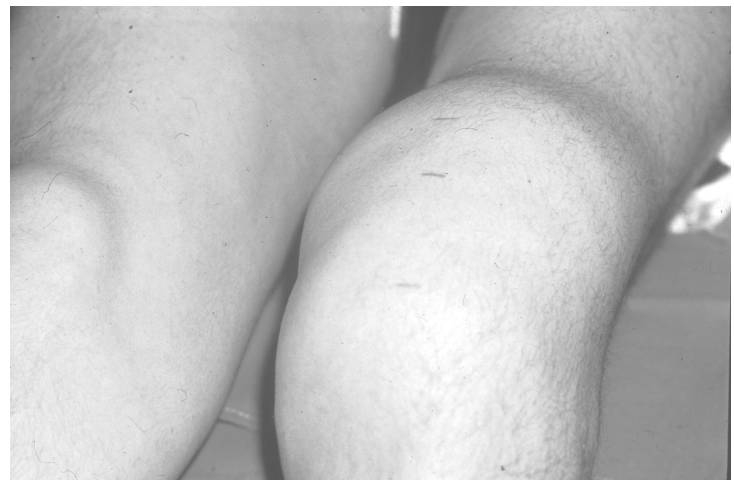


Figure 1.5 Clinical view of a haemophilic knee with intense synovitis (take the contralateral side for comparison).

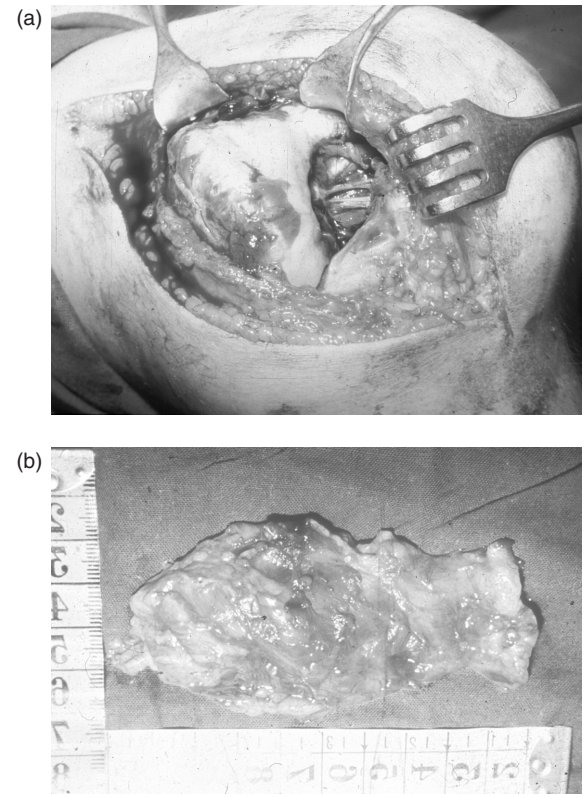


Figure 1.6 Open surgical synovectomy sometimes is needed for the treatment of chronic haemophilic synovitis: (a) intraoperative view of the synovium and (b) macroscopic view of the resected synovial tissue.

portals). In other words, at least three portals are needed to perform a "complete" synovectomy. The synovectomy should be performed with a motorized resector. After surgical synovectomy, the knee should be immobilized in a Robert Jones dressing for 3 days and active movement encouraged. Holmium:Yag laser would appear to be superior to conventional arthroscopic synovectomy, which utilizes mechanical devices, because laser therapy might improve the quality of local haemostasis and the rapidity of postoperative recovery.

Knee Flexion Contractures

The management of an articular contracture in a patient with haemophilia represents a major challenge (Figure 1.7). The treatments available are physiotherapy, orthotics and corrective devices, and surgical

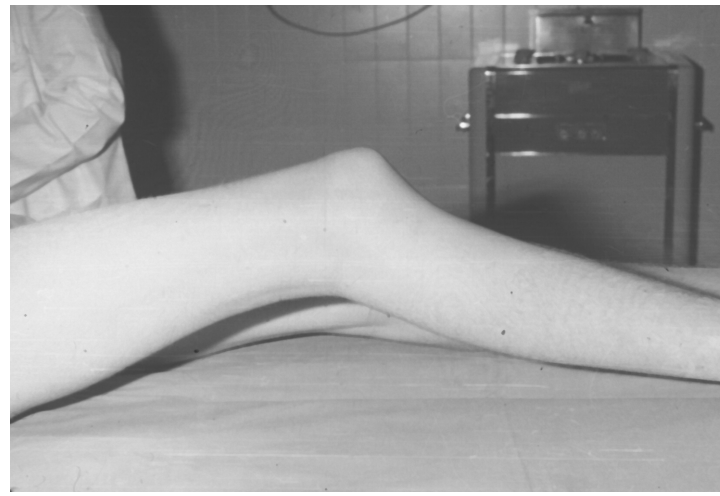


Figure 1.7 Clinical view of a knee joint with fixed flexion contracture.

procedures. End-stage arthropathy of the knee is the most frequent cause of severe pain and disability in haemophiliacs. Some patients have such severe arthropathy that a total joint arthroplasty is required.

Severe Haemophilic Arthropathy

There are a number of orthopaedic procedures that can be carried out in the haemophilic knee when a severe degree of arthropathy is reached (Figure 1.8).

Joint Debridement

A joint debridement is commonly performed in young patients suffering from severe haemophilic arthropathy, who are too young for a total joint replacement. In other words, debridement is a procedure that can alleviate articular pain and bleeding for a number of years, delaying the need for a total joint arthroplasty. A joint debridement consists of the opening of the joint to remove the existing osteophytes, and resect the synovium. Some authors do not believe in the efficacy of debridement, and therefore when facing a severe degree of arthropathy in a young patient, they recommend a total joint replacement. It should be emphasized that if debridement fails, a joint arthroplasty can be performed by the same approach. Some authors perform joint debridement by arthroscopic means with results similar to those obtained by open surgery. In many occasions, a synovectomy

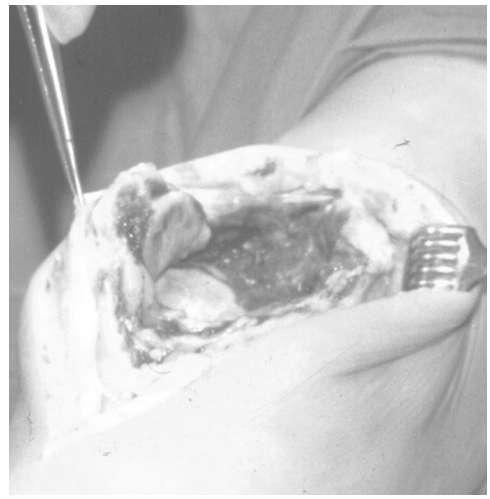


Figure 1.8 Severe haemophilic arthropathy.

and a debridement are performed together, because haemophilic synovitis and early arthropathy commonly coexist. Again, postoperative rehabilitation is paramount to avoid loss of range of motion and, therefore, adequate control of rebleeding is essential.

Alignment Osteotomy

Sometimes, during childhood, adolescence, or early adulthood, some haemophilic joints suffer from an alteration of the normal axis. It is common that haemophilic ankles and knees show varus, valgus, and flexion deformities. When the misaligned joint is painful, the patient will need an alignment osteotomy. The most common osteotomies performed in haemophiliacs are proximal tibial valgus osteotomy (Figure 1.9), supracondylar femoral varus osteotomy, ankle alignment osteotomy, and knee extension osteotomy.

In all of them, the rationale is to produce a fracture at an adequate area to re-align the joint to a normal axis. After the osteotomy, it would be necessary to get an adequate bone fixation by any kind of internal fixation device. It is interesting to note that sometimes I have corrected a flexion contracture of the knee at the same time as a spontaneous supracondylar fracture of the femur.

Curettage of Subchondral Bone Cysts

Some haemophilic patients present great subchondral cysts on the proximal tibia. When such cysts are symptomatic, curettage and filling with fibrin glue and/or cancellous bone graft should be recommended (Figure 1.10).

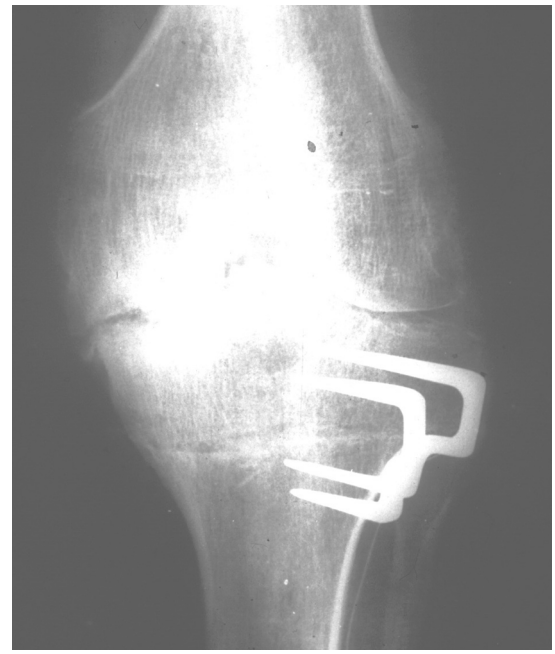


Figure 1.9 Valgus osteotomy for the correction of a varus deformity fixed by means of two staples.

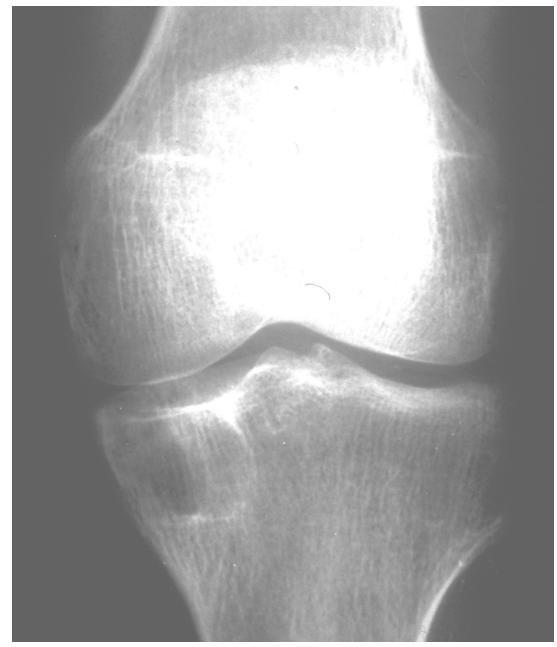


Figure 1.10 Subchondral cyst in the proximal tibia.

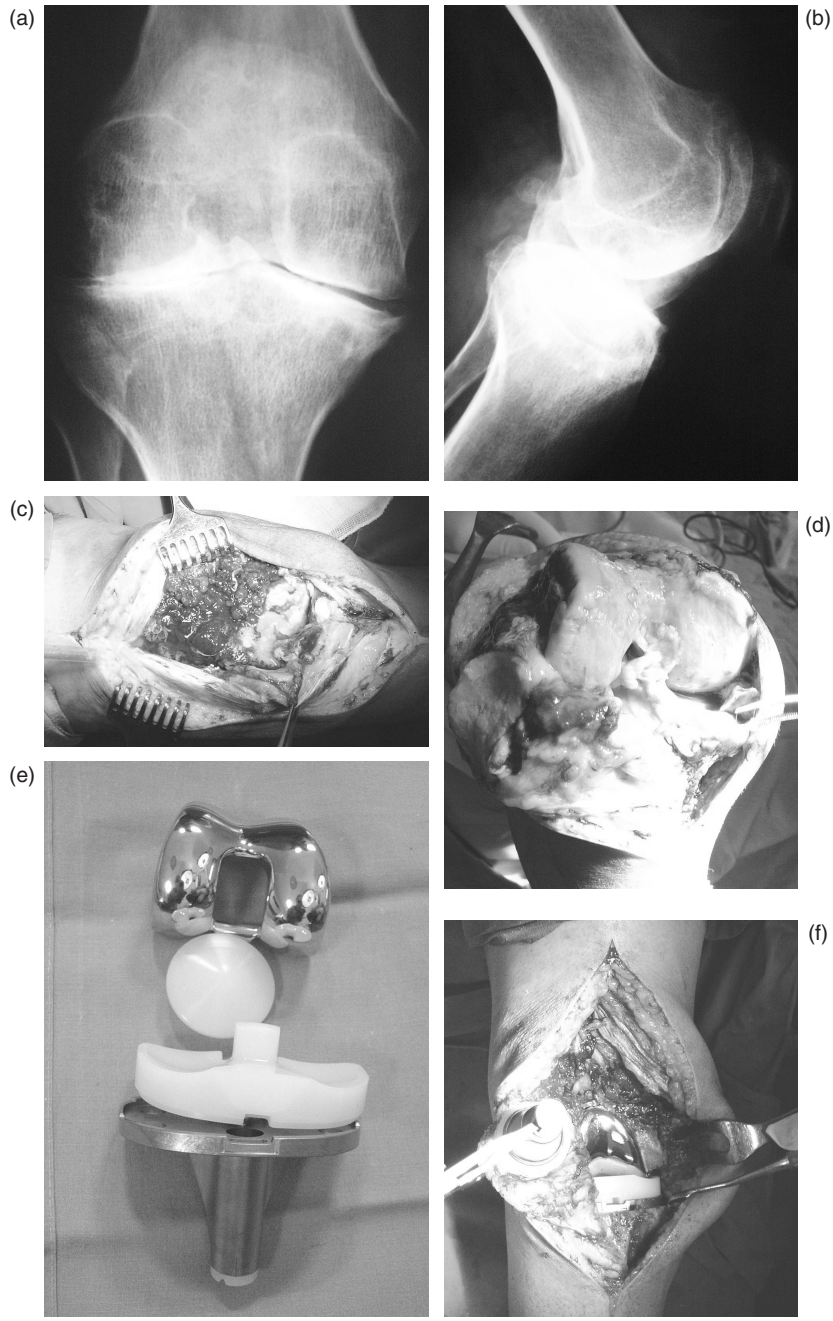


Figure 1.11 TKA in a young haemophilic patient: (a) preoperative AP radiograph; (b) lateral preoperative view; (c) intense synovitis can be noted; (d) severe arthropathy is seen; (e) prosthetic components; (f) TKA implanted.

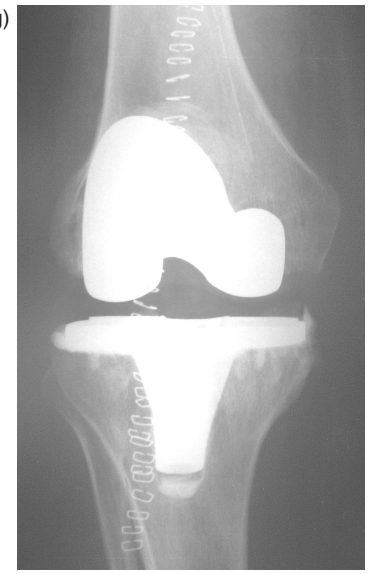
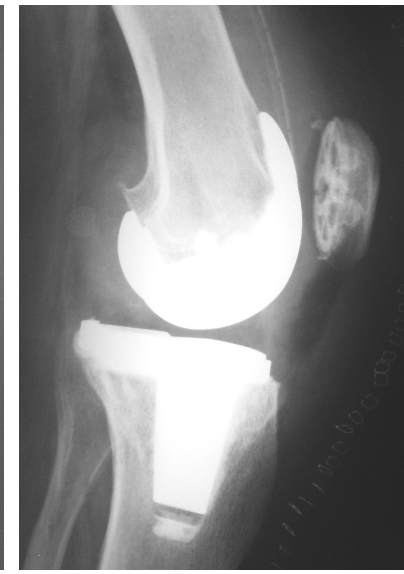
(g)   (h)

Figure 1.11 (continued) (g) postoperative AP radiograph; and (h) postoperative lateral view.

Total Knee Arthroplasty

Between the second and the fourth decades, many haemophilic patients develop severe articular destruct ion. For the knee, the best solution is a total knee arthroplasty (TKA) (Figure 1.11). The role of total knee replacement in persons with haemophilia is very important. Haemophilic patients infected by human immunodeficiency virus are at risk of bacterial and opportunistic infections because of immunosuppression. In these patients, the risk of infection after orthopaedic surgery is of considerable concern. Arthroplasty appeared to have seven times the risk of infection than other procedures.

Total knee replacement for advanced haemophilic arthropathy has good or excellent results in about 85% of cases. The principal risk is late infection that can occur regardless of HIV status. However, this risk appears increased in patients with CD4 counts under 200/μl. Although the message of this article may seem conservative, it should not be inferred that a total knee replacement should be avoided in an HIV-positive haemophilic patient today, but that the orthopaedic surgeon, treatment team, and the patient should weigh the risks and benefits carefully.

Conclusions

Radiation synoviorthesis is a very effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage. It can also be used in patients with inhibitors with minimal risk of complications.

Radioactive synoviorthesis is the best choice for patients with persistent synovitis. Personal experience and the general recommendation among orthopaedic surgeons and haematologists are that when three early consecutive synoviortheses (repeated every 3 months) fail to halt synovitis, a surgical synovectomy (open or by arthroscopy) should be immediately considered.

For advanced haemophilic arthropathy of the knee, the best solution is a total knee replacement. In polyarthritic conditions the repair of a single joint may not improve functional ability, and the aim should be to create a functional limb. Some authors have reported the use of multiple joint procedures on haemophilic patients in a single operative session (double knee arthroplasty). This succeeded in achieving a functional limb. The complication rate was less than expected and the rehabilitation period was relatively short [1].

[For a more detailed discussion, please see the original submission by Dr. Rodriguez-Merchan at www.haemostasis-forum.org.]

Editors' Note

Please see the note on the two cases of ALL following radioactive synovectomies in the chapter on the hemophilic ankle.

Reference

1 Rodriguez-Merchan E. *The Haemophilic Joints: New Perspectives*. Oxford: Blackwell, 2003.

Combined Haemophilia A and B Carrier

Question/ Case	I am a genetic counselling student. A 35-year-old man with haemophilia A presented recently. His partner is a confirmed carrier of haemophilia B. In evaluating the pattern of X-linked recessive inheritance with an affected male and a carrier female, the question arose as to whether a female carrier of both haemophilias A and B would be more severely affected than would a carrier of either one alone.

Response from **Edward Tuddenham, MD**
Royal Free Hospital, London, UK

I find this a very interesting question, particularly as I have been working on combined factor V and VIII deficiency for the last 4 years. In that particular combined deficiency the levels of factors V and VIII range from 5% to 20%, but even individuals with the lowest levels did not bleed more than one would expect with a single factor deficiency. The best explanation I can give for this is that the rate-limiting step for one factor does not affect the rate limitation set by the other factor.

The speed of an army is that of the slowest soldier, but if there are two equally slow soldiers that does not slow things up any more. Now, in the case of factors VIII and IX one is a cofactor for the other and they actually form a binary complex, which activates factor X. I think the slowest soldier argument applies to this and, therefore, would advise that a carrier of factors VIII and IX would not have a greater bleeding risk than a carrier of either deficiency alone. However, an additional consideration is that the couple in question, should they have a double-carrier daughter, will have transmitted the defects on different X chromosomes.

Therefore, in the process of X inactivation (Lyonisation), the levels of the factors will be reciprocally affected so that their sum is 100%. In the worst case of extreme Lyonisation, one factor would be normal and the other zero. The net effect of all this is that the bleeding chances of a double-carrier daughter are exactly the same as those of a single-carrier daughter, neither better nor worse.

Things get a bit more complicated when the double-carrier daughter has offspring. Due to meiotic crossover, her children can be of eight different types: normal males/normal females; double-carrier females/doubly affected males; haemophilia A carriers/haemophilia A males; haemophilia B carriers/haemophilia B males. I leave it to the questioner (who is a student of human genetics) to work out the expected proportions based on the fact that the loci F8C and F9 are about 30 centiMorgans apart on Xq (2.8 and 2.6). Obviously, the worst-case scenario is a doubly affected male.

However, that just means that he would have to use a mixture of factors VIII and IX for therapy.

Editors' Note

Professor Tuddenham's answer is supported by experiments in haemophilic dogs. It has been shown that combined haemophilias A and B in male or female dogs bleed no more than dogs with either defect alone. As stated by Professor Tuddenham, they require replacement with both factors VIII and IX.

A Complex Case of Haemophilia with HIV and Hepatitis C

Question/ Case	A 17-year-old male with severe haemophilia A is on prophylaxis with recombinant FVIII. He is on his high-school varsity team and, so far, has had no problems with bleeds. He was found to be HIV positive by ELISA and western blot tests. Ten years later, his HIV viral load was found to be <400 copies/ml by PCR analysis. The most recent HIV-1 PCR RNA quantitative test was <25 (normal = 0–25) copies/ml. His CD4 count has varied between 518 and 910 cells/μl. He has not required anti-retroviral therapy. His most recent HCV RNA is approximately 450,000 copies/ml. His ALT and AST are normal. The patient does not know about his HIV or HCV status, and the parents have steadfastly refused permission for the health team to discuss this with him. They have, however, allowed discussions of universal precautions. The university lawyers have upheld the parents' rights. My questions are as follows: (1) Would you treat this asymptomatic patient for HIV or HCV or both? (2) If, in view of the low HIV viral load and normal liver function, treatment is not yet required, then what arguments can one make about telling the patient his status (both the parents and the patient swear that he is not sexually active)? (3) In a co-infected patient, does HIV viral load or HCV RNA load have any prognostic implications in the face of normal liver function? (*Note*: The parents do not want a liver biopsy.)

Response from **Margaret Ragni, MD**
University of Pittsburgh Physicians, Pittsburgh, Pennsylvania, USA

The case presented is of interest from both a scientific and an ethical perspective. It is very likely, in view of both the patient's age and immune function "after at least 13 years of HIV infection he maintains a CD4 count of 520 cells/μl and undetectable HIV viral load", that he is a slow progressor. Medically, the experts are not in agreement

about how to approach such a patient. Some advise treatment, while others suggest waiting for the CD4 to fall below 500 cells/μl. Ethically, given the importance of informed consent in initiating drug treatment and in explaining why treatment is given and considering the potential side effects, it would be very difficult to treat a patient who does not know his diagnosis. If there is a convincing argument for treatment now, then I would strongly suggest persuading the parents that, to receive treatment, the patient must be informed. On the other hand, if you wait just one more year, he will be 18 and legally able to decide for himself. Your institutional review board and your Ethics Committee might be able to assist in discussing this with the parents. Parents want the best for their children, in general, and if it becomes medically clear that the patient needs treatment and that you cannot do so without discussing this with him, then my guess is that they will agree with your plan.

With regard to hepatitis C, the hepatology literature suggests that the HCV viral load is not directly related to the pathology or severity of chronic liver disease, and despite all the molecular techniques available, the liver biopsy remains the gold standard for diagnosis. As discussed earlier, it would be difficult to initiate treatment without informed consent.

Finally, certainly, given the patient's age and current or potential sexual activity (no matter what the parents think is the case), it is crucial that the patient be informed of his HIV status so that he can take appropriate precautions to prevent sexual transmission or transmission to others through exposure to his blood (e.g. with cuts or bleeds or with potential trauma). This is a societal issue, and unknowing HIV transmission would be inexcusable!

One last word: from the ethical literature, the majority of patients who have not been informed of a "bad diagnosis" often suspect it and may hold resentment and anger towards those who withhold information important to their future. This boy deserves to know his diagnosis and the potential benefits of antiviral treatment for HIV and HCV in planning his future life. My guess is that involving the parents in a discussion with you and other hospital personnel or other haemophilia providers would help them see the significant benefits in disclosing this information. The longer they wait, the greater the likelihood that potential medical disaster may occur (sexual transmission), and the greater the potential for anger, hard feelings, and psychological difficulties in their teenager.

Editors' Note

Professor Ragni wishes to remind the audience that HIV/AIDS is a continuously changing disease. Treatment patterns for this disease were current at the time of above response. Since 1999, new guidelines have been published and can be found in Hammer SM, Saag MS, Schechter M, *et al*., Treatment for Adult HIV Infection: 2006 Recommendations of the International AIDS Society – USA Panel. *J Am Med Assoc* 2006;296:827–43.

A Case of Haemophilia B, Mild VWD, and a Factor IX Inhibitor

Question/ Case	I have a 7-year-old patient with severe hemophilia B and mild von Willebrand disease (VWD) type 1. The patient has a low titre inhibitor to factor IX and has developed an anaphylactic reaction to plasma-derived FIX concentrates. We have treated haemorrhagic episodes with recombinant FVIIa (rFVIIa). Last year he suffered from repeated haemarthroses. He did not report trauma or possible bleeding early enough, so that his ankle was swollen when he arrived at our centre. Our problem is: how, and for how long should we treat this patient? We have used rFVIIa at 180 μg/kg as the first dose followed by 90 μg/kg after 2 h. We have also used oral tranexamic acid and intravenous desmopressin acetate. The manufacturer's recommendation is to continue rFVIIa treatment as long as the bleeding continues, but it is difficult to assess whether the bleeding has stopped when the ankle is swollen. What protocols are recommended? Do other practitioners have recommendations for the length of treatment for articular bleeds?

Response from **Ulla Hedner, MD, PhD**
University of Lund, Malmo, Sweden; Novo Nordisk A/S, Denmark

This patient is a complicated haemophilia B patient. He has anti-factor FIX antibodies and experiences anaphylactic reactions to FIX concentrates [1,2].

To achieve optimal efficacy of rFVIIa in the treatment of bleeds, the drug should preferably be administered very soon after the start of bleeding, and it is clear that one of the problems is that this patient tends to delay his visit to the centre when he experiences a bleed. Would it be possible to administer rFVIIa in a home treatment setting? It was shown in the Home Treatment Study in the USA that an

average of 2.2 doses was needed to achieve haemostasis in the moderate-to-mild bleeds treated in that study [3]. Many centres do apply home treatment, teaching the parents and the patient himself how to inject the rFVIIa to allow immediate initiation of treatment as soon as the patient experiences any signs of a bleed.

The pharmacokinetics of rFVIIa exhibit a shorter half-life and higher clearance in haemophiliacs below the age of 15 years compared with adults [4]. However, if you did not perform a pharmacokinetic study in the patient, a dose of 180 μg/kg is most probably high enough. It seems unlikely that this dose would not give him a satisfactorily high peak level of FVII:C right after the injection. It may, however, be a good idea to use this dose for the next injection(s) given at 2 h intervals.

The questions of how long the treatment should be continued and how to decide when to stop are difficult in a patient with a joint that is already swollen. The best marker of the cessation of bleeding would be relief of pain. Most haemophilic patients can accurately assess when the bleeding has stopped.

There is no firm protocol for how long to continue rFVIIa in joint bleeds. One has to rely on the patient's assessment or until the swelling diminishes. As already mentioned, pain is a good marker. If the patient is experiencing repeated bleeds in the same joint, he may develop a target joint characterized by chronic swelling, which makes it even more difficult to tell whether the discomfort is due to an acute bleeding episode or to inflammatory changes in the joint.

To prevent the development of a target joint, I would recommend that such patients be given 2–4 injections of rFVIIa using the high-dose regimen (180 μg/kg/dose) at 2 h intervals to make sure full haemostasis is achieved. Ideally the first dose should be given at home.

The use of tranexamic acid is recommended as an adjunct therapy, although its effect in joint bleeds may not be as effective as for mucocutaneous bleeds and surgery. If DDAVP is being used, tranexamic acid should be given, since DDAVP releases not only FVIII, but also fibrinolytic activators.

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Premature Infant with Haemophilia B

Question/ Case	We recently discovered severe haemophilia B in a neonate born prematurely after 27 weeks of gestation. He had a patent ductus arteriosus that needed surgical closure. Factor IX was 1% and his family history was negative. The patient was diagnosed with an intraventricular haemorrhage. He was treated with FIX prior to surgery. Now he needs large amounts of factor IX to maintain an adequate level. Does anybody have experience with a premature infant with severe haemophilia B? What are the pitfalls one could expect? What is a safe level of factor IX for a patient in severe respiratory distress on the ventilator, who may receive corticosteroids?

Response from **Donna M. DiMichele, MD**
New York Presbyterian-Weill Cornell Center, New York, USA

The management of a sick newborn with haemophilia is indeed challenging. Prematurity adds further to its complexity. The major challenges include (1) uncertainty about true factor recovery and survival in neonates; (2) concerns about inhibitor development with long-term high-dose exposure to factor in this age group (although somewhat less of a concern with haemophilia B); (3) venous access difficulties; (4) the need for frequent invasive procedures associated with concurrent illnesses; and (5) the difficulties in educating and supporting the emotional needs of the family when the diagnosis is made under such stressful circumstances. Unfortunately, there are no published evidence-based guidelines for managing haemophilia in a premature or a full-term infant.

Considering the issues at hand, some recommendations for the management of babies of this type would include the following.

Given the extraordinarily large extracellular volume of the premature infant (80–90% of weight) and the presumably higher factor IX clearance rate in the young infant, it is not surprising that high doses of FIX were required to achieve haemostatic levels for both the PDA

repair and subsequent prophylaxis. This is especially the case if recombinant FIX is used.

If the baby is undergoing frequent invasive procedures, it might be safer to maintain a minimum haemostatic FIX level of 15–20% and use intermittent bolus dosing to achieve FIX levels of 50–70% to cover the baby for major interventions (surgery, venous access placement, etc.). This could be accomplished on a daily dosing schedule, or if central venous access is available, by continuous FIX concentrate infusion. The latter will reduce the total daily FIX requirement, maintain constant target FIX levels, and simplify FIX plasma monitoring.

Alternatively, if the baby is stable and not undergoing frequent invasive procedures such as arterial punctures, etc., the infant may not need a persistent haemostatic FIX level. In that case, haemostasis could be maintained using a more "routine prophylaxis" regimen. However, I suspect that this regimen would have to be augmented both with respect to bolus dose and frequency of administration, based on the FIX recovery and half-life data that you will be able to collect.

Given the above recommendations, permanent central venous access is highly recommended.

Although inhibitor development is less likely in haemophilia B, the risk for this complication remains high in individuals with large or complete gene deletions. In patients like these from the FIX Inhibitor Registry, inhibitor development can occur after as few as 2 or as many as 180 FIX exposures and can be accompanied by mild-to-severe allergic manifestations. For these reasons, I would strongly recommend early gene-based diagnosis for this infant. In the meantime, regular monitoring of FIX plasma levels is recommended for inhibitor surveillance.

Lastly, I recommend intensive ongoing reassurance, support, and education for the family.

Haemophilic Carriers and Delivery

Question/ Case	I would very much like to ask the panel of how best to deal with a pregnant woman who is an asymptomatic carrier of severe haemophilia A and expects a male baby. No prenatal diagnosis has been done. Would you recommend caesarean section over spontaneous delivery? Is the newborn, who may well be a haemophiliac, at risk? Is the mother at risk? I am aware that bleeds are very rare in newborns with severe haemophilia and that carriers usually do not bleed, but is the risk actually zero? Would you recommend delivery in an obstetric department associated with a haemophilia centre or is it appropriate for the mother to deliver in a local hospital?

Response from **Jeanne Lusher, MD**
Wayne State University School of Medicine, Detroit, Michigan, USA

In response to the query concerning delivery, if the newborn is affected (i.e. has severe haemophilia), the most severe potential risk is intracranial haemorrhage (ICH). While the risk is not great, it is a definite risk of which all concerned should be aware. Assuming that there is no cephalopelvic disproportion, most clinicians would recommend vaginal delivery. However, vacuum suction and forceps should be avoided, as should prolonged labour. Since it is not known whether the foetus in question has haemophilia or not, all these recommendations should apply. In addition, a cord blood sample should be obtained at birth (from a vessel on the foetal side of the placenta) for a FVIII assay. If there is any question about a possible ICH in the neonate, imaging studies should be carried out, and FVIII should be given. While all efforts should be made to avoid an unusually difficult, precipitous, or otherwise traumatic delivery, should this occur, I would recommend imaging studies to rule out ICH. Otherwise, ICH may go unrecognized for several days and become much more extensive before obvious symptoms develop.

While the exact incidence of ICH in haemophilic neonates is not known, most surveys indicate an incidence of around 1%. However, most surveys have been relatively small and data appear "soft".

With regard to the place of delivery, I would definitely recommend that delivery take place in an obstetric department associated with a haemophilia centre. There should be close cooperation between haemophilia centre personnel and the obstetrician.

The risk of unusual maternal haemorrhage is uncommon. However, it would be helpful to know what the woman's baseline FVIII level is. If she has a very low level, there may be a risk of vaginal bleeding several days post delivery (levels generally rise during the third trimester of pregnancy, so bleeding at delivery related to low FVIII levels would be unusual). If bleeding occurs a few to several days postpartum, and the mother's FVIII level has fallen to 20% or less, desmopressin (DDAVP) could be given.

Mild Haemophilia in Women

Question	Can women have mild haemophilia A?
Case	I am a middle-aged woman with a diagnosis of mild haemophilia, although I am constantly told by physicians that only males are haemophiliacs. My medical history is rather confusing since I am the only one in my family with a history of haemophilia. I have a factor VIII level of 22%. Over a period of several years, I have experienced post-surgical haemorrhage, postpartum haemorrhage, haemarthroses, and bleeding after tooth extraction. Some haemorrhages were sufficiently severe to require transfusions with blood and/or cryoprecipitate. I have been diagnosed with hepatitis and mild haemophilia. I am to undergo further surgery and I would value your explanation of my diagnosis of mild haemophilia without any family history. Would you consider the surgery to be relatively safe provided there is meticulous and adequate (to 100% of normal) replacement of factor Vlll for a period of about 10 days after surgery?

Response from **Barbara Konkle, MD**
University of Pennsylvania, Philadelphia, Pennsylvania, USA

Mild haemophilia is characterized by trauma-induced bleeding and the symptoms described would be compatible with the diagnosis of mild haemophilia. To confirm that diagnosis requires additional laboratory data to rule out von Willebrand disease (VWD). In all patients with a low factor VIII level, VWD should be ruled out. FVIII binds to, and is stabilized by, von Willebrand factor. Thus when von Willebrand factor is decreased, so is factor VIII. While both mild haemophilia and VWD usually respond to treatment with desmopressin (DDAVP), the approach may be different for treatment of severe bleeding or for

major surgery. Furthermore, the inheritance of VWD differs from classic haemophilia and correct diagnosis is important for genetic counselling and family studies. Rarely, patients can have a low factor VIII level due to a subtype of VWD, resulting from a mutation(s) in the factor VIII binding region of (VWD 2N, Normandy); this would not respond to DDAVP therapy. Also described are combined factor VIII and V deficiencies. In addition, one would want to rule out a factor VIII inhibitor by clinical history and laboratory analysis.

Carriers of haemophilia have widely varying factor VIII levels and often have levels low enough to result in symptoms compatible with haemophilia. In women, in cells expressing genes carried on the X chromosome, only one copy of each gene is expressed (the Lyon hypothesis). Within each cell, which gene is expressed is a random event. Thus the levels of factor VIII in women with one functioning and one non-functioning gene reflect the sum of these events and may vary. Women with sufficiently low levels to produce symptoms of mild haemophilia are often called symptomatic carriers.

Both haemophilias A and B are frequently due to new mutations. This happens more commonly in the germline of the mother, particularly with haemophilia due to the factor VIII inversion mutation that occurs, almost exclusively during gamete production in the carrier's father as described by Rossiter *et al*. [1]. In most new carriers, it will not be manifest until the woman has a son with haemophilia. The most famous carrier of haemophilia, without a family history of such, was Queen Victoria. She was not known to have bleeding symptoms. However, it is very possible that a new carrier of haemophilia would have levels that would produce symptoms compatible with mild haemophilia. For further information on bleeding in carriers of haemophilia, the reader is referred to Greer and Walker's chapter, "Bleeding in the Hemophilia Carrier," in *Hemophilia*, Forbes, Aledort, and Madhok (eds.), Chapman and Hall, 1997 [2].

In patients with mild haemophilia without inhibitors who respond well to factor VIII therapy, surgery can be safely performed with factor VIII replacement pre- and postoperatively. Major surgery on patients with haemophilia should always be performed under the supervision of a physician with experience in haemophilia care and at an institution where factor VIII levels can be followed and can be obtained on an emergency basis, if needed.

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Treatment of the Pregnant Haemophiliac

Question	I understand haemophilia is rare in women. Is there any current literature on the treatment of the pregnant haemophiliac: antepartum, intrapartum, and postpartum?

Response from **Keith Hoots, MD**
Gulf States Hemophilia & Thrombosis Center, University of Texas Houston Health, Houston, Texas, USA

Two recent studies have been published concerning the management of pregnancy in the two most common clinical situations that result in phenotypic haemophilia among women of child-bearing age: a Lyonized carrier of haemophilia A or B; and the onset of a Type I or Type II factor (F)VIII inhibitor arising prior to the third trimester of pregnancy and extending well into the postpartum period [1,2]. Kadir *et al*. followed 82 pregnancies among 24 carriers of haemophilia A and 8 carriers of haemophilia B [1]. Thirty-two of the 82 pregnancies were spontaneously or electively aborted. Thirty-five per cent of the women opted for prenatal diagnosis, with five male foetuses being diagnosed; three of these women opted for termination.

Foetal blood sampling on four occasions was without incident. However, a ventouse delivery resulted in a huge cephalohaematoma in one foetus. Eight caesarean sections were performed that might have been avoided had gender been determined. Most importantly, 22% of the deliveries resulted in primary postpartum haemorrhage and 11% had secondary bleeding; this despite all deliveries having occurred in a hospital with a large comprehensive haemophilia centre.

This experience strongly supports aggressive factor replacement and other haemostatic support for women with low or moderately low FVIII or FIX levels prior to, during, and following delivery. Ultra-high-purity factor concentrates should be chosen for viral safety.

Michaels *et al*. report four women with acquired haemophilia in association with pregnancy and delivery [2]. Three had Type II FVIII inhibitors (typical of acquired inhibitors) and one had a Type I (more typically seen in individuals with haemophilia). High-dose FVIII was

effective in the two of three Type II patients who experienced postpartum bleeding, but not in the woman with the Type I antibody.

Immunosuppression was unsuccessful in significantly reducing the inhibitor in any of the women.

Management of obstetrical events in women with acquired haemophilia continues to be fraught with peril. Advice from only the most experienced coagulationists should be sought to assist with ante-, intra-, and postpartum inhibitor therapy.

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Anticoagulation for Atrial Fibrillation in a Haemophiliac

Question/ Case	When a 23-year-old patient with haemophilia A (factor VIII of 4%) has atrial fibrillation (AF), what do you choose to prevent thromboembolism: anticoagulation or antiplatelet therapy?

Response from **Brigit Brand, MD**
University Hospital, Zurich, Switzerland

Venous and arterial thromboses are rare occurrences in patients with haemophilia, but this subject has gained considerable attention in recent years. Recently, all reported cases of non-catheter associated venous thrombosis in haemophilia have been carefully evaluated by Girolami *et al.* [1]. They found the most frequent risk factor to be the administration of FEIBA or rFVIIa. The same authors published an evaluation of all 42 reported cases of myocardial infarction and other arterial thromboses [2]. Neither article offers general recommendations on antithrombotic prophylaxis. There is little experience in this field, and treatment must be individualized.

Strong data have emerged to support anticoagulation with warfarin to prevent stroke in non-haemophilic patients with AF [3,4]. When warfarin is contraindicated, aspirin or other antiplatelet agents are also efficacious, but less than warfarin. Haemophiliacs have been reported to be treated safely with anticoagulation in conjunction with factor replacement, usually for short periods of time.

With these points in mind, I suggest, for a haemophilic patient, that the first aim must be to convert the AF back to sinus rhythm for prevention of thromboembolism. I personally prefer aspirin rather than anticoagulation with warfarin or with direct thrombin inhibitors. Vitamin K antagonists have too many variables in predicting a safe, but efficient dose. Due to lack of data from the literature, the treatment has to be individualized and closely watched.

Response from **Miguel A. Escobar, MD**
University of Texas Health Science Center at Houston; Gulf States Hemophilia & Thrombophilia Center, Houston, Texas, USA

AF is uncommon among individuals less than 50 years old. Prospective studies show that the rate of ischaemic strokes is about 4.5% per year in untreated patients. Certainly most of the individuals included in the studies are more than 50 years old. Stroke in individuals with AF appears to be as a result of cardiogenic embolism.

When it is decided to treat a patient with AF, one has to take into account the age and risk factors for stroke (prior ischaemic stroke, transient ischaemic attack, systemic embolism, impaired left ventricular function and/or congestive heart failure, hypertension, or diabetes). Management with anticoagulants is usually indicated in the older patient with any of the above risk factors or valvular heart disease.

For individuals younger than 65 years with no other risk factors, the recommendation is to use aspirin 325 mg/day only (Grade 1B).

More specifically in this young individual with moderate haemophilia A, I suggest the following:

1 Find the underlying cause of the AF given his age.
2 Cardioversion will be my first treatment option if there is no contraindication. First, I suggest doing a transesophageal echocardiogram to rule out a thrombus in the heart. If the echo is normal then cardioversion without the use of anticoagulation should be considered, as the patient could be considered "already anticoagulated" due to his haemophilia.
3 If cardioversion is not an option, my second choice would be the use of an aspirin 325 mg/day.
4 I would not recommend anticoagulation with vitamin K antagonists given the increased risks for bleeding.

For more details you can read the recently published recommendations from the ACCP (*The Eighth American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy*. Evidence-based guidelines. Northbrook, IL: ACCP, 2006). These are only guidelines taken from clinical studies and should be used as such. These guidelines may not apply to cases like the one described here.

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Anticoagulation for a Cardiac Valve in a Haemophiliac

Question/ Case	We are treating a 42-year-old patient with mild haemophilia A (factor VIII level 20%) with a bicuspid aortic valve and severe aortic regurgitation. We are planning an aortic valve replacement operation. Our question is: should we use a prosthetic or a mechanical valve? Considering the age of the patient, a prosthetic valve would require future replacement; however, with a mechanical heart valve, life-long anticoagulation will be required in a patient who already suffers from a congenital bleeding tendency. If we did use a mechanical valve, what international normalized ratio (INR) range would you recommend?

Response from **Jørgen Ingerslev, MD**
University Hospital Skejby, Aarhus, Denmark

The question raised is very difficult to answer. Since I have no personal experience with artificial valves in patients with haemophilia, a literature search helped me to identify two cases. One case report concerned a patient with severe haemophilia A who had a double (aortic and mitral) valve replacement [1]. The abstract did not report on the subsequent use of oral anticoagulants. The second report concerned a patient with moderate haemophilia who underwent an aortic valve replacement [2]. In this case, doctors deferred coumarin therapy postoperatively "due to the prolonged partial thromboplastin time time." Though these two reports do not answer the question, they do signify that, with the availability of modern replacement therapy (factor VIII), major surgery of this kind can be successfully accomplished in patients with haemophilia. For intraoperative thromboprophylaxis, it is advisable to use heparin as in other patients, and monitoring can follow the same principles. It is important to note that, to achieve the activated thrombin time or other unactivated clotting measures, the requirements for heparin dosage during extracorporeal circulation will be lower than in non-haemophilic patients. The choice of valve

prosthesis is not easy. In my hospital, we would probably focus on the postoperative thromboembolic/bleeding balancing problem and select a biological valve. Since experience in this field is so extremely limited, the choice of a postoperative INR level cannot be based on solid evidence, but rather subjective criteria. Patients with mild haemophilia can die from an acute myocardial infarction, and there is no reason to believe a mild haemophiliac could not produce other kinds of thrombi. Hence, postoperative anticoagulation is advisable, but the best therapeutic level is not known. The judgement should clearly consider the risk of untoward excessive bleeding, including central nervous system and other serious bleeds. I would be in favour of an initial INR level of around 2.0, but lower levels should be chosen if bleeding poses problems.

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Cardiac Catheterization in a Haemophiliac

Question/ Case	A 45-year-old haemophiliac with factor VIII levels of 5% has unstable angina with a 90% proximal left-anterior-descending artery occlusion. He needs angioplasty with stent placement, and he will need heparinization and may require an antiplatelet agent like abciximab (ReoPro®) post-procedure. Does he need factor VIII infusion during the procedure? Can he be heparinized and which type is better, unfractionated heparin or low-molecular-weight heparin? Should he need factor VIII at the time of femoral sheath removal?

Response from **Craig M. Kessler, MD**
Georgetown University Medical Center, Washington, DC, USA

This is not an uncommon problem in individuals with haemophilia and coronary artery disease. I believe that these patients need to have factor replacement therapy, initially up to 100% of normal, when the angioplasty and stent placement are performed and the abciximab and heparin are given. This way, this patient's risk of bleeding is equivalent to any other individual with normal coagulation. I would also ensure the patient has factor replacement to >50% of normal when the femoral artery sheath is pulled. Thereafter, I would not think the patient would need replacement, unless bleeding occurs.

As for the type of heparin to be used in this situation, I would opt for the low-molecular-weight heparins since they have been shown to be associated with better patency rates post angioplasty. I would treat the patient just like anyone else, as long as the factor VIII level is adequate to sustain normal blood coagulation.

Anticoagulation for a DVT in a Haemophiliac

Question	How do you manage a deep venous thrombosis (DVT) in the presence of haemophilia?
Case 1	We have an elderly patient with moderate haemophilia B (factor IX level of 2%) with a history of DVT. Is there an indication for oral anticoagulation? If yes, what is the level of INR recommended?
Case 2	This question is regarding a patient with severe haemophilia A who developed pulmonary embolism during the peri-operative period (surgery was for abdominal trauma sustained in a motor vehicle accident). His FVIII level did get up to 150% on one occasion. The patient was also found to be heterozygous for FV Leiden. No other sites of DVT were detected. Would you send the patient home on anticoagulation and how long would anticoagulation be continued? How aggressively would you address the FVIII deficiency while the chronic anticoagulation is ongoing?

Response from **German A. Marbet, MD**
University Hospital Basel, Basel, Switzerland

Venous thromboembolism is a rare event in haemophiliacs. It may occur if several risk factors accumulate. A special condition is central venous catheter-associated thrombosis, mainly in children receiving coagulation factor concentrates. A recent review of the literature showed an average prevalence of 11% – 45 catheter-related thromboses in 419 catheters placed [1]. Interestingly, deep vein thrombosis is quite rare in haemophiliacs undergoing orthopaedic surgery despite vigorous replacement of the deficient coagulation factor. However, the DVT risk may be substantial in haemophilia B patients receiving prothrombin complex concentrates as a source of factor IX instead of highly purified plasma-derived or recombinant factor IX.

We do not know which risk factors had favoured DVT in the elderly patient with moderate haemophilia B. Anyway, I would not use vitamin K antagonists in a haemophilia B patient. The bleeding risk appears excessive as factor IX activity would drop to values below 1% accompanied by the reduction of other vitamin-K-dependent factors to 20–30%. Therefore, I would treat acute venous thromboembolism with therapeutic doses of unfractionated or low-molecular-weight heparin. In the presence of a bleeding lesion (e.g. postoperatively), treatment with factor IX replacement would continue. After 10–14 days, it may be possible to reduce heparin in parallel with decreasing factor IX replacement. If possible, other thrombogenic risk factors (e.g. stasis, venous compression) should be removed. Low-molecular-weight heparin could then be administered in prophylactic doses for about 6 weeks. Later, the low factor IX level could be expected to prevent recurrence of DVT.

Response from **Sam Schulman, MD**
Hamilton Health Sciences – General Hospital, Hamilton, Ontario, Canada

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The second case is an obvious challenge where you have two potentially life-threatening conditions, but in opposite ways. One would theoretically think that by just stopping the FVIII substitution, the effect of severe haemophilia will be sufficient to prevent extension or progression of the venous thromboembolism, so that the body can take care of the fibrinolytic issue. This may be the case, but it is impossible to know how well the two diseases can balance each other. In addition, the patient is in the postoperative period after both trauma and major surgery. Thus, it would be too risky to leave him without factor replacement therapy.

I had a patient with von Willebrand disease and bilateral total knee replacement, complicated by sub-massive pulmonary embolism. This patient was managed by continuing factor replacement therapy (bolus injections of FVIII-von Willebrand factor concentrate) and treating with anticoagulants. The factor replacement was kept at the minimum dose required to control bleeding. Postoperatively a level of 50–60% of FVIII is sufficient, and every 3 days this can be lowered by 10 percentage points. However, with anticoagulant therapy on board, you have to be more careful and perhaps double the interval between lowering the FVIII dose. When you reach a maintenance level of 20%, you may switch to prophylaxis by intravenous injections with

20 IU/kg every 2 days, at least until anticoagulation therapy is completed. I would give full heparinization by intravenous infusion of unfractionated heparin, aiming at an APTT of 1.5–2 times prolongation of the upper limit of normal (thus a bit conservative) for 5 days. For secondary prophylaxis, I would not give warfarin but rather low-molecular-weight heparin for 3 months at a dose of 40 mg or 5000 units once daily. Another alternative is to give the secondary prophylaxis only for 1 month and at that point also reduce the FVIII substitution. A third alternative is to insert a vena cava filter to reduce the need for secondary prophylaxis, but the initial treatment of pulmonary embolism is necessary.

Reference

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DDAVP for Treatment of Mild Haemophilia during Surgery

Question	Can we use desmopressin acetate (DDAVP) for treatment during and after a total hip replacement in a patient with mild haemophilia A?
Case	A mild haemophilia A (19%) patient is scheduled to undergo a total hip replacement for osteoarthritis. A post-IV DDAVP peak level recently was 61% peak. His past bleeding history has been mild, consistent with his FVIII level. There is no family history of thrombophilia. Should we treat with DDAVP or with FVIII replacement?

Response from **Jørgen Ingerslev, MD**
University Hospital Skejby, Aarhus, Denmark

If I understand the question right, your patient suffers from mild haemophilia, and the consideration is the use of DDAVP to raise and maintain a safe level of factor VIII. In my numerous years of experience with DDAVP in my patients, I have never attempted to use DDAVP for a truly major surgery like this. There are several reasons here. Importantly, you cannot rely on a response like the one seen previously (60%) when DDAVP is used on a daily basis, and the half-life of FVIII released from patient's own stores may be shorter compared to exogenous factor VIII. If DDAVP is used once daily, the trough level of factor VIII will be close to patient's residual F VIII level of 19%, and there will be a significant risk of excessive bleeding. Further, there is the important issue of tachyphylaxis, that is the gradual or abrupt exhaustion of FVIII stores. This is very unpredictable. Even with dual or multiple daily recordings of the FVIII level, I would fear bleeding problems.

So, if this were my patient, I would prefer factor VIII replacement therapy. If the patient's response to a factor VIII concentrate (*in vivo* recovery) has been tested some time during previous 1–2 years, I would trust this as a basis for calculating the correct dose for surgery

itself, so as to raise the level to 100%. I would certainly check the factor VIII level 15 min after the first infusion.

In the postoperative setting, I would raise the factor VIII level by infusions, according to local preferences, to maintain a factor VIII level that should not go below 50% at any time for the first 3–5 days. From day 5 onwards, I would still suggest a level of factor VIII kept above 40% at all times for 2–3 days with a gradual decrease in the dose until day 10. From that time on, I would give a dose of factor VIII every morning prior to rehabilitation training.

Editors' Note

An alternative approach would be the continuous infusion of factor VIII maintaining the levels suggested by Dr Ingerslev.

Haemophilia and Haemodialysis

Questions/ Cases	Case 1: A 50-year-old patient with severe haemophilia B and no inhibitors has suffered from diabetes mellitus for 25 years. He now has renal insufficiency and will soon require chronic dialysis. Does anyone have any experience in the management of chronic dialysis in haemophilia patients? Case 2: Would you recommend antithrombotic prophylaxis with heparin during haemodialysis in severe haemophilia patients?

Response from **Jørgen Ingerslev, MD**
University Hospital Skejby, Aarhus, Denmark

The first patient illustrates that, in severe haemophilia, vascular complications due to diabetes can develop with quite dramatic results. Peritoneal dialysis might be a good solution because this procedure does not require heparin, and there is absolutely no need for replacement therapy during dialysis sessions. Should haemodialysis be preferred in this case, the critical issue to address is the requirement for heparin. Adequate vascular access can be achieved through a shunt or an arterio-venous fistula. The surgical establishment of the latter will require replacement with factor IX concentrate. Since this patient has clinical evidence of a vascular disorder, the factor IX concentrate should be carefully selected to avoid thrombogenic complications. Prothrombin complex concentrates should be avoided.

Haemodialysis in itself may require heparin to avoid formation of platelet aggregates in the artificial kidney, but the requirements must be established empirically. For the first session, priming with a very small dose of heparin, such as 500 IU, may be sufficient. Theoretically, there may be no need for heparin at all, but it should be remembered that this patient may have quite dramatically increased levels of von Willebrand factor. To avoid oozing from puncture sites and prevent haematomas on the arterial side, prolonged compression and replacement with factor IX at the end of dialysis may be required.

Response from **Victor Marder, MD**
School of Medicine at UCLA, Los Angeles, California, USA

Would I recommend anticoagulation during dialysis? The short answer is "yes", for the simple reason that I would normalize patients with prophylactic factor prior to accessing the arterio-venous shunt or fistula with a large gauge needle. This being the case, the haemophilic patient is essentially the same as a non-haemophilic in regard to the need to anticoagulate the dialysis machine.

Haemophilia and Hepatitis C Treatment

Question/ Case	Should the patient with mild haemophilia A (12% FVIII) and hepatitis C be treated with interferon therapy? For more than 15 years, the patient has had elevated transaminases, without symptoms. He has not received FVIII for more than 10 years. We have recently done virus screening and we have found HCV positivity.

Response from **German A. Marbet, MD**
University Hospital Basel, Basel, Switzerland

I think that the patient with mild haemophilia A and laboratory evidence of chronic hepatitis C (increased transaminases, anti-HCV positive by immunoenzymatic assay and positive with a qualitative PCR-based HCV RNA assay) should be further evaluated for combined treatment with one of the two available pegylated alpha-interferons and ribavirin.

A quantitative HCV RNA assay and HCV genotyping will provide information about the chance of a durable response and are required for the follow-up of therapy. In most patients with chronic hepatitis C, liver biopsy is required for appropriate therapeutic decisions. Liver histology will show the degree of inflammatory activity and of fibrosis and may also detect stigmata of surreptitious alcohol abuse and other pathologic conditions.

Because of the higher bleeding risk, there is much reluctance to perform liver biopsy in haemophiliacs. However, a recent article by Stieltjes *et al*. in the *British Journal of Hematology* 2004 reports successful transjugular liver biopsy (88 transjugular liver biopsies in 69 individuals) in adult patients with haemophilia or other congenital bleeding disorders infected with hepatitis C virus [1]. Earlier positive reports about liver biopsies in smaller numbers of haemophiliacs are also quoted by the authors. Before and after biopsy, the patients require appropriate replacement of coagulation factors. Stieltjes *et al*. gave about 40 IU/kg in severe haemophilia A and 60 IU/kg in severe haemophilia B patients, respectively, before biopsy and followed by appropriate doses for 24–48 h. There is also a regimen in the guidelines on hepatitis by Makris *et al*. in *Hemophilia* 2001 [2].

In this mild haemophilia A patient, I would first exclude the presence of a factor VIII inhibitor and then test the effect of an infusion of 0.3 μg/kg desmopressin. If there were an increase of factor VIII to 80%, desmopressin could be administered before biopsy and then at 12 and 24 h post-biopsy. If the increase were smaller, factor VIII concentrates would be required before biopsy to reach 80–100% factor VIII. Desmopressin or factor VIII concentrates (20 IU/kg) would be given at 12 and 24 h post-biopsy. After biopsy, the patient should remain in the hospital for at least 24 h for clinical monitoring and factor VIII control.

Ultimately, the decision to treat with pegylated alpha-interferon and ribavirin will depend on:

(a) treatment indication based on histology (inflammatory activity, fibrosis)
(b) absence of contraindications
(c) informed consent
(d) capability of adherence to the treatment regimen and to the required controls (clinical and blood tests).

It may be worth noticing that 37% of all assessable biopsies in the series of Stieltjes *et al*. showed only minor or no histological alterations. In these patients, no treatment was started and regular clinical follow-up was recommended.

Response from **Sam Schulman, MD**
Hamilton Health Sciences – General Hospital, Hamilton, Ontario, Canada

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On one hand, many of the patients with hepatitis C will live with their chronic infection for decades without any complications. On the other hand, we have already had several patients who developed liver cirrhosis, and some unfortunately also developed hepatocellular carcinoma. The latter is rarely curable.

Policies may vary from country to country, depending on resources, but if affordable, I think the patient should be offered the possibility to eliminate the chronic infection.

The first step is to verify that the elevated aminotransferases really are caused by hepatitis C. Thus, a PCR analysis of hepatitis C RNA should be performed and must be positive to justify therapy. In addition, it is very useful to perform genotyping of the virus. Patients

with genotype 2 or 3 only need 6 months of combination therapy, while the other genotypes will need 12 months. Other liver disorders like haemochromatosis, Wilson's disease, diabetes, or autoimmune hepatitis should be excluded.

It is a matter of taste whether Pegasys® or PEG-Intron® should be chosen. It should be combined with ribavirin 1000 mg/day or more if body weight is >100 kg. If the repeat PCR is still positive at 6 months, continuing antiviral therapy is futile. Patients with bleeding disorders may suffer increased bleeding from mucous membranes during this treatment.

We do not perform liver biopsies in these patients unless a malignancy is suspected.

References

1 Stieltjes N, Ounnoughene N, Sava E, Paugy P, Roussel-Robert V, Rosenberg AR, *et al*. Interest of transjugular liver biopsy in adult patients with haemophilia or other congenital bleeding disorders infected with hepatitis C virus. *Br J Haematol* 2004;125(6):769–76.

2 Makris M, Baglin T, Dusheiko G, Giangrande PL, Lee CA, Ludlam CA, *et al*. Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia. *Haemophilia* 2001;7(4):339–45.

Haemophilia and Physical Therapy

Question	I am a physiotherapist attending a haemophilia clinic. I would like to know more about safe exercises to teach our patients for strengthening their muscles. What is safe practice when there are already contractures present? Also, which electrical apparatus, for example ultrasound, is safe to use for pain when patients are not bleeding?

Response from **Sam Schulman, MD, PhD**
Hamilton Health Sciences – General Hospital, Hamilton, Ontario, Canada

In any exercise, the basic rule is to start carefully and increase the load gradually and even more so when contractures are present. It is generally better to keep the exercise periods short and repeat it several times per day. A simple tool to assist the patient in exercise is a rubber band, such as the Thera-band® (The Hygienic Corporation, USA). They can easily be used for both leg and arm exercises. Weight cuffs can also be used if one needs to change the load, but these are more expensive. The electrical instrument we have found most useful against pain is transcutaneous electrical nerve stimulation (TENS). We know that in some countries ultrasound or short wave is also being used for this purpose. However, we only use ultrasound to enhance reabsorption of large muscle haematomas. For acute pain cold packs are helpful, whereas in chronic pain heat may be better. This is particularly true when the patient starts exercising a contracted extremity. Ideally, this is started in a warm swimming pool (up to 37°C) so that the load on the joint is minimal and the tissues become more flexible.

Response from **E. Carlos Rodriguez-Merchan, MD** and **Karen Beeton**
La Paz University Hospital; and Autonoma University, Madrid, Spain

All the information needed for the practical treatment of the musculoskeletal complications of haemophilia can be found in a single volume [1].

Safe Exercises To Teach Patients for Strengthening Their Muscles

This is difficult to say without more information. Basically, all patients should be fully assessed by both a subjective and a physical examination prior to treatment to establish if there are any precautions to treatment or contraindications. Chapter 1 in *Physiotherapy Management of Hemophilia* provides an overview of the assessment process [2]. Following this, a suitable treatment programme can be determined. Generally, weight-bearing exercises should be started with caution, particularly if patients have arthropathy. All treatments should be tailored to the individual.

Safe Practice If There Are Contractures

Again, a careful and thorough assessment is the key to management. It is important to determine the severity of the contracture, availability of factor replacement therapy for physiotherapy, and whether there is a soft tissue or bony end feel. A bony or hard end feel is less likely to respond to physiotherapy, and other means will have to be considered. The *Haemophilia* supplement on articular contractures may be useful further reading [3].

Electrical Apparatus

Physiotherapists often use ultrasound pulsed short wave, interferential or TENS for patients with haemophilia. The physiotherapy book has a good chapter on electrotherapy use in haemophilia [2].

References

1 Rodriguez-Merchan EC, Goddard NJ, Lee CA. *Musculoskeletal Aspects of Hemophilia*. Oxford: Blackwell Science Ltd, 2000.

2 Buzzard B, Beeton K. *Physiotherapy Management of Haemophilia*. Oxford: Blackwell Science Ltd, 2000.

3 Rodriguez-Merchan EC. Therapeutic options in the management of articular contractures in haemophiliacs. *Haemophilia* 1999;5(Suppl 1):5–9.

Haemophilia and Renal Bleeds

Question	Is it possible to use inhibitors of fibrinolysis when treating renal bleeding?

Response from **Tom Abshire, MD**[1] with **Roshni Kulkarni, MD**[2]
[1]*Emory University School of Medicine, Atlanta, Georgia, USA*
[2]*Centers for Disease Control and Prevention, Atlanta, Georgia; and Michigan State University, East Lansing, Michigan, USA*

It turns out that the overall incidence of renal disease in haemophilia is approximately 35%, so haematuria and other renal abnormalities may be more common than we think [1]. For mild renal bleeding, inhibitor or not, fluids and rest are probably adequate.

In more severe bleeding, defined by pain, drop in haemoglobin, or persistent bleeding despite hydration and rest, the following treatment should be considered: renal imaging (ultrasound) to define an anatomic problem, factor replacement for non-inhibitor patients and by-passing agents for inhibitor patients, and consideration of steroids for 3–5 days.

The issue of anti-fibrinolytic therapy is tricky: the maxim is not to use them in renal bleeding because of the possibility of a clot within the collecting system.

Reference

1 Small S, Rose PE, McMillan N, Belch JJ, Rolfe EB, Forbes CD, *et al*. Haemophilia and the kidney: assessment after 11-year follow-up. *Br Med J* (*Clin Res Ed*) 1982;285(6355):1609–11.

Haemophilia and Scuba Diving

Question	Should we worry about scuba diving in our haemophilia population?
Case	I have several patients with haemophilia who participate in scuba diving. Currently, I recommend that they perform prophylaxis prior to a dive. Should I be more worried?

Response from **Craig M. Kessler, MD**
Georgetown University Medical Center, Washington, DC, USA

There are no data regarding the safety of scuba diving in individuals with a propensity to bleed; however, recent articles suggest that individuals with iatrogenic qualitative platelet dysfunction may be at increased risk of developing spontaneous bleeding and death with scuba diving. I believe that these findings could be extrapolated to individuals with haemophilia. Essentially, spontaneous intrapulmonary bleeds can occur in divers [1]. Also, there is an anecdotal report of spontaneous spinal haemorrhage [2]. Along with the above, there is a report of massive variceal bleeding caused by scuba diving that illustrates the bleeding propensity in otherwise normal individuals who have taken aspirin [3].

The aetiology of the spontaneous bleeds is thought to be due to pressure changes that are proportional to the depth of diving. Intrathoracic pressures become equal to ambient pressure and force more blood flow to these areas of the body, thus inducing spontaneous bleeds. If the haemorrhagic potential appears increased with aspirin use alone, I believe that haemophiliacs and other coagulopathic individuals may be at increased risk of spontaneous bleeding. I concur with your decision to provide haemophiliacs with prophylactic replacement therapy if they choose to dive; however, the data suggest that they may remain at increased risk if they are taking anti-inflammatory medications that could affect platelet function. Haemophiliacs should be educated about the increased risks of spontaneous bleeding proportional to depth of diving. All these risks are certainly compounded by the inherent

physical risks to bleeding with trauma during diving (e.g. cuts from coral reefs).

References

1 Boussuges A, Pinet C, Thomas P, Bergmann E, Sainty JM, Vervloet D. Haemoptysis after breath-hold diving. *Eur Respir J* 1999;13(3):697–9.

2 Hida K, Iwasaki Y, Akino M. Spontaneous spinal hemorrhage during scuba diving. Case illustration. *J Neurosurg* 2002;96(Suppl 3):351.

3 Nguyen MH, Ernsting KS, Proctor DD. Massive variceal bleeding caused by scuba diving. *Am J Gastroenterol* 2000;95(12):3677–8.

Haemophilia and Ventricular Septal Defect Repair

Question	What is the standard protocol in a patient with severe haemophilia A and an elective cardiac surgery such as a ventricular septal defect (VSD) repair?

Response from **Margaret Ragni, MD**
University of Pittsburgh Physicians, Pittsburgh, Pennsylvania, USA

There is probably no "standard protocol" for VSD repair in a patient with severe haemophilia A.

A review of the literature adds little to this notion [1–7]. However, there are probably a few points worth noting. These might be grouped into three categories: (1) the surgical approach (extracorporeal bypass or not), (2) the surgical procedure (valve repair also involved or not), and (3) postoperative procedures (drains removed or not).

A couple of general points: Preoperatively, it would be important to check a peak factor VIII level aiming for 100%. It would also be important to discontinue non-steroidal anti-inflammatory drugs (NSAIDs), which the patient might be using for painful haemophilic arthropathy. Perioperatively, standard perioperative factor VIII dosing might be initiated, that is, dosing to 100% FVIII level prior to sternotomy, 50% just after the procedure, every 8 h for the next 24 h, then every 12 h for 14 days, and then daily for 7 days, for a total 3 weeks of coverage. Monitoring activated partial thromboplastin time (APTT), and FVIII levels, nadir (just before the next dose) if available, may also be helpful in avoiding preventable bleeding.

Surgical Approach

It is important to establish whether the VSD repair will be done by minimally invasive techniques with skin incisions and robotically assisted repair vs. use of extracorporeal bypass with heparin. If the latter is planned, some recommend antifibrinolytic agents, such as aprotinin, amicar, or tranexamic acid, be maintained during the surgical

procedure. Whether antifibrinolytic agents are necessary is not established as there have been no controlled trials in haemophilia. However, at least five separate randomized, double-blind clinical trials have shown that antifibrinolytic agents reduce blood loss in individuals without haemophilia. It is important to note, however, that a small number of case reports in patients with haemophilia, including some with severe disease, find factor coverage alone sufficient to cover VSD repair.

Surgical Procedure

If valve repair will be part of the surgery planned, it is important to be sure tissue valves rather than prosthetic valves, which require anticoagulation, be used. The risk with the latter is that anticoagulation in the setting of an underlying bleeding disorder is not standardized. Although the target INR in a patient without haemophilia is 3 or higher, whether in a haemophilic patient, a level of 1.5–2 is sufficient to prevent thrombosis, but not high enough to precipitate bleeding, remains unknown.

Postoperative Procedures

Although seemingly less important in the realm of septal defect or valvular repair procedures, it is important to ensure factor coverage for removal of drains and chest tubes, or placement of drains, should haematomas form. This is particularly important for those individuals in which new problems arise in an outpatient setting. Raising the factor level to 50–100% dose would be appropriate for drain removal.

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3 Ghosh K, Shetty S. Anticoagulation in haemophilia patients with prosthetic valve replacement. *Haemophilia* 2004;10(6):743.

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Haemophilia with Hepatitis C and Recurrent Bleeding

Question/ Case	Two haemophilic patients who develop chronic hepatitis C were found to bleed more frequently. Despite repeated injections of FVIII, it seems that FVIII products are not as efficacious in treating this recurrent bleeding (haemarthroses), as they were prior to the development of hepatitis. The platelet count is about 60K/μl. Neither a FVIII inhibitor nor other coagulation abnormalities have been detected. Has someone on the panel experienced such cases? How can we manage these patients?

Response from **Margaret Ragni, MD**
University of Pittsburgh Physicians, Pittsburgh, Pennsylvania, USA

Potential causes of bleeding in patients with end-stage liver disease and bleeding disorders include the other coagulopathies that occur. As the case points out, thrombocytopaenia is very commonly the problem. Normally, most individuals would not experience bleeding problems at a platelet count of 60,000 but the likely bleeding tendency could be multifactorial (platelet dysfunction, other medications, and/or anatomic lesions (e.g. varices)). We generally begin factor treatment on a daily basis if the patient has a bleed. One could also consider prophylactic therapy in the absence of a bleed. Occasionally, revising the medication list or avoiding penicillin or other antibiotics that inhibit platelet function may be helpful. DDAVP may also be helpful in improving platelet function.

Response from **Sam Schulman, MD, PhD**
Hamilton Health Sciences – General Hospital, Hamilton, Ontario, Canada

Thrombocytopaenia could indicate liver cirrhosis with hypersplenism. This is often associated with acquired platelet function defects. This should be registered as a prolonged bleeding time, whereas the PFA-100 instrument (Dade Behring) is not always sufficiently sensitive to

pick up such abnormalities. One reason for the acquired defect is reduced clearance of fibrin split products (D-dimers, etc.), which may coat platelets and thereby impair their function. Desmopressin (DDAVP) is often effective in shortening a prolonged bleeding time, irrespective of the acquired risk factor, and even if the patients had haemophilia and no increment of the factor VIII level is expected, the effect on the bleeding time remains. Another possibility is reduced clearance of fibrinolytic factors due to decreased liver function, and in that case it would be important to use tranexamic acid in combination with any other treatment given.

Response from **Francis E. Preston, MD**
Royal Hallamshire Hospital, Sheffield, UK

Is there any evidence of impaired hepatic synthetic function (i.e. low serum albumin and/or prolonged prothrombin time)? We have observed surprisingly low factor IX levels in some patients with haemophilia A and chronic hepatitis C. When bleeding has occurred, this has necessitated the use of both factor IX and VIII concentrates.

Isotretinoin in Haemophilia

Question/ Case	A 17-year-old patient with mild haemophilia (FVIII = 6%) has to be treated with isotretinoin because of severe acne, resistant to previous therapy. Increased bleeding risk due to isotretinoin has been described, which could be related to enhancement of tissue plasminogen activator (t-PA) levels. Has someone experienced increased bleeding episodes in haemophilic patients during treatment with isotretinoin as described in case reported by Dootson? [1]

Response from **Kaan Kavakli, MD**
Ege University Hospital, Izmir, Turkey

I have just investigated the topic using the Internet and I have spoken with my colleagues about this subject. Unfortunately, neither my dermatologist friends nor I have any clinical experience about this vitamin A metabolite (isotretinoin) in acne treatment and increased bleeding risk in haemophilic patients. However, as far as I learned from related references, this drug causes t-PA (tissue plasminogen activator) secretion from human endothelial cells. So this drug may accelerate fibrinolysis. Hence, there is a theoretical possibility that haemophilic boys may experience increased bleeding. The patient mentioned is a mild haemophiliac. Therefore, in my opinion, I don't think that he will have any problem with this drug. Perhaps, tranexamic acid capsules may be recommended for this patient to inhibit fibrinolysis.

Response from **Erik Berntorp, MD, PhD**
Lund University, Malmo, Sweden

It is true that retinoic acid can promote fibrinolysis, at least in experimental systems, and probably also cause vessel growth and skin fragility. Going through the literature this does not seem to be an obvious clinical problem in ordinary acne patients. I am not aware of any reports, written or verbal, other than that by Dootson *et al*., saying that haemophilia patients treated this way may experience an increased bleeding tendency. However, the changed bleeding pattern

reported by Dootson *et al*. may indicate increased fibrinolysis in their patient.

In cases such as this, with a basal factor VIII level of 6%, I would not hesitate to treat with isotretinoin. If the patient experiences increased bleeding symptoms, tranexamic acid may be given to inhibit fibrinolysis. This can also be given as a long-term treatment.

Editors' Note

If the simple addition of tranexamic acid does not prevent bleeding, infusion of Factor VIII concentrate to levels of 30–50% could be considered.

Reference

1 Dootson GM, Keidan J, Anderson JA. Exacerbation of bleeding tendency in a patient with haemophilia A during treatment with isotretinoin. *Br J Dermatol* 1992;127(2):186–7.

Laser Eye Surgery in a Haemophiliac

Question	Should we cover a patient with severe Haemophilia A who is undergoing laser eye surgery for the correction of short-sightedness?

Response from **Walter B. Greene, MD**
OrthoCarolina, Charlotte, North Carolina, USA

Based on my discussion with a local Chairman of Ophthalmology, there are two techniques of refractory surgery using a laser. The older photorefractive keratectomy (PRK) technique is suitable for milder cases of myopia and should not cause bleeding. With the newer technique, a small cut is made in the cornea and a suction cup is used. This would entail a small risk of corneal bleeding and/or a "black eye". If the latter technique is used, then a single transfusion of factor VIII would advisable.

Editors' Note

To be on the "safe" side, some clinicians would administer FVIII concentrate to levels close to 100% of normal. The eye could be considered a vital organ, and unexpected surgical complications might jeopardise the patient's vision if the patient is left untreated.

Managing Haemophilic Pseudotumours

Question	How do you manage haemophilic pseudotumours?
Case	A patient with haemophilia B and a low inhibitor titre (1 BU) presented with a painless, slow-growing mass over his upper inner right thigh, which disturbed his gait. An X-ray of his right femur showed a calcific mass compatible with a pseudotumour. I would like to hear the panel's experiences regarding management of haemophilic pseudotumours.

Response from **Jørgen Ingerslev, MD**
University Hospital Skejby, Aarhus, Denmark

Recently we had to solve a problem of the same nature:

The patient with a known inhibitor developed a haemophilic pseudotumour of the thigh after surgery to fix a fracture of the femoral bone by osteosynthesis. This tumour was removed under the cover of tranexamic acid 25 mg/kg every 6 h and rFVIIa (NovoSeven®) at 100 μg/kg every 2 h for 36 h. This was followed by the same dosing regimen of rFVIIa every 3 h for another 3 days, after which the injection intervals were shifted to every 4 h. We kept the patient's wound well packed with very careful haemostasis. He subsequently underwent rehabilitation training from day 8 onwards. The final outcome was excellent.

This approach is probably the one that you should use too. Since the inhibitor level is quite low at this time, you even have the chance to dose the patient with a highly purified factor IX concentrate (if bleeding occurs while the patient is on rFVIIa). It is not advisable to simultaneously use rFVIIa together with any older type of factor IX concentrate because such concentrates contain various other coagulation factors and there is a risk of thrombosis.

Continuous NovoSeven: Pros and Cons

Question	Could someone on the panel tell me what the current opinion is with respect to using factor VIIa as a continuous infusion (CI)? Is this better than intermittent dosing given the fact that a lot of people now think that higher bolus doses are needed? Is continuous dosing safer and less expensive?

Response from **Ulla Hedner, MD, PhD**
University of Lund, Malmo, Sweden and Novo Nordisk A/S, Denmark

Continuous infusion of rFVIIa

The mechanism of action of rFVIIa is, according to current understanding, to enhance the thrombin generation on thrombin-activated platelets. By doing so, the fibrin structure of the haemostatic plug will be tighter and more resistant against premature lysis. It has been shown that the amount of thrombin as well as the rate of thrombin generation is important for fibrin structure [1]. To obtain this effect, bolus dosing seems to be most adequate. A high bolus dose will give a peak of thrombin generation, which should be optimal in creating a firm and stabile fibrin plug.

Using CI of rFVIIa has been tried to save product [2,3]. This concept was based upon the experience of using CIs of FVIII and FIX in the treatment of haemophilias A and B, respectively. However, the concept of using rFVIIa in treatment of bleeding is totally different, since rFVIIa is not used as substitution therapy. As pointed out earlier, the effect of rFVIIa most probably is to enhance thrombin generation independent of the presence of FVIII or FIX. Therefore, the most adequate dosing schedule of rFVIIa would be bolus dosing.

Two studies of CI of rFVIIa in patients undergoing surgery, including major surgery, have been performed in the UK. The first one, using the originally recommended dosing (one bolus of 90 μg/kg initially followed by 16.5 μg/kg/h in a CI), was published [3]. This study showed several failures with increased bleeding in association with

major surgery in haemophilia patients. The conclusion therefore must be that this regimen does not represent adequate dosing for surgery in haemophilia. The second study used a bolus of 90 μg/kg followed by 50 μg/kg/h in a CI. This study showed an effect comparable to previous studies of rFVIIa therapy in surgery [4,5]. However, the regimen in this study used more drug than the bolus dosing schedule recommended previously.

The conclusion regarding the use of CI of rFVIIa in the treatment of bleeding episodes would be that in cases where it is going to be used, one has to use: (1) doses of up to 50 μg/kg/h in the CI or (2) a dose that has to be adjusted carefully in each patient with respect to pharmacokinetics performed repeatedly in each patient during each treatment. The pharmacokinetics has been reported to vary in some patients during treatment [2]. The dose has to be adjusted and extra bolus doses have to be administered in case of breakthrough bleeds.

Based on the above information, CI is not recommended for rFVIIa treatment. Rather, bolus dosing with high initial doses is recommended.

Response from **Sam Schulman, MD, PhD**
Hamilton Health Sciences – General Hospital, Hamilton, Ontario, Canada

CI with recombinant factor VIIa (rFVIIa) is not endorsed by the manufacturer and is an off-label use. However, there are several publications on case series, where there has been a mixture of successes and failures in the treatment peri- and postoperatively or for a major haemorrhage [6,7]. The failures have to a large extent been associated with the omission of antifibrinolytic therapy (tranexamic acid), sometimes with pump failures, subcutaneous infusion, or surgical bleeding.

The clearance of rFVIIa is very variable, partly age dependent. It is therefore advisable to perform a single-dose pharmacokinetic study before a treatment course. There is software available to calculate the clearance.

A bolus dose must always be given intravenously at the start of the treatment, typically with 90 μg/kg. For major surgery with extensive muscle trauma, a repeat bolus dose after 2 h seems beneficial and should be given for total hip replacement. Some centres give bolus doses for a couple of days before switching to CI. CI follows the last bolus dose with an infusion rate that is based on the clearance and desired factor VII level. When the latter has been kept at >10 IU/ml together with a well-functioning pump and tranexamic acid, most cases

using CI have been a success. The main exception is total hip replacement, where the level should be 20 IU/ml for the first 2–3 days.

In patients with factor XI deficiency much lower levels are needed, probably around 3 IU/ml and in FVII deficiency, where the treatment is pure substitution, a level of 0.5–0.8 IU/ml suffices.

Monitoring is done with a factor VII one-stage clot assay, but some reagents have a thromboplastin that is not as sensitive as required. A shortening of the prothrombin time should also occur, but this test alone is not useful for the monitoring.

To avoid local thrombophlebitis, a parallel infusion with saline 20 ml/h is given in the same peripheral vein. Unfractionated heparin should not be mixed in the factor concentrate, since it affects the activity. Low-molecular-weight heparin causes agglutination in the factor concentrate and, therefore, should also be avoided.

The CADD pump is very reliable, but other minipumps can be used, provided that they have alarm functions for end of infusion, occlusion, low battery, and pump failure.

Substantial savings can be achieved with CI, but only if the surgical outcome is successful. The chance for this increases with the experience of the staff with constant infusion of rFVIIa.

CI is not safer than bolus doses, but the latter are inconvenient (every 2 h dosing initially). Bolus dosing can also be unsafe, if a dose is missed, especially shortly after surgery. This may well happen at night if the staff suddenly gets occupied with another big problem.

There are some centres that have been using rFVII in CI for several surgical procedures with repeated success, and they would not consider reverting to bolus injections on this occasion.

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Haemophilia B and Immune Tolerance with Anaphylaxis

Question/ Case	I have a question about immune tolerance (IT) in haemophilia B. I was concerned about the low reported response rate and the possible development of the nephrotic syndrome or anaphylaxis. The patient has experienced an anaphylactic reaction. I would like advice on how to proceed. Should desensitization be attempted and if so how? Should Rituximab be considered? The child (age 1 year) has significant bleeding and requires frequent treatment with rFVIIa.

Response from **Erik Berntorp, MD, PhD**
Lund University, Malmo, Sweden

It is true that the reported response rate to IT induction is low in haemophilia B. It is important to consider that IT induction in haemophilia B is not as well documented as for haemophilia A. This is due to the rarity of the disorder and the fear of inducing thromboembolic complications with older factor IX products. In Malmö, we have used the Malmö protocol in eight high-responding haemophilia B patients and have been successful in six of these [1]. One conclusion from our experience is that the Malmö protocol gives a high response rate in the treatment of high-responding factor IX inhibitor patients and, given the short treatment time compared to other protocols, could be an option to reduce treatment complications such as the development of the nephrotic syndrome. Thus, I think the Malmö protocol really should be considered as a first-line IT therapy in patients with haemophilia B, and we have never seen any anaphylactic or nephrotic complications in our patients.

The problem then comes up about what to do in a patient who already has an anaphylactic reaction. Rituximab could be considered, but the documentation for using Rituximab in that situation is lacking. The use of Rituximab in other inhibitor situations is also lacking. Another alternative is to try to desensitize the patient and then try IT induction. Desensitization could be achieved by giving slow intravenous

injections or by step-wise infusions of factor IX concentrates under cover of hydrocortisone therapy [2,3].

The use of plasmapheresis and antigen exposure has also been reported [4].

We have our own experience with one patient who was successfully desensitized by giving very low doses of a high-purity factor IX concentrate: 30 units subcutaneously three times per week during one week; 40 units subcutaneously three times per week the following week; and then 50 units subcutaneously three times per week for about 3 months. After desensitization, the patient could be treated with regular factor IX doses although we never achieved IT to the factor IX inhibitor.

The management of haemophilia B inhibitor patients, who have developed allergic reactions, is thus very difficult and no established guidelines have been developed as far as I know. However, the chance to desensitize the patient is quite good and my recommendation is to follow up by trying the Malmö protocol (cyclophosphamide + intravenous gammaglobulin + factor IX concentrate with hydrocortisone administration the first two days). If applying this protocol, the inhibitor titre should be below 10 Bethesda units at the start of treatment. Extracorporeal adsorption of the inhibitor can be used if the titre is above 10 BU, but in a young child this can be technically difficult. If the patient is a high responder, the desensitization procedure may boost the inhibitor to very high level. Therefore, the patient should be treated with recombinant factor VIIa for a long period of time, allowing the inhibitor titre to decline to a level below 10 BU.

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rFVIIa (NovoSeven)

Question/ Case	The patient is a middle-aged woman who underwent a caesarean section. Postoperatively, she became hypotensive and suffered from continued bleeding. Laboratory investigation revealed a marked shift to the left in the white blood cell differential, with many immature granulocytes. Hypoalbuminaemia and thrombocytopaenia were also present. The patient developed the fulminate syndrome known as streptococcal toxic shock syndrome. Group B streptococci were isolated from surgical wound cultures, and the patient subsequently developed diffuse intravascular coagulation (DIC) as evidenced by prolonged clotting times, decreased fibrinogen levels, and the presence of fibrin degradation products. She was given supportive care in the form of fluid resuscitation, vasopressors, and mechanical ventilation, in addition to antimicrobial therapy, and transfusions of blood combined with fresh-frozen plasma and platelets. Presently, her platelet count is 25,000–40,000/μl and she has no bleeding. Standard treatment for severe thrombocytopaenia consists of platelet transfusions. However, a considerable proportion of recipients of multiple transfusions of platelet concentrates from random donors become allo-immunized to HLA antigens. Is recombinant factor VIIa (rFVIIa) recommended as alternative therapy when a patient becomes "refractory" to platelet transfusions or when a life-threatening bleed occurs? Promising results have been reported with rFVIIa in thrombocytopaenic patients with overt bleeding [1]. However, no controlled clinical trials of rFVIIa in thrombocytopaenic patients have yet been reported. Recombinant FVIIa is currently only licensed for use in haemophiliacs with inhibitors. It may also be possible for significant amounts of

tissue factor to be present in circulating blood in situations such as sepsis and DIC, and for this to cause thrombotic complications. However, we are not aware of any published reports of such complications.

Do others have experience with rFVIIa in patients with thrombocytopaenia, sepsis, DIC, and bleeding? Would other users administer rFVIIa under these circumstances?

Response from **Harold Ross Roberts, MD**
University of North Carolina Medical School, Chapel Hill, North Carolina, USA

This case raises interesting questions based on thrombocytopaenia occurring in a patient with DIC and toxic shock syndrome.

Firstly, the question/case asks whether rFVIIa is recommended as alternative therapy when a patient becomes refractory to platelet transfusions. Recombinant FVIIa has been used in patients with mild-to-moderate thrombocytopaenia (platelet counts not lower than 20,000–30,000/μl) [1]. Bleeding times were improved in about 50% of the patients and haemostasis should also be improved. Most of these patients had haematological malignancies with thrombocytopaenia due to the malignancy itself or to concomitant chemotherapy. In a series of eight patients with haemorrhage due to thrombocytopaenia, rFVIIa was administered in doses of 50–100 μg/kg body weight and in six patients bleeding stopped. One patient with Glanzmann's thrombasthenia also responded to infusions of rFVIIa. Whether rFVIIa would be of benefit in acquired platelet disorders is not clear, although there is an anecdotal report of benefit in a patient with renal disease.

The rationale for using rFVIIa in thrombocytopaenia and platelet qualitative disorders is that the tissue factor (TF)-FVIIa pathway is necessary for the initial platelet activation. It has also been shown *in vitro* that, at the doses of rFVIIa mentioned above, FVIIa binds to activated platelets with low affinity, but sufficient to support activation of factor X on the platelet surface [2,3]. These data suggest that rFVIIa might represent useful adjunctive therapy for haemostasis in thrombocytopaenic patients but, as yet, there are not sufficient data to make this an official recommendation.

With respect to the possibility of rFVIIa inducing DIC, one should remember that in any disease in which there is active tissue factor circulating, DIC will occur whether or not the patient receives rFVIIa. Tissue factor will result in activation of endogenous zymogen factor VII with the result that *in vivo* coagulation will be triggered if the stimulus is sufficient. It has been clearly shown that even haemophilic animals given infusions of TF will experience DIC. In patients such as the one described here, it is possible that infusion of rFVIIa will enhance DIC. Recombinant FVIIa has been given to many patients with chronic persistent and chronic active hepatitis without inducing DIC. It has also been given to patients with sepsis without complications but, in these patients, there was no evidence of pre-existing DIC. DIC has been reported, following the use of rFVIIa in one haemophilic patient with an inhibitor who had an extensive haemorrhage into the lower extremity that became necrotic and infected [4]. When surgically manipulated this patient developed DIC. The DIC seemed to be as much related to the surgical manipulation as to the infusion of rFVIIa. This is to be expected since the patient presumably had normal levels of zymogen FVII circulating. The patient received rFVIIa again before surgery, and DIC, which had been corrected, occurred again after surgical manipulation of the wound. The patient died with extensive haemorrhage.

Other reports of DIC are less convincing and have occurred under circumstances where one would expect DIC or have been reported as DIC on the basis of elevated fibrin degradation products or other markers of thrombosis. In many of these patients, the increased levels of such markers were of a degree that would be compatible with uncomplicated surgery, rather than actual DIC. All in all, rFVIIa has proven to be remarkably safe. This is not surprising since in most cases of haemorrhage, there is in fact a separation between the initiation of coagulation and the subsequent propagation of thrombin generation.

Would the administration of rFVIIa be recommended in this specific patient? It would not be recommended in the acute phase of her illness since there is no rationale for use of rFVIIa as treatment for DIC. Replacement therapy is indicated for this condition and some physicians would even use heparin therapy in selected patients. From the description, the cause of thrombocytopaenia in this patient was DIC, so correction of DIC by usual means should represent therapy for the secondary thrombocytopaenia. Recombinant FVIIa would not be recommended in a thrombocytopaenic patient who is not bleeding.

Although not stated in the case report, the patient has apparently responded to replacement therapy and presumably her streptococcal infection has been eradicated. If so, one would expect the thrombocytopaenia to gradually disappear as the patient recovers.

Recombinant FVIIa has been shown to be of benefit in patients with mild-to-moderate thrombocytopaenia due to decreased production; increased sequestration; and selected conditions of increased destruction, such as auto-immune thrombocytopaenia. Further clinical trials of rFVIIa for thrombocytopaenia are indicated.

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Thrombosis in PCCs vs. APCCs

Question	Is the risk of thrombosis greater with Prothrombin Complex Concentrates (PCCs) or activated Prothrombin Complex Concentrates (APCCs – FEIBA)?

Response from **Jeanne Lusher, MD**
Wayne State University School of Medicine, Detroit, Michigan, USA

In general, I do not think that PCCs are more thrombogenic than APCCs when used in persons with haemophilia complicated by an inhibitor. The greatest risk of the thrombogenicity is when persons with haemophilia B receive repeated doses of PCCs at frequent intervals. In fact, shortly after the introduction of factor IX complex concentrates (so-called PCCs) in the late 1960s, reports of thrombotic complications began to appear. Deep vein thrombosis, pulmonary embolism, and disseminated intravascular coagulation (DIC) occurred most often in persons with haemophilia B who were undergoing orthopaedic (or other) surgical procedures or who had crush injuries or extensive intramuscular haemorrhages – situations in which thromboplastic substances entered the circulation. Persons with significant hepatocellular disease were also at risk, as they often had low levels of antithrombin and could not clear clotting intermediates from the circulation. It was speculated that partially activated clotting factors (FIXa, FXa), and/or platelet-active phospholipids might be responsible for the thrombotic complications. In surveys conducted on behalf of the International Society of Thrombosis and Hemostasis' Scientific and Standardization Committee (SSC), factor VIII/factor IX Subcommittee, it was apparent that such complications were still occurring in persons with haemophilia B in the early 1990s. However, throughout the 1980s and 1990s, their incidence declined – no doubt due to greater awareness of this potential complication and more judicious use of PCCs.

Since inhibitor patients receive considerably more PCCs per bleeding episode than non-inhibitor patients, one might have expected that more thrombotic episodes would have occurred in inhibitor patients. However, this was not the case. Possible explanations for the lower

incidence in inhibitor patients include the fact that, unlike the situation in haemophilia B, PCCs given to inhibitor patients do not correct the underlying haemostatic defect. Additionally, far fewer elective orthopaedic surgical procedures were being performed in inhibitor patients because of the unpredictability of maintaining haemostasis with either "standard" or activated PCCs (APCCs).

From a theoretical stand-point, one might expect to see a higher incidence of thrombotic complications in inhibitor patients being treated with PCCs than with APCCs, as the latter are more effective than PCCs and thus fewer doses would be used. On the other hand, APCCs contain more activated clotting factors, and thus might be expected to be more thrombogenic, even in inhibitor patients.

However, since some inhibitor patients do develop thrombotic complications when treated with PCCs or APCCs, one should consider an alternative therapy (e.g. rFVIIa, or porcine FVIII, if available) for patients with situations known to predispose to venous thrombosis and/or DIC.