Hemophilia and Hemostasis

A Case-Based Approach to Management

2nd edition

Edited by **Alice D. Ma, Harold R. Roberts, and Miguel A. Escobar**

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Foreword

I am delighted to respond to the invitation to provide a brief introduction to the second edition of *Hemophilia and Hemostasis: A Case-Based Approach to Management*. The popularity of this text stems from its unique case-based approach. Drs Roberts, Ma, and Escobar are renowned and frequently consulted experts in the management of patients with bleeding disorders. Although the hemophilias and other inherited bleeding disorders have been the focus of a comparatively large body of literature, there are remarkably few randomized-controlled clinical trials on which to base firm evidence-based recommendations. This fact was most recently brought home to me as a member of the team charged with revising the World Federation of Hemophilia's *Treatment Guidelines*; our goal was to provide appropriately graded recommendations of the literature and generally accepted practices for the practicing clinician. Unfortunately, the paucity of high-quality level 1 evidence does not obviate the need to make clinical decisions on a daily basis when caring for patients with bleeding disorders. The authors address these management dilemmas in a comprehensive series of "mini-chapters" that provide an easy reference format for the reader. In this day and age of electronic fingertip access to state-of-the-art reviews on PubMed, it is sometimes said that textbooks are obsolete before they are even published. While there may be some truth to this viewpoint in the case of standard texts, no amount of electronic searching can provide the ready access to the august consensus opinions of these seasoned experts, who have "been down that same road" before. As such, this book is a must for every hematologist or nurse who is charged with taking care of patients with bleeding disorders.

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PART I
Hemophilia A and Hemophilia B

SECTION I
General Overview

INTRODUCTION 1

The Hemophilic Ankle: An Update

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Q What is the latest information regarding the treatment of hemophilic arthropathy in the ankle?

It is well known that the ankles in hemophilic patients 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 hemophilic 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 hemarthrosis–synovitis–hemarthrosis, which eventually will result in hemophilic arthropathy (Figure I1.1).

Pathogenesis of synovitis and cartilage damage in hemophilia: experimental studies

Hooiveld *et al.* (2004) 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. 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 hemorrhages without joint loading do not. The authors suggest that this might reflect a possible mechanism of joint damage in hemophilia. In two other papers (Hakobyan *et al.* 2004;

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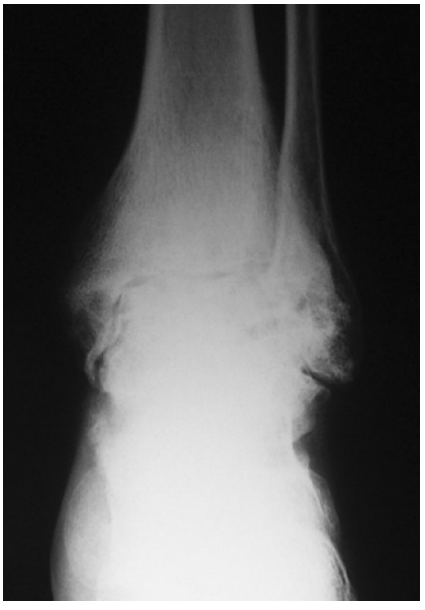

Figure I1.1 Severe hemophilic arthropathy of the ankle in an adult hemophilia patient.

Valentino *et al.* 2004), hemophilic arthropathy was studied in animal models. Despite these interesting papers, the pathogenesis of hemophilic arthropathy remains poorly understood.

The best way to protect against hemophilic 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 the use of a central venous access device, such as a PortaCath, which is otherwise 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 hemophilia center. The reported complication rates for infection and thrombosis have varied considerably from center to center. 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, radiosynovectomy, together with primary prophylaxis to avoid joint bleeding, can help to halt hemophilic synovitis. Ideally, however, radiosynovectomy should be performed before the articular cartilage has eroded. Radiosynovectomy is a relatively simple, virtually painless, and inexpensive treatment for chronic hemophilic

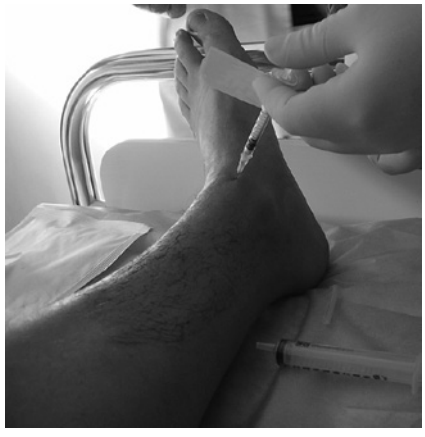

Figure I1.2 Radiosynovectomy of the ankle with 186 rhenium.

synovitis, even in patients with inhibitors, and is the best choice for patients with persistent synovitis.

Radiosynovectomy

Radiosynovectomy is the intra-articular injection of a radioactive material to diminish the degree of synovial hypertrophy and to decrease the number and frequency of hemarthroses (Figure I1.2). Radioactive substances have been used for the treatment of chronic hemophilic synovitis for many years. 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 radiosynovectomy is chronic hemophilic synovitis causing recurrent hemarthroses, unresponsive to treatment. There are three basic types of synovectomies: chemical synovectomy, radiosynovectomy, and arthroscopic synovectomy. 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.

Radiosynovectomy (Yttrium-90, Phosphorus-32, and Rhenium-186) can be repeated up to three times at 6-month intervals. Chemical synovectomy can be repeated weekly up to 10–15 times if rifampicin is used. After 35 years of using radiosynovectomy world wide, no damage has been reported in relation to the radioactive materials. Radiosynovectomy 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 papers that focus on the treatment of chronic hemophilic synovitis. Corrigan *et al*. (2003) have used oral D-penicillamine for the treatment of 16 patients. The drug was given as a single dose in the morning before breakfast. The dose was 5–10 mg/kg bodyweight, 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, 3 had a reduction in palpable synovium and 3 had no response. Minor reversible drug side effects occurred in 2 patients (proteinuria in one and a rash in the other).

Radossi *et al*. (2003) have used intra-articular injections of rifamycin. 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 program and developed single or multiple joint chronic synovitis. The indications for chemical synovectomy were symptoms of chronic synovitis referred by patients reported in a questionnaire. In Radossi's series there were 5 patients with inhibitors to factor VIII. 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, i.e. 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 6 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 synovectomy: 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 (Radossi *et al*. 2003). However, they make no mention of the pain associated with the injections. They also state that rifamycin may be indicated when radiosynovectomy 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 radiosynovectomy, or why patients should reject such an efficient and safe procedure. The Italian authors state that, to date, they cannot say if their program 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 synovectomy appears to be effective in reducing joint pain and in improving the range of motion.

The study of Corrigan *et al*. (2003), which used D-penicillamine, has two main limitations: the small number of patients and the lack of use of