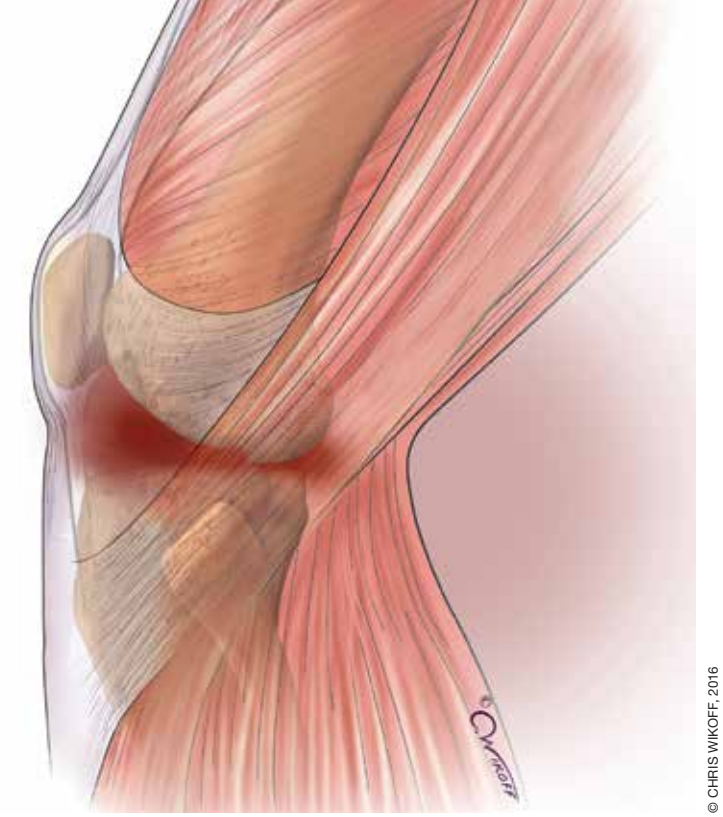
Haemophilic arthropathy: can it be prevented?

MATTHEW J.S. PARKER MB ChB, MRCP
LIANE KHOO BSc, MB BS, PhD, FRACP, FRCPA
JANE F. BLEASEL MB BS, PhD, FRACP



Safe and effective replacement clotting factor concentrates are available for treating patients with haemophilia, but challenges remain in the management of haemophilic arthropathy. Primary prophylaxis with additional on-demand treatment offers the optimal management strategy for minimising long-term joint damage.

MedicineToday 2016; 17(11): 55-60

Dr Parker is an Advanced Trainee in Rheumatology at Royal Prince Alfred Hospital, Sydney. Dr Khoo is a Staff Specialist in Haematology at Royal Prince Alfred Hospital, Sydney. Professor Bleasel is a Senior Staff Specialist in Rheumatology at Royal Prince Alfred Hospital, Sydney, and Co-Director of the Sydney Medical Program, The University of Sydney, Sydney, NSW.

SERIES EDITORS: Dr Bethan Richards MB BS(Hons), FRACP, MMed(ClinEpi), MSportsMed, Senior Clinical Lecturer, The University of Sydney, and Head of Rheumatology, Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, NSW. Professor Lyn March, MB BS, MSc, PhD, FRACP, FAFPHM, Liggins Professor of Rheumatology and Musculoskeletal Epidemiology, Institute of Bone and Joint Research, University of Sydney, and Senior Staff Specialist Rheumatologist, Royal North Shore Hospital, Sydney, NSW.

Australian Rheumatology Association

Patients with haemophilia are characteristically at risk of spontaneous haemorrhage, and haemophilic arthropathy is the single major cause of morbidity.[1,2] Recurrent haemarthrosis, which accounts for approximately 70 to 80% of bleeding episodes, is the predominant cause of chronic disability (Figure 1).[3] Spontaneous bleeds also occur in muscle, soft tissue, other organs and the central nervous system but are less common. Despite the availability of safe and effective treatment for haemophilia, most commonly in the form of replacement clotting factor concentrates, the prevention and management of joint bleeds remain challenging.

What is haemophilia?

Haemophilia is an X-linked bleeding disorder caused by primary deficiency of coagulation factor VIII (in patients with haemophilia A) or factor IX (in patients with haemophilia B). The incidence of haemophilia A is 1 in 5000 and of haemophilia B is 1 in 30,000 male births.[4]

Haemophilia has an X-linked recessive inheritance pattern; however, approximately one-third of patients have no family history, with their disease occurring either as a result of a spontaneous genetic mutation or in a family that has preceding generations of phenotypically unaffected female carriers. More than 2000 individual mutations in the factor VIII gene and more than 1000 mutations in the factor IX gene have been described. Identification of the individual mutation is important for any subsequent prenatal diagnosis and also for carrier screening in affected families.[4]

Haemophilia is classified as mild, moderate or severe according to clotting factor level, and the frequency and severity of bleeding is correlated with the level of circulating factor (Table). Chronic arthropathy is usually seen in patients with severe haemophilia but can be seen in patients with factor levels up to 20% of normal.[2] This observation underlies the rationale for prophylactic factor replacement.

TABLE. SEVERITY CLASSIFICATION OF HAEMOPHILIA

Severity	Clotting factor (% of normal level)	Bleeding characteristics
Mild	>5%	Spontaneous bleeds are rare
Moderate	1 to 5%	Occasional spontaneous bleeds may occur, but bleeds are usually associated with surgery or trauma
Severe	<1%	Spontaneous bleeds into joints and muscles are common

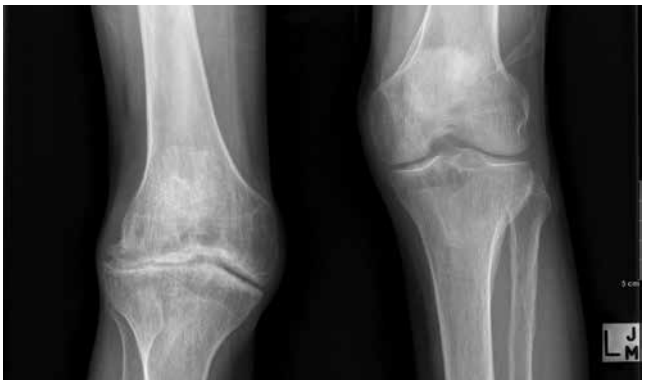


Figure 1. Severe haemophilic arthropathy of the knee.

Bleeding and joint damage

The presence of blood within a joint is an intensely inflammagenic event, resulting in the hallmark pentad of symptoms: localised severe pain, swelling, erythema, warmth and loss of function. Each episode of bleeding can result in permanent joint damage secondary to chronic synovitis and cartilage degradation (Figure 2). The pathogenesis of blood-induced joint damage involves an interplay between degenerative and inflammatory processes involving a wide range of cell types and extracellular components (Figure 3). The joints that are most commonly affected are the elbows, knees and ankles (the 'target joints'), followed by the hips.

Management strategy

The optimal management strategy for minimising long-term joint damage in patients with haemophilia is conceptually two-fold:

- to prevent acute haemarthrosis, and
- to treat acute bleeds as promptly as possible.

Safe and effective treatment for haemophilia is available, mainly in the form of replacement factor concentrates. Transmission of bloodborne diseases has not occurred through blood products for many years in Australia but is still a significant problem globally. Optimal patient care involves a multidisciplinary team, which includes haemophilia treatment nurses, doctors and allied health professionals, often with support from the Haemophilia Foundation in the State or Territory. Further information is available from the Haemophilia Foundation website (www.haemophilia.org.au) or from the recently updated Australian guidelines (www.blood.gov.au/haemophilia-guidelines).[5] The World Federation of Hemophilia (WFH) *Guidelines for the Management of Hemophilia*, which were revised and updated in 2013, provide evidence-based and practical information on all aspects of management and are available online (www.wfh.org/en/resources/wfh-treatment-guidelines).[3]

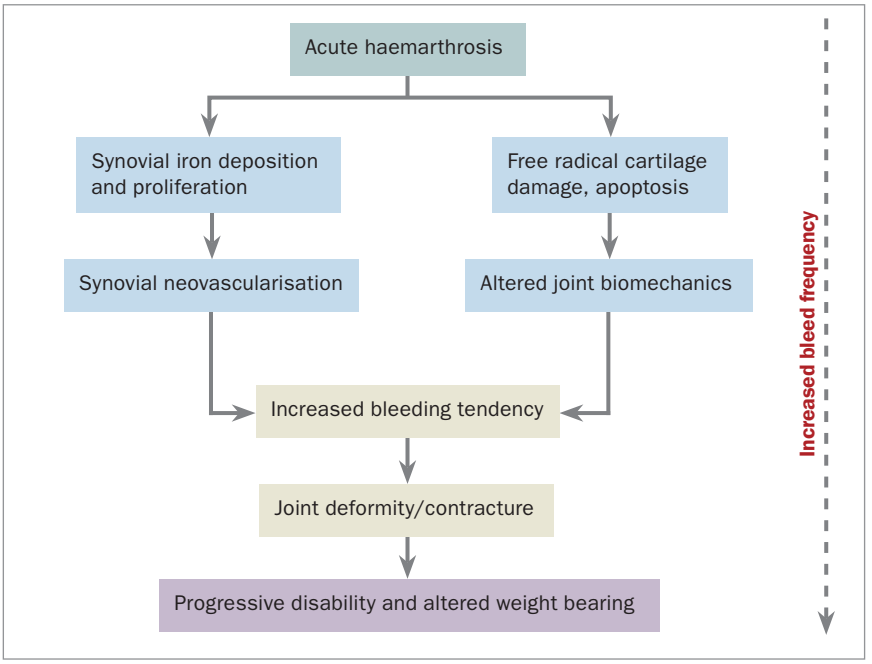
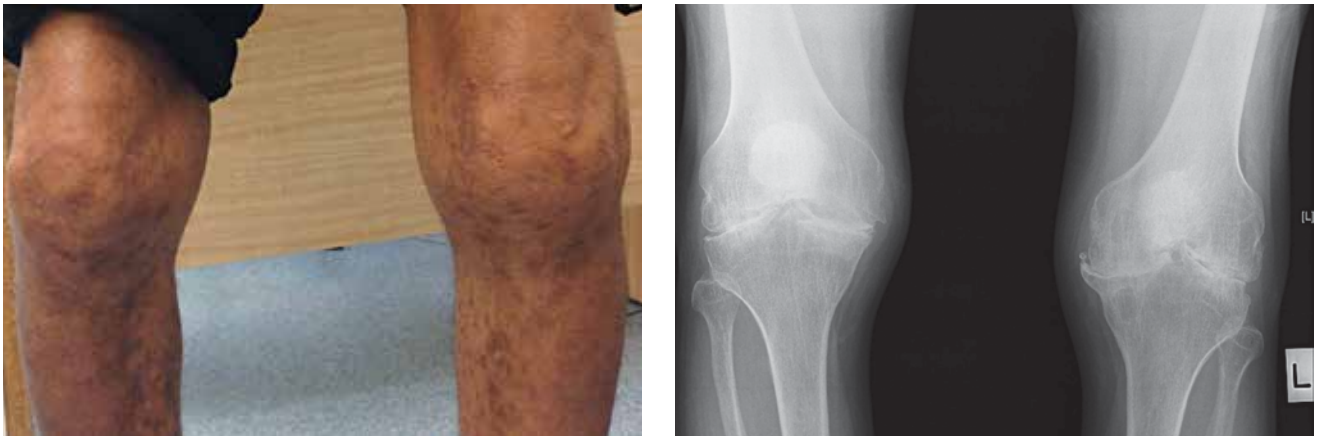


Figure 2. Progression of joint disease caused by recurrent haemarthrosis. Every acute haemarthrosis can contribute to an increased likelihood of subsequent bleeding by mechanical and inflammatory mechanisms.

Prophylaxis

Prophylaxis in haemophilia is defined as regular treatment with clotting factor concentrates (or alternative novel agents) to prevent bleeding episodes. There is strong evidence that prophylactic factor



Figures 3a and b. A 43-year-old man with severe haemophilia A, living in a developing country without regular access to factor VIII replacement, and a history of multiple haemarthroses, most often in his dominant right knee. a (left). Severe haemophilic arthropathy with a 30-degree fixed flexion deformity of the right knee. b (right). The corresponding weightbearing x-ray appearances show advanced arthropathy in both knees, which is most severe on the right.

replacement prevents the development of haemophilic arthropathy.[6-8] When prophylaxis is started at diagnosis, children accumulate virtually no joint damage and maintain normal joints. All patients with severe disease or with recurrent haemarthroses should be receiving prophylaxis. In addition, all patients – even those with mild disease – who require invasive or surgical procedures need prophylactic factor replacement, usually aiming for near-normal plasma factor levels.

All forms of replacement factor are administered intravenously, usually twice a week for haemophilia B and three times a week for haemophilia A. For many young patients, an indwelling port is inserted to improve access. The burden of treatment is significant and many patients choose to modify their prophylactic regimens or to treat their haemophilia 'on demand' (i.e. at the first symptoms of a joint bleed).

Acute joint bleeds

Patients need to be educated from a young age (along with their families) about the signs and symptoms of an impending or evolving joint bleed. These include sensations of 'pins and needles' or 'burning' within the joint before the development of a more obvious haemarthrosis. If a patient experiences a number of joint bleeds then it can become increasingly difficult to distinguish ongoing haemarthroses from accelerated degenerative arthritis on the basis of symptoms. Regular imaging, including bedside ultrasound, can be invaluable in making management decisions.

Every patient with haemophilia should have an individualised treatment plan for acute bleeds, developed in conjunction with their haemophilia care team. This often involves extra factor replacement for around 72 hours after the onset of bleeding.

Complete rest of the affected joint is advisable and is generally appropriate for 48 hours. Analgesia is important, with COX-2 inhibitors such as meloxicam and celecoxib favoured over the less-specific NSAIDs because they have less impact on platelet function. Opiates are safe but should be prescribed judiciously. Cold compression bandaging or ice packs applied around the joint can help to reduce symptoms.

Although aspiration of a haemarthrosis may seem logical, it is often impractical and can be quite traumatic, especially for younger patients, and usually requires a large-bore (16 G) needle. It is considered occasionally in the setting of a persistent tense effusion when there is neurovascular compromise or when infection is suspected. After the bleed has stabilised (typically 24 hours), isometric exercise and subsequently graduated exercise should be commenced, focusing on improving range of motion to help reduce the risk of contracture or flexion deformity.

Chronic arthropathy

The development of 'boggy' synovitis and characteristic radiographic changes indicates significant permanent joint damage and necessitates careful treatment.[9] Factor prophylaxis and prompt treatment of acute bleeds, as described above, remain the priority. Physiotherapy to maintain strong muscle groups around target joints is also important. Intra-articular corticosteroid injection with appropriate prophylactic factor cover can provide significant symptomatic benefits, especially when there is evidence of synovitis clinically or on imaging.

Regular use of outcome assessment tools helps to monitor for chronic arthropathy and prompts earlier intervention. Useful tools in specialised haemophilic arthropathy centres include the Haemophilia Joint Health Score and the Haemophilia Early Arthropathy Score using Ultrasound (HEAD-US). More information about functional and physical assessment tools

1. HAEMOPHILIC ARTHROPATHY: ROLES FOR THE GP IN MANAGEMENT

- Consider haemarthrosis as a cause for joint pain in children. Remember that not all children with haemophilia have a family history of haemophilia.
- Encourage urgent clotting factor replacement in the setting of a suspected joint bleed. Provide advice on nonpharmacological interventions, such as joint rest and cold compression.
- Help reinforce healthy lifestyle advice, including regular exercise with appropriate treatment prophylaxis.
- Harness the unique relationship between GP and individual patients and families to promote adherence to burdensome treatment regimens and support them through the many psychosocial challenges presented by living with a chronic condition.
- Provide advice about pain management, remembering that a substantial proportion of patients with haemophilia live with chronic pain and its consequences.

is available on the WFH website (www.wfh.org/assessment_tools).

Radionucleotide synovectomy with yttrium-90 or rhenium-186 is often a successful intervention for reducing the frequency of pain and bleeding by around 70% in joints where there is ongoing evidence of inflammation or bleeding despite appropriate management.[10] Intra-articular needle placement is confirmed radiologically before injection. The joint needs complete rest for 24 hours after the procedure and there is a small risk of surrounding soft tissue injury if there is any extravasation of the radionuclide.

Surgery can be very effective for reducing pain and improving function in joints with chronic arthropathy. The type and timing of surgery are complex decisions best made in consultation with the entire treating team. Surgical interventions include synovectomy, arthroplasty and arthrodesis (especially useful in knees or ankles). Maintaining preoperative clotting factor levels around 80 to 100% of normal reduces complications.

Associated conditions

Patients with well-managed haemophilia often live very normal lives. However, haemophilia is associated with accelerated osteoporosis, especially around severely affected joints. Patients with haemophilia may seek information regarding pain management, as a substantial proportion of patients live with chronic pain and its physical and psychological consequences. Advice from their GP about pain management, sometimes with input from a specialist pain team, can be invaluable.

As a consequence of the bloodborne virus epidemic in haemophilia patients acquired from blood products prior to widespread screening protocols, many middle-aged patients currently live with hepatitis B or C and/or HIV infection. These conditions provide their own challenges and can have multiplicative risks, such as secondary osteoporosis or development of inhibitors.

Physical activity

Usual physical activity should be encouraged. Although patients and their families and treating teams are often anxious about perceived 'risky' activities, it is important for quality of life that patients maintain physical activity.[11] They should be encouraged to involve themselves as much as possible in the activity of their peers. Good muscle strength and coordination may help to prevent injury and bleeding. It stands to reason that some sports (such as swimming) have a significantly lower risk of bleeding compared with more high impact activity (such as basketball or contact sports). An individualised risk assessment should be discussed with the patient, but there are reassuring examples of elite sportsmen with haemophilia and plenty of anecdotal reports of patients safely engaging in, for example, alpine sports and even bungee-jumping without any increase in bleeding because of sensible precautions and adapted treatment schedules.

As a general rule, replacement factor should be administered prior to activity to minimise risk. For patients treated with factor prophylaxis, bleeds and subsequent arthropathy have become more common in the ankle than in the knee, and patients should be educated about wearing appropriate cushioned footwear. The advice of an orthotist may be helpful.

Management challenges

Primary prophylaxis with additional on-demand clotting factor replacement offers the optimal management strategy for minimising long-term joint damage in patients with haemophilia. In practice, however, there are many complicating factors that can make implementation of this strategy difficult.

Inhibitors

'Inhibitors' in haemophilia refer to IgG antibodies that neutralise clotting factors VIII or IX. Development of these inhibitors represents the most severe treatment-related complication because usual factor replacement becomes less effective.[4] Inhibitors occur in up to 30% of patients with haemophilia A and up to 5% of patients with haemophilia B.

The management of patients with inhibitors remains challenging, with the optimal strategy yet to be proven. In cases where there is a low titre inhibitor, treatment can consist of increased doses of factor concentrates (to 'overcome' the inhibitor). In cases where there is a high titre inhibitor, factor replacement is no longer effective and 'bypass' agents such as recombinant factor VIIa and 'factor eight inhibitor bypassing activity' (FEIBA) are required to trigger coagulation and stop bleeding. Strategies to eradicate the inhibitor include immunotolerance, where high doses of factor are used, sometimes in conjunction with other treatments such as cyclophosphamide or rituximab. Patients with inhibitors have a generally worse quality of life and an increased frequency of joint bleeds.

2. PRACTICE POINTS

- Haemophilic arthropathy is the major cause of morbidity in patients with haemophilia.
- Primary prophylaxis with additional on-demand clotting factor replacement offers the optimal management strategy for minimising long-term joint damage in patients with haemophilia.
- When managed with appropriate factor prophylaxis, patients with haemophilia should be encouraged to participate in all but the highest risk activities.
- Challenges in the treatment of patients with haemophilic arthropathy include the management of inhibitors and associated chronic conditions.
- Sustaining patient engagement in a burdensome treatment regimen and ensuring access to treatment are important aspects of management for patients with haemophilia.

Patient engagement

Haemophilia is a chronic condition that spans an individual's entire life. Understandably, maintaining optimal treatment is often most limited by a lack of sustained patient motivation. Unfortunately, however, even a short period of suboptimal treatment often results in irreversible joint damage and disability. Regular ultrasound assessments can be used to monitor arthropathy, but visual feedback can also be a very useful motivational tool.

Information for patients is available from the Haemophilia Foundation website (www.haemophilia.org.au).

Access to treatment

The logistics of managing a chronic condition such as haemophilia can be intimidating and difficult for patients. This is especially true for those who live in remote areas, have language barriers or are culturally suspicious of blood products or the environment in which health care is provided.

Foreign travel is a particular challenge that should be planned for carefully. There are haemophilia management centres across the world in most major cities that are usually happy to provide treatment to travellers. A sobering reality is that approximately 80% of countries worldwide do not have widely accessible treatment, and many of these use human-derived clotting factors for on-demand management of major bleeds which increases the risk for transmissible diseases.

Future treatment options

One of the major limitations of conventional treatments for haemophilia is the short half-life of the replacement factor. A number of bioengineered products are in various stages of human testing that could significantly improve the burden of treatment by extending the half-life of factor VIII and IX products. There is also research into the subcutaneous route of administration and into other components of the coagulation cascade. There have been promising results in the area of gene therapy, and some early success demonstrated for treatment of patients with haemophilia B.[12]

Conclusion

The improved patient outcomes from optimal treatment of haemophilia can be seen as a great achievement in medicine in the last century. Prophylactic clotting factor replacement and prompt treatment of acute bleeds allow patients with haemophilia the opportunity for a more 'normal life'. A comprehensive model of care, with interacting health professionals fine-tuning treatment at regular follow up offers patients the best chance of achieving this.

GPs play a key role in supporting patients through the challenges of living with a chronic condition and promoting adherence to the optimal management strategy. Some roles for the GP in the management of patients with haemophilia are described in Box 1; practice points are summarised in Box 2. MT

References

1. Bleasel JF. Hemophilia and other bleeding disorders. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. Rheumatology. Philadelphia PA: Elsevier; 2015. p. 194.
2. Steven MM, Yogarajah S, Madhok R, Forbes CD, Sturrock RD. Hemophilic arthritis. Q J Med 1986; 58: 181-197.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al; Treatment Guidelines Working Group on Behalf of The World Federation of Hemophilia. Guidelines for the management of hemophilia. Hemophilia 2013; 19: e1-e47. Available online at: http://www.wfh.org/en/resources/wfh-treatment-guidelines (accessed October 2016).
4. Peyvandi F, Garagiola I, Young G. The future of haemophilia: diagnosis, treatments and its complications. Lancet 2016; 388: 187-197.
5. Australian Haemophilia Centre Directors' Organisation, and the National Blood Authority. Guidelines for the management of haemophilia in Australia. Australian Haemophilia Centre Directors' Organisation, 2016. Available online at: https://www.blood.gov.au/haemophilia-guidelines (accessed October 2016).
6. Nilsson IM, Berntorp E, Logqvist T, Pettersson H. Twenty five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med 1992; 232: 25-32.
7. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007; 357: 535-544.
8. Gringeri A, Lundin B, Von Mackensen S, et al. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). J Thromb Haemost 2011; 9: 700-710.
9. Pettersson H, Ahlberg A, Nilson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res 1980; 233: 153-159.
10. De La Cort-Rodriguez H, Rodriguez-Merchant EC, Jimenez-Yuste V. Radiosynovectomy in hemophilia: quantification of its effectiveness through the assessment of 10 articular parameters. J Thromb Haemost 2011; 9: 928-935.
11. Pasta G, Mancuso M, Perfetto OS, et al. Synoviorthesis in hemophilia patients with inhibitors. Haemophilia 2008; 14: 52-55.
12. Nathwani AC, Reiss UM, Tuddenham EG, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. N Engl J Med 2014; 371: 1994-2004.

COMPETING INTERESTS: None.