Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia

A United Kingdom Haemophilia Centre Doctors’ Organisation (UKHCDO) guideline


*Haemophilia Centre, Royal Victoria Infirmary, Newcastle upon Tyne; †Department of Haematology, Derby Hospitals NHS Foundation Trust, Derby; ‡Haemophilia Centre, Royal Cornwall Hospitals NHS Trust, Truro; §Haemophilia Centre, Guys and St. Thomas’ NHS Foundation Trust, London; ¶Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, London; **Institute of Translational Medicine, University of Liverpool, Liverpool; ††Haemophilia Centre, Churchill Hospital, Oxford; ‡‡Haemophilia Centre, Queen Elizabeth Hospital Birmingham, Birmingham; and §§Haemophilia Centre, Manchester Royal Infirmary, Manchester, UK

Keywords: arthropathy, haemarthrosis, haemophilia, radioactive synovectomy, synovitis

Introduction

Prior to the availability of clotting factor concentrates, the natural history of arthropathy in severe haemophilia was well described, with recurrent bleeds into joints leading to progressive joint damage and ultimate destruction with associated functional problems. The prophylactic use of factor concentrates has dramatically modified the natural history of haemophilic arthropathy. The early use of prophylaxis can prevent joint bleeding and avoid the cycle of damage associated with recurrent haemarthrosis. Children who are treated on prophylaxis schedules often reach skeletal maturity with well-preserved joint function. However, in addition to the clinically obvious bleeds, recurrent subclinical episodes may also contribute to joint damage [1]. Once joint arthropathy is established, prophylactic treatment may not prevent further joint deterioration.

Although the exact pathogenesis of haemophilic arthropathy has not been elucidated, several in vitro animal and human experiments have demonstrated blood-induced changes in all the ‘components’ of large synovial joints including the synovium itself, cartilage and the subchondral bone. The two major changes in the synovium are hypertrophy and hypervascularity. The key stimulant for these changes is iron released into the synovial fluid, which is both pro-inflammatory and proangiogenic [2–4]. The consequence of neovascularisation in the synovium is predisposition to more bleeding since these new vessels are friable. This leads to a vicious circle of bleeding, iron accumulation, synovial hypertrophy and hypervascularization leading to further bleeding and ultimately progressive joint damage. Interventions aimed at preventing or breaking this cycle are key strategies for the preservation of joint function in people with haemophilia. Bleeding is particularly problematic in the diarthrodial-hinged joints such as the knee, elbow and ankle. It is therefore important that acute bleeds in patients on either ‘on demand’ or ‘prophylaxis’ regimens are treated optimally with the aim of minimizing the synovial proliferation secondary to bleeding which is central to the pathogenesis of arthropathy.

A recent survey has shown significant variation in practice in the UK [5], which suggests that there is a
need for guidelines as a framework for best practice. Evidence-based guidelines were developed summarizing best practice for the assessment and management of acute joint bleeds and chronic synovitis in persons with haemophilia. This guideline does not include surgical procedures such as surgical synovectomy, arthrodesis and arthroplasty.

Materials and methods

The information contained in this guideline was gathered from an appropriate and pertinent literature search in relation to UK practice. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the United Kingdom Haemophilia Centre Doctors’ Organisation (UKHCDO) Advisory Board. The ‘GRADE’ system was used to quote levels and grades of evidence, details of which can be found at: http://www.gradeworkinggroup.org. Strong recommendations (grade 1, ‘recommended’) are made when there is confidence that the benefits either do or do not outweigh the harm and costs of treatment. Where the magnitude of benefit or not is less certain, a weaker grade 2 recommendation (‘suggested’) is made. Grade 1 recommendations can be applied uniformly to most patients, whereas grade 2 recommendations require a more individualized application. The quality of evidence is graded as high (A), based on high quality randomized clinical trials, moderate (B), low (C) or very low (D).

Management of acute haemarthrosis

Prophylaxis is the current standard of care, although individual patients continue with on-demand treatment [6]. In patients receiving on-demand treatment, spontaneous and traumatic bleeds are common [7]. For those receiving prophylaxis, trauma is often the major precipitant of bleeding but inadequate trough levels, missed doses, underlying synovitis or established joint damage may be contributory factors. The signs and symptoms associated with joint bleeds are shown in Table 1. A re-bleed is defined as worsening of the condition either on treatment or within 72 h after stopping treatment [7].

The objective of initial factor replacement therapy is to improve haemostasis in order to arrest bleeding. Subsequent treatment aims to prevent recurrent bleeding and the onset and progression of joint damage. Prompt treatment of bleeding is important and as it has the advantage of potentially preventing permanent damage and this is best achieved with home therapy and patients have been traditionally advised to treat any early symptoms and signs of bleeding. The advantages of home therapy include significant decreases in days lost from work and school, days hospitalized and hospital visits [8]. In those with established arthropathy, it may be difficult to distinguish early bleeds from flares of arthritic pain [9,10].

Haemostatic management of patients with Haemophilia A and B

Dose of initial therapy. Early bleeds in patients who are on prophylaxis are usually adequately treated by a single dose with resumption of usual prophylaxis thereafter. Early studies attempted to investigate the optimum treatment for bleed resolution. The interpretation of these studies is complicated by the variable severity of the bleeds included and the lack of standardized assessment criteria. Prior to the availability of factor concentrates, it was demonstrated that doses of cryoprecipitate achieving FVIII plasma levels of 28%, 35% and 53% correlated with successful treatment in 90%, 95% and 99% of bleeding episodes respectively [11]. Many early studies demonstrated that prompt, low doses of factor were equally effective in resolution of bleeds [12–14] but more rapid improvements were demonstrated with higher factor levels [15].

There are few randomized trials which have compared different initial doses of factor. One study found that an initial treatment with factor VIII 28 IU kg\(^{-1}\) was no more effective than 14 IU kg\(^{-1}\) in terms of time to symptom resolution and requirement for further treatment [16]. However, the beneficial effect of a higher initial dose has been demonstrated where patients with levels of 40% compared to 20% had shorter time to full functional recovery [17]. Pivotal studies of recombinant factor VIII and Factor IX concentrates, including studies of extended half-life

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<td>Early bleed</td>
<td>A sensation of fullness, stiffness, discomfort, pain or tingling at the end of range of movement in the absence of trauma. Often described as aura by patients and at times can be difficult to distinguish from arthritic pain</td>
<td>Normal motion</td>
<td>[7,73]</td>
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products, have shown variation in the doses used, and the median dose used for bleed resolution was around 30 IU Kg\(^{-1}\) in most studies, with 90 to or \(-95\%\) of the bleeds requiring one or two infusions for complete resolution [12,18–21]. In a retrospective study factor, doses of 25 to \(-40\) IU kg\(^{-1}\) per bleeding episode were inferior only to prophyaxis in terms of reducing the progression of arthropathy [22].

Subsequent factor treatment. Subsequent factor therapy depends on the severity of the bleed. Serial ultrasound of joint bleeds show a persistent effusion for a few days and confirms previous clinical observations that time to complete resolution is longer than the time to loss of pain [23]. Early minor bleeds are generally adequately treated by a single dose, resuming usual prophylaxis thereafter. For more significant bleeds or in those who are not on prophylaxis, treatment should continue for a couple of days after symptomatic relief. This is usually achieved by a daily dosing schedule. For severe bleeds, 12-hourly dosing may be required initially.

Non - Inhibitor patients - Recommendations

1. All patients with severe haemophilia A and B and other patients at risk of joint bleeding should be offered home treatment (1B).
2. All patients must have an individual treatment protocol that explains the management of joint and other bleeds with instructions on initial dosage, frequency and when to contact the haemophilia centre for advice (1C).
3. The initial treatment of early and moderate bleeds should aim for a peak factor VIII/IX of between 50 to 60 IU dl\(^{-1}\). This is equivalent to 25 to 30 IU kg\(^{-1}\) for severe haemophilia A for standard and extended half-life products and 40 to 60 IU kg\(^{-1}\) for severe haemophilia B with extended half-life factor IX being dosed at the lower end of the recommended range. Early bleeds often do not require a second infusion, and moderate bleeds often respond to a single infusion but may require up to two infusions (1B).
4. Children may require more frequent or higher doses as they have a shorter factor half-life compared to adults (1B).
5. For joint immobilizing bleeds, higher initial doses are recommended which aim to raise the peak factor VIII/IX level to 60 to 80 IU dl\(^{-1}\). Doses should be administered every 24 h until complete resolution of pain. For severe bleeds, more frequent administration may be required in the initial 48 h with standard factor VIII or IX(1B).
6. Patient education on the identification and management of bleeds should be ongoing (1C).
7. Patients on home therapy should be encouraged to contact the haemophilia centre for review if there is inadequate response in the first 36 to 48 h (1C).

Haemostatic management of patients with inhibitors to Factor VIII and IX

Patients with inhibitors do not necessarily have an increased frequency of spontaneous joint and soft tissue bleeds compared to non-inhibitor patients but do have a higher tendency to develop target joints, which can be difficult to manage. Many inhibitor patients are now well established on home therapy for the treatment of bleeds. However, to enable the optimal management of bleeding episodes, there should be close liaison between the patient and centre staff. As for bleeds in patients without inhibitors, treatment should be initiated as early as possible to restrict the extent of the bleed. Early treatment optimizes the chance of a single treatment settling the bleed, thereby minimizing patient incapacity and factor consumption. Troublesome bleeds should be reviewed early at the haemophilia centre and there should be a low threshold for admitting the patient for optimization of bleed management.

Patients with inhibitors should be treated with either the activated prothrombin complex concentrate aPCC (FEIBA\(^\text{®}\), Factor Eight Inhibitor Bypassing Activity) or recombinant factor VIIa (Novoseven\(^\text{®}\), rFVIIa). Through personal experience of bleed responsiveness, patients tend to prefer one product over the other. Some patients, however, favour the use of rFVIIa for the treatment of certain types of bleed and FEIBA for others. Furthermore, some patients find rFVIIa effective in arresting bleeds that can be treated early but favour aPCC for bleeds which have been established for longer before they are treated. It is therefore becoming increasingly common for patients to have both products supplied for home treatment needs. aPCC is usually dosed between 50 and 100 IU kg\(^{-1}\) depending on the severity of the bleed and further doses administered between 12- and 24 h-intervals until the bleed is fully controlled. The total dose of aPCC administered over a 24-h period should not exceed 200 IU kg\(^{-1}\). rFVIIa is now usually given as a single dose of 270 µg kg\(^{-1}\) which is as efficacious and more convenient than the previous conventional two to three doses of 90 µg kg\(^{-1}\) given every two hours [24,25]. If a bleed is not responding to one agent, then the other can be used in the hope that this will be effective. If both products are not effective, use of sequential alternating therapy can be considered in the hope of achieving a synergistic effect [26]. Use of tranexamic acid should be considered to optimize treatment of bleeding episodes. The concomitant use of tranexamic acid and rFVIIa has not been associated with increased thrombotic risk [27]. Historically, however, due to a perceived risk of thrombosis, tranexamic acid has been contraindicated in combination with aPCC. It is now considered that this risk is likely to
have been exaggerated and it is becoming increasingly common practice to use tranexamic acid alongside aPCC [28].

Inhibitor patients - Recommendations
1. Inhibitor patients should be encouraged to be on a home treatment programme and bleeds should be treated as early as possible (1A).
2. There should be close liaison with haemophilia centre staff members to agree upon appropriate management of difficult bleeds (1C).
3. aPCC 50–100 µg kg\(^{-1}\) or rFVIIa 270 µg kg\(^{-1}\) as a single dose (or 90 µg kg\(^{-1}\) 2–3 hourly) are equally acceptable treatments for joint or soft tissue bleeds with repeated doses as necessary. The frequency of infusion and duration of treatment should be determined by the clinical response (1B).
4. The total daily dose of aPCC should not exceed 200 IU kg\(^{-1}\) (1B).
5. Tranexamic acid can be considered as adjunctive therapy to aPCC and rFVIIa (2C).
6. Sequential alternating treatment of aPCC and rFVIIa can be considered for the management of limb/life threatening bleeds, and this is associated increased risk of thrombosis (2B).

Non-haemostatic management
Joint aspiration. Small, non-randomized studies have assessed the utility of joint aspiration in acute haemarthroses and some have reported a good long-term outcome [29]. However, there is no definite evidence that joint aspiration helps to accelerate the recovery from a haemarthrosis or improve outcome. There is the potential concern of introducing infection into the joint. Aspiration may be helpful when there is severe bleeding and pain with a tense haemarthrosis [23]. If aspiration is performed, factor cover and an aseptic technique are required.

Joint aspiration - recommendations
1. Joint aspiration is not routinely recommended unless there is concern about potential septic arthritis (1C).
2. Joint aspiration may be useful for pain relief in tense haemarthrosis under appropriate haemostatic therapy (2B).

Pain relief. In acute haemorrhage, ice cooling as part of the PRICE protocol may alleviate pain (see Physiotherapy section below). Using the principles of an analgesic ‘ladder’, common to pain relief guidance, medication should be prescribed with a stepwise progression from ‘simple’ paracetamol through to ‘strong’ opioid analgesics. This process matches the ceiling effect of analgesic drugs to the degree of pain present, such that if pain is severe or analgesia ineffective, then an ascent of the ladder is recommended.

Paracetamol (acetaminophen) is the accepted basis of acute pain relief, although there are no randomized trials in haemophilia. Non-cyclo-oxygenase-2 (COX-2) selective non-steroidal analgesics (NSAID’s) such as ibuprofen carry an excess incidence of gastrointestinal bleeding and perforation and so are not advisable. By comparison, studies in haemophilia have shown COX-2 selective NSAID’s to have a lower risk for gastrointestinal side effects [30] and offer relief of pain and chronic synovitis [31,32]. However, COX-2 NSAID’s do have a greater risk for cardiovascular disease, particularly in those with established cardiovascular disease, cerebrovascular disease, peripheral arterial disease, and mild to severe heart failure, when they are contraindicated [33]. Both selective and non-selective NSAID’s may impair renal function. Therefore, COX-2 selective NSAID’s, for example, celecoxib and etoricoxib, which are effective and safe in haemophilia joint bleeds can be used with due caution for the shortest duration possible [34].

Opioid analgesics range in strength from weaker opioids such as codeine, dihydrocodeine and tramadol, to the stronger morphine, oxycodone and fentanyl preparations. Data to support the use of opioid analgesic in haemophilia are limited to anecdotal experience and derived from non-cancer analgesic guidance. For acute analgesia, a short acting preparation may be advisable.

Pain relief - recommendations
1. Ice cooling as part of the PRICE process may alleviate pain (1C).
2. Analgesia should be prescribed by a stepwise progression; of which paracetamol is generally the most appropriate initial treatment (1C).
3. COX-2 selective NSAID’s are effective and safe in haemophilia joint bleeds (1B).
4. Opioid analgesia is appropriate in patients with moderate to severe or refractory pain (1C).

Physiotherapy
Although consensus guidelines recommend physiotherapy following acute haemarthrosis [12], there is a very limited objective evidence base in relation to the optimal timing and types of rehabilitation strategies following resolution of a joint bleed. Clinical physiotherapy intervention is aimed at symptom control, prevention of bleed recurrence, prevention of joint damage and restoration of full function and activity. Early management strategies are often encapsulated within the mnemonic PRICE - Protection, Rest, Ice, Compression and Elevation.

Acute phase
Protection and joint rest—The aim in the early stages is to relieve the acute pain and decrease the risk of re-
bleeding. Unloading the affected joint protects injured tissue from excessive mechanical stress thereby minimizing ongoing bleeding and aiding healing [35–37]. Animal models have demonstrated that weight bearing in the presence of a haemarthrosis may have a deleterious effect on joint cartilage [38]. However, prolonged rest can negatively affect joint function through reduction in muscle strength affecting tissue biomechanics and dynamic joint control [39,40].

Where bleed symptoms persist for more than 24 h, a period of non-weight-bearing/partial weight-bearing for a lower limb joint bleeds and immobilization for upper limb bleeds has been recommended. World Federation of Haemophilia (WFH) guidelines suggest immobilization until pain resolves [7] with empirical reports suggesting initial early bed rest for 1 day and avoidance of weight bearing for up to 4 days [41]. However, in practice, relative rest/protection should continue until all clinical symptoms of haemarthrosis (acute swelling, acute palpable localised tissue warmth, acutely reduced range of joint motion and acute joint pain) have resolved and potentially lasting rest can negatively affect joint function through reduction in muscle strength affecting tissue biomechanics and dynamic joint control [39,40].

Compression and elevation. Both compression and elevation are potentially beneficial treatment adjuncts when swelling and pain compromise function and attempts to restore the pressure gradients within affected tissue are perceived to be beneficial [37]. These changes are usually short-lived, with recurrence of swelling once the limb is returned to a dependent position [49]. No advantage has been established for the effectiveness of any individual protocol (method of compression/compression pressure). Guidelines suggest that if compression is to be used, then it should configure as best as possible to the limb/joint shape, provide a graduated compressive force and be comfortable for the individual [37,50].

Sub-acute phase and rehabilitation. Once adequate haemostasis is assured, and both subjective and objective signs of improvement are forthcoming, the rehabilitation programme should commence. At this stage it is also important to consider other aspects of joint health such as the chronicity of joint swelling, the risk of target joint formation as well as already established arthropathic or biomechanical changes in the affected joint and the wider musculoskeletal system.

Chronic effusions and long-term changes to a joint capsule as a result of recurrent effusions, coupled with inflammatory mediators, are likely to decrease proprioceptive ability in a joint [51,52]. Following injury to a joint, the barrage of nociceptive input from the joint pressure and injury site decrease afferent activity in the surrounding muscles and disrupt joint mechanoreceptors [53,54], further affecting proprioception. Joint damage associated with existing arthropathy has also been shown to decrease afferent activity in the surrounding muscles [55]. If both scenarios were to occur together, such as in an acute haemarthrosis, a large reduction in activation may prevent the threshold for stimulation of muscle hypertrophy from being reached, potentially impeding rehabilitation [56].

Early intervention to reduce nociceptive input may reduce potential motor control dysfunction. Therefore, the introduction of exercises aimed at maintaining motor control patterns may be of considerable importance [53]. Motor control of everyday actions is task specific; therefore, functionally orientated exercise should be incorporated as early as possible in the management [57]. Exercise programmes should encompass local joint control and global conditioning, such as weight-bearing activity to improve joint position sense [55] and strengthening activity [23]. This will also promote neuromuscular feed-forward changes – important for the overall functional outcome and to minimise the risk of future recurrence of injury [57].

Physiotherapy – recommendations
1. Review by a physiotherapist is recommended as soon as a patient presents with or reports a joint bleed – advising and educating on the anticipated timeline for rehabilitation (1B).
2. Initial assessment should be comprehensive – including history of trauma/injury as well as baseline joint health/function (1C).
3. Rest/immobilization – should be monitored closely and kept to a clinical minimum (1C).
4. Cryotherapy to be used with the limb in elevation, preferably with crushed ice, and for no more than 20 mins per application. Gel packs and cyrocuffs can be used, but ice cubes or cooling blocks that do not mould to joint contour should be avoided (1B).
5. Compression/elevation – to be used according to patient comfort and monitored closely (2B).
6. Rehabilitation should focus on regaining dynamic joint control and towards improvement in baseline function. Techniques used in routine clinical practice can be used in persons with haemophilia. This should be preceded by a discussion with the haematologist to ensure appropriate clotting factor support if indicated (1C).

Management of chronic synovitis and target joints

Target joint definition

Bleeding into joints leads to the development of synovitis, which is characterized by a painless chronic swelling of the affected joint. Such joints are more prone to recurrent bleeds and progressive joint damage. The term ‘target joint’ is defined as a joint with recurrent bleeds, and the most recent International Society of Thrombosis and Hemostasis (ISTH) definition suggests three or more spontaneous bleeds into single joint within a consecutive 6-month period. The joint ceases to be target joint when there have been less than two bleeds into the joint within 12 consecutive months [58]. The PEDNET registry has a more narrow definition of three or more bleeds in a 6-month period, and for the joint to cease being a target joint, there must be no bleeds over a 12-month period [59]. In order to prevent progressive joint damage, further intervention may be needed.

Such definitions are appropriate for registries and clinical trials, but in patients on prophylaxis any joint which has more than two bleeds over a 6-month period should be considered an ‘at risk joint’ requiring thorough examination and investigations. This includes ensuring an adequate trough level for those receiving prophylaxis, and imaging to assess for synovitis and to exclude a mechanical cause of bleeding. Ultrasound assessment in patients presenting with acute and chronic pain in joints commonly shows inflammatory soft tissue change [60]. An approach to the management of target joints is outlined in Fig. 1.

Radioactive synovectomy (synoviorthesis)

Radioactive synovectomy offers a conservative alternative to surgical synovectomy in patients with a target joint associated with synovitis and recurrent bleeding which has proved refractory to intensive treatment with clotting factor concentrates. It is a particularly attractive option for patients with inhibitors or those unsuitable for surgical synovectomy [61]. Radioactivity emitted by the appropriate isotope causes atrophy and fibrosis of the synovium, with a consequent reduction in the bleeding tendency. Patients suitable for consideration for radioactive synovectomy are those with demonstrable synovitis, not just evident on clinical examination but also proven by soft tissue imaging such as ultrasound and/or MRI.

A number of isotopes have been used for this procedure, including phosphorus P32, yttrium Y90, erbium Er169, gold Au198 and rhenium Re186 [62]. Properties to be taken into consideration when selecting a suitable isotope include particle size, type of emission, range of soft tissue penetration and half-life. Re186 and Y90 have been increasingly adopted in recent years and they have relatively short half-life of 2.7 to 3.7 days and a soft tissue penetration range of 1 to 5 mm. The precise dose used will depend on both the joint and the size of the patient. This procedure can only be performed in hospitals which have the necessary equipment and protocols in place to handle radioactive isotopes [63]. It may be cost-effective to arrange for several patients to receive treatment on the same day. An infusion of clotting factor concentrate is required prior to the procedure. The isotope is introduced into the joint using a 16 or 18 gauge needle, after aspiration of any intra-articular effusion or blood.

Although not obligatory, fluoroscopic monitoring is advised to ensure correct needle placement to avoid extra-articular leak of the radioisotope and to ensure that no blood vessels are inadvertently punctured. Imaging may also help to document uniform distribution of the isotope, as loculation due to fibrosis in the joint can hinder this.

Inflammatory reactions, including fever and pain, have very occasionally been reported after the procedure. It is important to flush the needle with sterile water for injection before withdrawing the needle from the joint carefully as radioactive burns may occur along the needle track.Injecting an anti-inflammatory agent such as hydrocortisone acetate into the joint before removal also effectively flushes isotope out, reducing both the risk of leakage as well as a subsequent inflammatory reaction and radiation skin burn.

High dose radiation has been shown to damage articular cartilage in experimental studies, but at the therapeutic doses used in radioactive synovectomy this is unlikely [64]. A recent longitudinal study of 2412 patients who had undergone the procedure for synovitis of varying aetiology (mainly rheumatoid arthritis) showed no excess incidence of neoplasia [65]. There have been no confirmed reports of malignancy as a consequence of radioactive synovectomy including use in children [66], and the recommended radiation dose is below the recommended annual exposure limit [67].

Haemophilia (2017), 1–10 © 2017 John Wiley & Sons Ltd
Target Joint Identified
>2 breakthrough bleeds in 6 months

Check adequate trough level and inhibitor status
Consider half-life study
Commence or intensify prophylaxis if needed
Optimise physiotherapy/activity modification
Consider Ultrasound/MRI joint imaging

Good response

Poor response

MRI Imaging

Haemophilia MDT Clinic assesses need for radioactive synovectomy

Radioactive synovectomy required?

Yes

Arrange radioactive synovectomy

Revert to standard prophylaxis

No

MDT/Orthopaedic review for further orthopaedic intervention

Review by Haemophilia MDT

Good response

Poor response

Fig. 1. Management of Target Joints in PWH – suggested pathway.
A reduction in the bleeding tendency is usually evident within 2 to 3 weeks of the procedure. A positive response in terms of reduced bleeding frequency and reduction in pain has been documented in 75 to 85% of patients but no significant improvement in range of joint motion should be anticipated [62,63]. Established joint damage is not a contraindication to radioactive synovectomy where it is equally effective in reducing joint bleed frequency and pain [68].

Selective angiographic embolization
Successful control of recurrent bleeding into target joints and improvement of chronic synovitis has been reported using selective angiographic embolization [69–71]. There are no large studies but the approach may be useful in selected patients.

Chronic synovitis and target joints – recommendations
1. Recognition, imaging and intervention to minimize synovitis in any target joints should be based on an individualized approach which includes optimization of factor replacement therapy and evaluation for chronic synovitis or potential mechanical cause due to arthropathy (1B).
2. A radioactive synovectomy should always be considered when there is evidence of chronic synovitis which has not responded to more conservative interventions (1B).
3. Selective angiographic embolization may be useful in some patients (2C).

Intra-articular steroid injection
Steroid injections are used in a wide range of inflammatory arthritic conditions. There are no randomized or large non-randomized studies to inform an evidence base in relation to the use of intra-articular steroids in haemophilia with associated arthropathy. There are some reports of a temporary improvement in symptoms in patients with chronic synovitis [72] but there is no clear role for intra-articular steroids to control bleeding. There may be a role for intra-articular steroids as a pain control measure prior to surgical intervention.

Intra-articular steroid injections – recommendations
1. No firm recommendation for the use of steroid injections can be made. Individually selected patients may derive some short-term symptomatic benefit (2D).

Author contributions
JP, AM, DC, SC, PM, NG, PB, SF, PG, JW, JT and PC contributed to the literature review and interpretation, and drafting and revision of the manuscript. All authors had access to the final data, participated in the interpretation, and vouched for the completeness and interpretation of the literature.

Disclosures
The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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