

# Diagnosis and treatment of chronic synovitis in patients with haemophilia: consensus statements from the Italian Association of Haemophilia Centres

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## Summary

Although synovitis is recognized as a marker of joint disease activity, its periodic assessment is not included in routine clinical surveillance of patients with haemophilia (PwH). In order to evaluate the current knowledge and to identify controversial issues, a preliminary literature search by the Musculoskeletal Committee of the Italian Association of Haemophilia Centres (AICE) has been conducted. Statements have been established and sent to the Italian AICE members to collect their level of agreement or disagreement by a Delphi process. Thirty-seven consensus recommendations have been drafted. We found a general agreement on the indication to consider the presence of synovitis as a marker of joint disease activity in PwH. Accordingly, there was agreement on the indication to search for synovitis both in patients reporting joint pain and in asymptomatic ones, recognizing ultrasound as the most practical imaging technique to perform periodic joint screening. Interestingly, after detection of synovitis, there was agreement on the indication to modify the therapeutic approach, suggesting prophylaxis in patients treated on demand and tailoring treatment in patients already under prophylaxis. Whereas the need of an early consultation

with a physiotherapist is recommended for PwH affected by chronic synovitis, the exact timing for an orthopaedic surgeon consultation is currently unknown.

**Keywords:** haemophilia, haemophilic arthropathy, synovitis.

## Introduction

Joint haemorrhage represents the most common type of bleeding in patients with haemophilia (PwH),<sup>1-3</sup> and recurrent haemarthrosis triggers chronic arthropathy, which is the most frequent complication of haemophilia.<sup>4</sup> In the absence of an adequate prophylaxis with FVIII (for haemophilia A) or FIX (for haemophilia B) concentrates, up to 85% of patients with severe haemophilia develop an evident joint disease.<sup>5-7</sup> On the other hand, recent data suggest that, despite adequate prophylaxis conducted in accordance with most recent guidelines, PwH can report joint status deterioration during long-term follow-up.<sup>8,9</sup> Thus, an adequate screening of early signs of joint disease is needed. From this perspective, synovial hypertrophy detection is considered one of the parameters to be taken into account for the diagnosis and the surveillance of joint status in PwH.<sup>10</sup>

The physiologic function of the synovium is to digest blood by means of the synovial cells (synoviocytes),<sup>11</sup> but following the exposure to repeated intra-articular bleedings, the synovium becomes hypertrophic and villous, with an increased vascularity.<sup>12,13</sup>

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After a haemarthrosis, the presence of haemosiderin in the joint space induces a pro-inflammatory status, an increase in the oxidative stress, an induction of transcription factors and angiogenesis mediators, thus leading to synovial hypertrophy.<sup>14</sup> The hypertrophic tissue is able to induce cartilage damage, by means of proteolytic enzymes, and to predispose to new intra-articular bleedings. This clearly suggests that synovial tissue plays a central role in the pathogenesis of the blood-induced joint damage by means of an auto-catalytic system, starting by synovial hypertrophy and leading to progressive and irreversible chondral and bone alterations.<sup>11,12,15,16</sup> However, synovitis assessment is not currently reported among recognized clinical outcomes used for evaluating efficacy of replacement therapy in PwH. In addition, the few available recommendations provide some insights on management of synovitis and several unmet clinical needs still exist.<sup>10,17</sup> The aim of the present study was to report the results of a modified Delphi consensus on the diagnosis and treatment of chronic synovitis in PwH.

## Material and methods

A modified Delphi consensus<sup>18–20</sup> was conducted between November 2018 and November 2019 among Italian physicians involved in haemophilia care, consisting of the following steps: (a) establishment of a steering committee of 12 Italian clinicians, orthopaedic surgeons, psychiatrists and radiologists, all experts in haemophilia and haemophilic arthropathy, to define consensus topics; (b) submission of the identified statements to clinicians from the Italian Association of Haemophilia Centres (AICE) for consensus evaluation; (c) discussion of the results by the steering committee; and (d) finalization of the consensus-based recommendations.

The steering committee included 12 members, whose expertise was proven by reputation, published papers, presentations at national and international scientific meetings, and participation in clinical trials and expert panels. The steering committee was represented by all members of the AICE Musculoskeletal Committee. A preliminary literature search was performed on PubMed, Scopus and Web of Science before the first meeting (Milan, Italy; September 2017) to gain insight into the current state of the art in diagnostic and clinical issues related to synovitis in haemophilia patients and to identify controversial issues using the following keywords in all possible combinations ‘*synovitis, synovial, synovium, hemophilia, haemophilia, hemophilic, haemophilic*’. Studies published from 1 January 1960 to 31 July 2017 with an English abstract were evaluated. A total of 570 results were obtained, of which 197 were reviews, 90 were studies on synovectomy, 68 pathophysiologic/pre-clinical studies, 48 case reports, 26 animal models, 25 imaging studies, 19 expert opinion, five editorials, seven clinical studies on haemophilic arthropathy, three on corticosteroid injection, two on platelet-rich plasma (PRP) injection, two on the use of COX2 inhibitors, three on hyaluronic acid injection, one on

intra-articular use of mesenchymal stem cells, two on endovascular embolization, one study on physiotherapy, and two recommendations. A total of 53 studies were off topic; all the evaluated studies were available in English, at least in the abstract form, except for 16 papers: one was in the Japanese language, three were in Chinese, six in German, two in Russian, two in Slovak and two in Spanish. Given the relative lack of original studies specifically focused on diagnosis and clinical management of synovitis, the steering committee decided to adopt the Delphi method to reach consensus based on expert opinion.<sup>21</sup>

## Statement development

The initial round of Delphi was aimed at identifying statements around each of various areas of interest. The chairs of the Musculoskeletal Committee (MNDDM and GP) had the primary responsibility of defining statements concerning the diagnosis and management of synovitis in patients affected by haemophilia based on results of literature search. For each statement, they defined the relevant population, management strategies in terms of diagnostic tools, medical, physical, and surgical treatments. Statements focused on PwH A and B, of any age and disease severity. Several medical treatments of haemophilia, indications for physiotherapy and/or orthopaedic surgery were the evaluated procedures. A first version of statements was shared with the 12 AICE Musculoskeletal Committee Members as an online survey (round one, Supplemental Tables SI–SIV). They expressed their agreement/disagreement on each statement, results were discussed, and a final list of statements was prepared. The panellists were instructed to consider only the clinical perspective, and to disregard financial costs, and other potential constraints to the availability of the intervention. This approach ensures that the expert recommendations are feasible for clinical practice and avoid the issue of discrepancy between experts and clinicians.<sup>21</sup>

The final list of statements is provided in Tables I–IV. After approval by the Executive Committee of AICE, the elaborated statements (written in the Italian language to optimize response rate) were uploaded on the official AICE site (<https://aiceonline.org>) and submitted using a secure website to 137 clinicians operating at 51 Italian haemophilia centres (round two). Access to the survey was reserved for AICE members only via personal ID and password. To increase response rate, periodic reminders of the pending survey were sent by e-mail.

Both for round one and for round two, participating clinicians anonymously expressed their level of agreement/disagreement on each statement, according to a five-point Likert-type scale (1 = strongly disagree, 2 = disagree, 3 = somewhat agree, 4 = agree and 5 = strongly agree). The number and percentage of participants who scored each item as 1–2 (disagreement) or as 4–5 (agreement) were calculated. To be as conservative as possible, a consensus was considered

**Table I.** Diagnosis of synovitis. Results of round two involving the 45 experts in haemophilia care from 33 haemophilia centres.

<i>n</i>	Statement	Agreement % ( <i>n</i> )	Disagreement % ( <i>n</i> )
1	Synovitis represents a disease activity marker in PwH	93 (42/45)	2 (1/45)
2	The presence of synovitis should be investigated in PwH with joint pain	89 (40/45)	2 (1/45)
3	The presence of synovitis should be investigated at each clinical follow-up visit only for target joints	16 (7/45)	70 (32/45)
4	The presence of synovitis should be investigated at each clinical follow-up visit regardless of the presence of joint symptoms	70 (32/45)	2 (1/45)
5	After detection of synovitis, its evolution should be evaluated periodically	98 (44/45)	0 (0/45)
6	The presence of synovitis should be investigated using clinical examination (HJHS or Gilbert score)	32 (14/45)	34 (15/45)
7	The presence of synovitis should be investigated using standard radiographic imaging examination	2 (1/45)	91 (41/45)
8	The presence of synovitis should be investigated using computed tomography imaging examination	0 (0/45)	98 (44/45)
9	The presence of synovitis should be investigated using magnetic resonance imaging examination	5 (2/45)	82 (37/45)
10	The presence of synovitis should be investigated using ultrasound examination	98 (44/45)	0 (0/45)
11	After detection of synovitis, the presence of haemosiderin should be investigated using magnetic resonance imaging	16 (7/45)	52 (23/45)
12	During US examination, the power/colour Doppler function should be used when synovitis is present	25 (11/45)	36 (16/45)
13	Functional analysis (i.e. gait analysis, baropodometric and stabilometric assessment) is necessary to diagnose synovitis	18 (8/45)	48 (22/45)

Agreement: percent of participants who scored each item as 4–5 (4 = agree or 5 = strongly agree). Disagreement: percent of participants who scored each item as 1–2 (1 = strongly disagree, 2 = disagree). HJHS, Haemophilia Joint Health Score (HJHS); PwH, patients with haemophilia; US, ultrasound.

**Table II.** Clinical implications. Results of round two involving the 45 experts in haemophilia care from 33 haemophilia centres.

<i>n</i>	Statement	Agreement % ( <i>n</i> )	Disagreement % ( <i>n</i> )
14	The detection of chronic synovitis suggests the need of anti-FVIII/FIX inhibitor	27 (12/45)	39 (18/45)
15	The detection of chronic synovitis supports the switch to a prophylaxis schedule in on-demand-treated patients	95 (43/45)	0 (0/45)
16	The detection of chronic synovitis supports changes in treatment schedule (dose/frequency) in patients under prophylaxis	93 (42/45)	0 (0/45)
17	Before changing prophylaxis schedule a pharmacokinetics assessment is necessary	61 (27/45)	7 (3/45)
18	In case of treatment schedule change a clinical follow-up is indicated after 3 months	75 (34/45)	0 (0/45)
19	The detection of chronic synovitis is an indication for treatment with paracetamol	20 (9/45)	52 (23/45)
20	The detection of chronic synovitis is an indication for treatment with corticosteroids	7 (3/45)	57 (26/45)
21	The detection of chronic synovitis is an indication for treatment with NSAIDs	5 (2/45)	64 (29/45)
22	The detection of chronic synovitis is an indication for treatment with COX-2 inhibitors	39 (18/45)	25 (11/45)
23	Analgesic and anti-inflammatory drugs should be used only in the presence of pain, beside chronic synovitis	45 (20/45)	30 (14/45)

Agreement: percent of participants who scored each item as 4–5 (4 = agree or 5 = strongly agree). Disagreement: percent of participants who scored each item as 1–2 (1 = strongly disagree, 2 = disagree). NSAID, non-steroidal anti-inflammatory drug.

to be reached when the sum for disagreement or agreement was  $\geq 70\%$ . Disagreement or agreement on statements was discussed by the steering committee during a second meeting and a series of practical consensus recommendations were drafted based on the results from the modified ask-the-experts Delphi process. A face-to-face discussion of results with all participating clinicians was not possible because of restrictions due to the COVID-19 pandemic.

## Results

A total of 45 experts in haemophilia care (35 haematologists, two radiologists, three orthopaedic surgeons, two physiatrists

and three physiotherapists) from 33 haemophilia centres evaluated 37 statements and reached consensus on 15, agreement on 11, and disagreement on four (Tables I–IV). The overall response rate was 33% (45/137) covering about 65% of Italian haemophilia centres (33/51). No missing answers were recorded on any statement.

The following are the statements of the final consensus, along with the evidence supporting the decisions.

### Diagnosis of chronic synovitis (Table I)

- *Statement 1: Synovitis represents a disease activity marker in PwH (93% agreement)*

**Table III.** Role of physiotherapy. Results of round two involving the 45 experts in haemophilia care from 33 haemophilia centres.

<i>n</i>	Statement	Agreement % ( <i>n</i> )	Disagreement % ( <i>n</i> )
24	A patient with chronic synovitis should always be assessed by a physiotherapist	80 (36/45)	5 (2/45)
25	All physiotherapeutic treatments should be performed after clotting concentrate replacement therapy	75 (34/45)	9 (4/45)
26	Physical therapy (laser, diathermy, magneto) is useful in the frame of a rehabilitation program for the treatment of chronic synovitis in PwH	36 (16/45)	23 (10/45)
27	Physical therapy (laser, diathermy, magneto) should be discouraged in patients with chronic synovitis	14 (6/45)	41 (18/45)
28	Manual therapy can be performed in patients with chronic synovitis without need for a preventive resting period	32 (14/45)	14 (6/45)
29	Manual therapy should be performed preferring passive mobilization in patients with chronic synovitis	39 (18/45)	14 (6/45)
30	In patients with chronic synovitis, posture control exercises are indicated to avoid pathologic postures due to antalgic positions	86 (39/45)	5 (2/45)
31	The use of zinc oxide tape is indicated for patients with chronic synovitis	7 (3/45)	45 (20/45)

Agreement: percent of participants who scored each item as 4–5 (4 = agree or 5 = strongly agree). Disagreement: percent of participants who scored each item as 1–2 (1 = strongly disagree, 2 = disagree). PwH, patients with haemophilia.

**Table IV.** Role of orthopaedic surgery. Results of round two involving the 45 experts in haemophilia care from 33 haemophilia centres.

<i>n</i>	Statement	Agreement % ( <i>n</i> )	Disagreement % ( <i>n</i> )
32	A patient with chronic synovitis should always be assessed by an orthopaedic surgeon	45 (20/45)	23 (10/45)
33	In case of chronic synovitis persistence after medical therapy optimization, a minor/major surgical approach should be considered	36 (16/45)	30 (14/45)
34	Viscosupplementation is a therapeutic option in patients with chronic synovitis	43 (19/45)	25 (11/45)
35	Radiosynoviorthesis is the first therapeutic option when medical therapy optimization fails	32 (14/45)	27 (12/45)
36	Angiographic embolization could be considered an effective therapeutic option <i>versus</i> radiosynoviorthesis for the treatment of chronic synovitis of the elbow and knee	27 (12/45)	30 (14/45)
37	Arthroscopic synovectomy is the first-choice treatment after failure of non-surgical synovectomy	59 (27/45)	9 (4/45)

Agreement: percent of participants who scored each item as 4–5 (4 = agree or 5 = strongly agree). Disagreement: percent of participants who scored each item as 1–2 (1 = strongly disagree, 2 = disagree).

Synovial hypertrophy may represent a key feature, potentially related to several conditions: undertreatment due to insufficient therapy regimens; limited compliance to treatment; pharmacokinetics variability; demanding daily/sport activities (Table 1). Some recent data support the hypothesis that joints with synovitis have significantly higher five-year bleeding rate, thus being more prone to progressive joint damage.<sup>10,22</sup> Accordingly, there was a general agreement on the indication to consider synovitis as a marker of joint disease activity in PwH.

- *Statement 2: The presence of synovitis should be investigated in PwH with joint pain (89% agreement)*

There was a general agreement on the indication to search for synovitis in patients reporting joint pain. This is based on the assumption that joint pain is the most common type of symptom observed in PwH,<sup>23,24</sup> with chronically painful joints being reported in about 50% of cases<sup>25,26</sup> and with 89% of PwH experiencing at least one pain episode during a four-week observation period.<sup>27</sup> Whereas degenerative

arthropathic changes can lead to chronic joint pain, the presence of acute pain or pain recurrence (flares) can be compatible with the presence of synovitis.<sup>28</sup> Moreover, the assessment of the presence/absence of synovitis could be also useful to exclude acute bleeding episodes and to distinguish a mechanical (arthritic) pain from a bleeding-related (inflammatory) pain.<sup>29</sup>

- *Statement 3: The presence of synovitis should be investigated at each clinical follow-up visit only for target joints (70% disagreement)*
- *Statement 4: The presence of synovitis should be investigated at each clinical follow-up visit regardless of the presence of joint symptoms (70% agreement)*

In recent years, in the context of the comprehensive care approach and after a shift of the treatment paradigm to actually preserve joint function and reduce joint deterioration,<sup>30</sup> growing attention has been given to the periodic assessment of joint status in haemophilia patients. The purposes of such evaluation were: the identification of early arthropathic changes; the prevention of

the development of a clinically evident joint disease in children; the attempt to limit the progression of arthropathy in adolescents and adults. Being difficult to detect, subclinical joint damage is seldom detected and recognized.<sup>31</sup> Moreover, given the multi-joint involvement demonstrated in PwH, a joint assessment limited to target joints is likely unable to identify early signs involving other joints. Accordingly, the panel agreed on the indication to screen all joints regardless of the presence of symptoms and a disagreement on the hypothesis to screen only target joints.

It is noteworthy that the degree of agreement/disagreement for these statements was quite low (70%). This is related to several doubts about the timing of joint assessment. Both statements suggested a screening for synovitis at 'each clinical follow-up visit'. This seems to be highly demanding and time-consuming in the setting of daily clinical practice. Some clinicians suggested at least a yearly joint screening for synovitis. Whereas recent guidelines suggest that, after synovitis detection, joint status should be assessed at all routine follow-up visits,<sup>17</sup> the proper timing for screening is currently unknown, and specific studies are needed to address this issue.

- *Statement 5: After detection of synovitis, its evolution should be evaluated periodically (98% agreement)*

No specific information is currently available about the time needed for synovitis resolution. This implies that, in case of active synovitis, a periodic assessment is highly recommended, regardless of symptoms variations, with the aim to define synovitis evolution and resolution. In the absence of specific evidence to define the most adequate timing for periodic assessment, it seems acceptable to perform a screening one month after the first diagnosis of synovitis and, then, at three months. In case of synovitis persistence for more than three months or in case of symptoms that patients highly complain about, despite adequate intensification of haematologic and non-haematologic treatment, it is recommended to involve an orthopaedic surgeon in the diagnostic/therapeutic workflow to evaluate the indication to a minimally invasive or invasive procedure.<sup>10,17</sup> Accordingly, the panel agreed that after detection of synovitis, its evolution should be evaluated periodically.

- *Statement 6: The presence of synovitis should be investigated using clinical examination (HJHS or Gilbert score) (NO agreement/disagreement)*

The Gilbert Orthopaedic Joint Score (OJS) and the Haemophilia Joint Health Score (HJHS) are widely used for the clinical assessment of joint status in PwH.<sup>4,32</sup> In particular, HJHS, increasingly used in recent years,<sup>33</sup> provides the most sensitive score for the physical examination in this clinical setting, although it is currently validated only for children.<sup>34</sup> However, the sensitivity and specificity of these clinical scores in the identification of early-stage and subclinical damages are widely challenged, and the risk for underestimating the

severity of joint deterioration cannot be ruled out.<sup>33</sup> Indeed, some recent data showed that ultrasound (US) examination is able to detect synovitis in joints with a totally negative clinical examination performed by OJS<sup>35</sup> or HJHS<sup>36</sup> Thus, because of the risk of underdiagnosing synovitis, the panel did not reach agreement on the indication to assess the presence of synovitis using clinical scores.

- *Statement 7: The presence of synovitis should be investigated using standard radiographic imaging examination (91% disagreement)*

Standard radiography is not able to identify signs of early-stage joint disease in haemophilia patients (synovial hypertrophy, joint effusion and early-stage osteochondral damages).<sup>37</sup> On the other hand, X-rays are very useful to assess late joint changes, usually expression of an advanced and irreversible arthropathy.<sup>6</sup> Thus, the panel judged that radiography, and the related Pettersson score, cannot be adopted as reliable tools to detect subclinical and early-stage joint impairment.<sup>38</sup>

- *Statement 8: The presence of synovitis should be investigated using computed tomography (CT) imaging examination (98% disagreement)*

CT has a minimal role in the assessment of chronic synovitis in haemophilic patients in clinical trials and practice, except in selected patients for whom US or magnetic resonance imaging (MRI) are not available or contraindicated.<sup>39,40</sup> This is mainly due to the limited sensitivity of CT for soft-tissue changes, including synovitis and tenosynovitis. The panel totally agreed on this.

- *Statement 9: The presence of synovitis should be investigated using magnetic resonance imaging examination (82% disagreement)*

At variance with CT and standard radiography, MRI is able to provide detailed information concerning early- and late-stage arthropathic changes, allowing an adequate evaluation of soft tissues in haemophilic patients.<sup>41</sup> For this reason, MRI is currently accepted as the gold standard for the assessment of haemophilic arthropathy. However, some limitations have to be considered: high costs, limited accessibility, need for sedation in children, need to evaluate only one joint per session. Furthermore, the clinical implications of minor changes revealed by MRI in terms of individual joint function remain to be determined.<sup>39</sup> In addition, in case of moderate/large haemosiderin deposition in the joint, the MRI visualization of synovial hypertrophy may be compromised by gradient-echo susceptibility artefacts, challenging synovial hypertrophy detection and scoring.<sup>42</sup>

Accordingly, MRI was not considered the best imaging tool for a periodic joint screening in PwH.

- *Statement 10: The presence of synovitis should be investigated using ultrasound examination (98% agreement)*

Because of several pitfalls reported for other imaging techniques (standard radiography, CT scan and MRI), a growing interest has been given to US as a possible tool to assess joint status and to monitor the joint disease progression in haemophilic patients.<sup>43,44</sup>

Over the last years, many US scores have been proposed for the study of joint status in haemophilia patients.<sup>31,45,46,47,48,49</sup> Each score considered several aspects of haemophilic arthropathy in different joints and with different scanning protocols, but all with the common purpose to optimize the diagnosis and surveillance of joint changes in haemophilia. The possibility of detecting and scoring the major markers of haemophilic arthropathy (synovial hypertrophy and osteo-chondral changes) by US examination allows a new approach to optimizing the diagnostic workflow, avoiding additional costs and long waiting lists for imaging in haemophilic patients.

Synovitis usually appears at US as a bulk of isoechoic/hypoechoic vegetations located inside the joint recesses.<sup>50</sup> Most protocols perform a comprehensive evaluation of the joints and of the amount of synovial tissue.<sup>31,45,46,49</sup> Thus, synovial hypertrophy is defined as present or absent<sup>45</sup> or quantified in different degrees<sup>31,46,49</sup> in most of the reported scores. This strategy of detection and grading for synovial hypertrophy has been used in some studies,<sup>35,51,52</sup> consistently suggesting that US is highly sensitive (>92%) for detecting synovial abnormalities with results comparable to those obtained with MRI.<sup>35,51,52</sup> Although some people may believe that joint screening with ultrasound would be highly demanding and time-consuming in the routine clinical practice, the advent of simplified point-of-care protocols is allowing clinicians to perform the examination of the six joints of interest in a very short time.<sup>53</sup> The use of ultrasound could not be considered a time-wasting activity if it is fully integrated with the physical exam to improve the sensitivity in the detection of early-phase joint alterations. Thus, there was a general agreement on the indication to use US as screening for the presence of synovitis in PwH.

- *Statement 11: After detection of synovitis, the presence of haemosiderin should be investigated using magnetic resonance imaging (NO agreement/disagreement)*

Contrasting results have been reported about the possibility of detecting haemosiderin deposition by US evaluation. Melchiorre *et al.*<sup>47</sup> and Zukotynski *et al.*<sup>49</sup> included haemosiderin visualization in their US scores. Doria *et al.*<sup>51</sup> suggested some criteria to distinguish between haemosiderin and synovium at US, assuming that the first is collected in hypoechoic pockets, has an irregular contour, is less displaceable, and less compressible than fluid, whereas the latter is non-displaceable, poorly compressible and hyperechoic in relation to fluid. However, considering that haemosiderin is embedded in the synovium and it is not collected into the joint cavity as an inert structure,<sup>13,54</sup> the distinction between haemosiderin deposition and synovium cannot be made by using US.<sup>55</sup>

It is noteworthy that synovial hypertrophy is consistently recognized as a major marker of blood-induced joint damage and, in haemophilia patients, it invariably corresponds to haemosiderin-enriched tissue (as assessed on gradient-echo MRI sequences). Accordingly, the panel did not confirm the need to search for the presence of haemosiderin using MRI after US diagnosis of synovitis.

- *Statement 12: During US examination, Power/Colour Doppler function should be used when synovitis is present (NO agreement/disagreement)*

An open issue is represented by the indication to use Power/Colour Doppler function for the joint assessment of PwH. Four out of the six available US scores also take into account synovial hyperaemia,<sup>45-48</sup> the result of synovial neo-angiogenesis, and defined as an increased flow signal at Colour Doppler<sup>46,48</sup> or Power Doppler.<sup>45,47</sup> In rheumatoid arthritis, the growth of the synovium requires angiogenesis. An increased vascularity and the synovial hypertrophy can form a *pannus* that invades and destroys the articular cartilage and underlying bone.<sup>56</sup> Power Doppler US has been shown to adequately mirror synovial vascularity and to provide an estimate of moving fractional blood volume, thus providing a strong tool to assess response to therapy and monitor joint disease activity.<sup>57</sup> Considering that increased vascularity is associated with clinically active synovitis also in other forms of arthritis,<sup>58</sup> it has been supposed that Power Doppler could also be a useful tool for the diagnosis and monitoring of joint disease activity in PwH.<sup>59</sup>

However, as suggested by some data<sup>35</sup> Power Doppler positivity is rarely found in haemophilic patients. In addition, in the few cases with a positive Power Doppler signal, only few isolated 'flags' are visualized, suggesting that, contrary to rheumatoid arthritis, this parameter cannot be considered a reliable predictor of joint disease severity. This was the panel's agreement.

- *Statement 13: Functional analysis (i.e. gait analysis, baropodometric and stabilometric assessment) is necessary to diagnose synovitis (NO agreement/disagreement)*

Although it is widely agreed that gait analysis, baropodometric and stabilometric assessment are not able to confirm the presence of synovitis, they could add some value to identify early functional impairment or underlying conditions (i.e. flat foot, etc.) potentially impacting on joint health in PwH. However, no agreement was achieved on the indication to perform functional analysis in PwH with synovitis.

#### *Clinical implications of chronic synovitis detection (Table II)*

- *Statement 14: The detection of chronic synovitis suggests the need of anti-FVIII/FIX inhibitor (NO agreement/disagreement)*

The presence of synovitis may be secondary to an inadequate haemostatic response to clotting factor replacement therapy because of the presence of inhibitors (Table II). However, it seems that several other clinical and laboratory signs can lead to a diagnosis of inhibitors before synovitis identification. Thus, no agreement was achieved on the indication to test FVIII/FIX inhibitors in PwH with synovitis as a first-line option. The potential presence of inhibitors could be considered as a second option, after ruling out other causes of partial response to replacement therapy.

- *Statement 15: The detection of chronic synovitis supports the switch to prophylaxis schedule in on-demand treated patients (95% agreement)*
- *Statement 16: The detection of chronic synovitis supports changes in treatment schedule (dose/frequency) in patients under prophylaxis (93% agreement)*

In case of chronic synovitis, the World Federation of Haemophilia guidelines recommend suppressing synovial activation and to reduce inflammation to preserve joint integrity. In patients receiving on-demand replacement therapy, a short-term (6–8 weeks) prophylaxis is recommended to avoid bleeding episodes and to control synovitis.<sup>17</sup>

The presence of synovitis is a marker of joint disease activity in PwH and the therapeutic approach should be modified accordingly. A high agreement was obtained by panellists on the suggestion to start prophylaxis in patients currently treated on demand and to tailor treatment (dose and/or frequency) in patients already under prophylaxis. This approach is also in line with the recommendations of United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO).<sup>10</sup> Aside from an inadequate compliance to treatment or pharmacokinetics (PK) variability, the presence of synovitis could be related to undertreatment due to insufficient dose regimens or increased factor requirement because of work/sport activities. Based on this, a switch from on-demand treatment to prophylaxis could be indicated both in severe and moderate PwH.<sup>17,25</sup> In addition, in those patients already receiving prophylaxis before diagnosis of synovitis, tailoring of the treatment schedule may be adequate. However, no study has yet evaluated the effect of replacement treatment schedule change on synovial status in PwH. This needs to be assessed in *ad-hoc*-designed studies.

- *Statement 17: Before changing prophylaxis schedule a pharmacokinetics assessment is necessary (NO agreement/disagreement)*

No agreement was obtained regarding the indication to perform a PK assessment to guide any treatment change. Although prophylaxis tailoring is usually intended as a PK-driven tailoring, some growing evidence suggests that PK is only part of a more complex and composite system to tailor prophylaxis, including bleeding rate, joint status, and work/physical activity.

- *Statement 18: In case of treatment schedule change a clinical follow-up is indicated after three months (75% agreement)*

After any change of replacement treatment protocol, there is agreement on the indication to perform a clinical follow-up after three months. Of note, the degree of agreement for this statement was relatively low. Several comments highlighted the need for a closer follow-up (i.e. one month) after changes in prophylaxis schedule.

- *Statement 19: The detection of chronic synovitis is an indication for treatment with paracetamol (NO agreement/disagreement)*
- *Statement 20: The detection of chronic synovitis is an indication for treatment with corticosteroids (NO agreement/disagreement)*
- *Statement 21: The detection of chronic synovitis is an indication for treatment with non-steroidal anti-inflammatory drugs (NO agreement/disagreement)*
- *Statement 22: The detection of chronic synovitis is an indication for treatment with COX-2 inhibitors (NO agreement/disagreement)*
- *Statement 23: Analgesic and anti-inflammatory drugs should be used only in the presence of pain, besides chronic synovitis (NO agreement/disagreement)*

The indication for anti-inflammatory/analgesic therapy in PwH with synovitis was also investigated and no agreement was achieved for treatment with paracetamol, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and COX-2 inhibitors after diagnosis of synovitis. This is in line with the available evidence on pain control in PwH.<sup>28,60</sup> All currently available guidelines and recommendations suggest the use of paracetamol, corticosteroids, NSAIDs, and COX-2 inhibitors in the presence of pain, whereas synovitis is usually defined as a painless chronic swelling of the affected joint.<sup>17</sup> Nevertheless, it is important to remember that some studies<sup>61–64</sup> showed a specific effect of COX-2 inhibitors on synovitis remission, besides pain relief.

#### *Role of physiotherapy (Table III)*

- *Statement 24: A patient with chronic synovitis should always be assessed by a physiotherapist (80% agreement)*

Recent literature articles demonstrate the benefits of a multidisciplinary approach including a musculoskeletal expert (i.e. physiatrist, physiotherapist, orthopaedic surgeon, etc.), allowing a synergic interaction of different health providers focused on a patient-centred care approach, customized according to the stage of the disease.<sup>65</sup> Therefore, the need of consultation with an experienced physiotherapist, for PwH affected by chronic synovitis, was advised by the panel (Table III).

- *Statement 25: All physiotherapeutic treatments should be performed after clotting concentrate replacement therapy (75% agreement)*

Although the use of a prophylactic clotting factor replacement could be reasonable to perform the rehabilitation programme at adequate factor plasma levels, no data or evidence are available in order to validate the need of replacement therapy before a physiotherapeutic treatment. Based on this, a low level of agreement was achieved by the panel. However, it is noteworthy that physical therapy should be always performed under the direction of a haemophilia treatment centre.<sup>66,67</sup>

- *Statement 26: Physical therapy (laser, diathermy, magneto) is useful in the frame of a rehabilitation programme for the treatment of chronic synovitis in PwH (NO agreement/disagreement)*
- *Statement 27: Physical therapy (laser, diathermy, magneto) should be discouraged in patients with chronic synovitis (NO agreement/disagreement)*

The use of electrical-based therapies (tens, muscle electrostimulation, interferential), magnetic stimulation-based therapies (magnetotherapy), light stimulation-based therapies (laser therapies), or radio frequency-based therapies (diathermy) has been part of physical therapy treatment in the past decades: research on the effects of each application is mandatory to assess its proper use.<sup>68</sup> Based on this, no agreement was reached on the indication for electrotherapy during the rehabilitation programme in PwH complaining of chronic synovitis.

- *Statement 28: Manual therapy can be performed in patients with chronic synovitis without need for a preventive resting period (NO agreement/disagreement)*
- *Statement 29: Manual therapy should be performed preferring passive mobilization in patients with chronic synovitis (NO agreement/disagreement)*

In recent years, manual therapy (hands-on techniques that aim to improve biomechanical elasticity through mobilization and stretching of articular and soft-tissue structures) has gained interest as a treatment modality to restore joint function in PwH. Growing evidence suggests that manual therapy reduces the frequency of arthrosis, improves joint health, range of motion and perceived joint pain in PwH.<sup>69</sup> However, no study has confirmed a specific effect of manual therapy on synovitis and standardized protocols on timing of rest following joint/muscle bleeding or optimal and safest method of reloading are currently lacking. Based on this, no agreement was reached on the use of manual therapy in PwH and chronic synovitis.

- *Statement 30: In patients with chronic synovitis, posture control exercises are indicated to avoid pathologic postures due to antalgic positions (86% agreement)*

Panellists gave advice on correct postural hygiene, to prevent altered compensatory strategies due to pain, for the treatment of chronic synovitis. The maintenance of a correct posture in young haemophilic subjects may contribute to preventing joint bleeds, chronic pain, and functional impairments.<sup>70</sup>

- *Statement 31: The use of zinc oxide tape is indicated for patients with chronic synovitis (NO agreement/disagreement)*

The use of zinc oxide taping in the management of PwH with chronic synovitis has been proposed in order to limit joint range based on its strong adhesion and elastic properties<sup>71,72</sup> However, no specific information is currently available. Based on this, no agreement was reached on the use of zinc oxide taping in this setting.

#### *Role of orthopaedic surgery (Table IV)*

- *Statement 32: A patient with chronic synovitis should always be assessed by an orthopaedic surgeon (NO agreement/disagreement)*
- *Statement 33: In case of chronic synovitis persistence after medical therapy optimization, a minor/major surgical approach should be considered (NO agreement/disagreement)*

No agreement was reached on the timing of assessment by an orthopaedic surgeon and timing of surgical indication (Table IV). Persistent or recurrent chronic synovitis inducing frequent bleedings poorly controlled by other means represents a key feature, potentially related to the progression of arthropathy. Although the exact timing of an orthopaedic surgeon consultation and following surgical indications is currently unknown, in case of synovitis persistence for more than three months or in case of patients highly complainkng about symptoms, despite adequate intensification of haematologic and non-haematologic treatment, it is recommended to involve an orthopaedic surgeon in the diagnostic/therapeutic workflow to evaluate the need for surgical approach.<sup>10,17</sup>

- *Statement 34: Viscosupplementation is a therapeutic option in patients with chronic synovitis (NO agreement/disagreement)*

Since viscosupplementation in patients with chronic synovitis could be advised to reduce pain or improve joint function, but not to treat chronic inflammation of the synovium<sup>73,74</sup> no agreement was reached on its use as a therapeutic option in PwH with chronic synovitis.

- *Statement 35: Radiosynoviorthesis is the first therapeutic option when medical therapy optimization fails (NO agreement/disagreement)*

In case of unresolved chronic synovitis, a non-surgical synovectomy as a first-line treatment option is recommended<sup>17</sup> More in detail, the procedure can be performed in different ways: intra-articular injection (synoviorthesis) of chemicals or radioisotopes, arthroscopic synovectomy; or open surgical synovectomy.<sup>75-77</sup>

Radioisotope synovectomy using a pure beta emitter (phosphorus-32, yttrium-90, and rhenium) is highly effective, has few side effects, and can be accomplished in a single outpatient procedure.<sup>78-82</sup>

However, limitations due to radionuclide availability and fear of potential related risk (seldom reported) should be considered. In addition, although synovectomy/synoviorthesis is known to reduce synovitis and, in turn, the frequency of bleeding episodes, no evidence about specific effects on articular degeneration are known. Accordingly, radiosynovectomy was not considered as the best therapeutic option. Furthermore, chronic synovitis may be resistant to treatment with radiosynovectomy. In such cases, chronic synovitis may be treated with selective embolization of the blood vessels that supply the synovium.

- *Statement 36: Angiographic embolization could be considered an effective therapeutic option versus radiosynoviorthesis for the treatment of chronic synovitis of the elbow and knee (NO agreement/disagreement)*

Although recent results assessing the safety and efficacy of embolization for treating arthrosis in patients with bleeding disorders demonstrated that trans-arterial embolization can be considered safe and effective in addressing recurrent arthrosis,<sup>83,84</sup> this procedure should be reserved for specialized medical imaging centres. Accordingly, no agreement was reached on the indication of trans-arterial embolization for the treatment of chronic synovitis in PwH.

- *Statement 37: Arthroscopic synovectomy is the first-choice treatment after failure of non-surgical synovectomy (NO agreement/disagreement)*

Arthroscopic synovectomy is indicated, when other less invasive procedures failed, to delay arthropathy progression, to reduce the frequency of joint bleedings and the need of replacement therapy. Although an open procedure is feasible, the vast majority of authors prefer the arthroscopic technique, as less invasive, applicable to nearly all joints<sup>80,85,86</sup> in combination with an additional procedure such as removal of tibial anterior osteophytes in ankles.<sup>76</sup>

The procedure must be performed by an experienced team at a dedicated haemophilia treatment centre with a long period of prophylaxis coverage sufficient for the procedure and postoperative rehabilitation. For this reason, panellists did not consider synovectomy as the treatment of choice after minimally invasive procedures for chronic synovitis in PwH.

## Discussion, perspectives and conclusions

Synovitis seems to represent an important sign of the process involving joints in PwH and results in progressive chondral and bone damages, until the joint is irreversibly compromised. However, synovial status assessment is not currently reported among recognized clinical outcomes used for evaluating the efficacy of replacement therapy in PwH.<sup>17</sup> World Federation of Haemophilia (WFH) guidelines<sup>17</sup> recommend regular physical/imaging assessment of the synovial condition after every bleed, until the situation is clinically controlled, but no indication on routine screening of asymptomatic joints is reported. In case of synovitis persistence, WFH recommends non-surgical treatment, including physical therapy to improve muscle strength and joint function, and selective COX-2 inhibitors to reduce pain and inflammation, besides a 6/8-week prophylaxis schedule for patients not under regular prophylaxis.

In case synovitis persists with frequent recurrent bleeding (two or more bleeds in the same joint over six months) synovectomy/synoviorthesis is indicated, with radioisotope/chemical synoviorthesis as first choice for all patients, and arthroscopic synovectomy, open surgical synovectomy, or selective angiographic embolization as second-line options.

United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guidelines<sup>10</sup> focused on invasive treatment of synovitis and confirmed that radioactive synovectomy offers a conservative alternative to surgical synovectomy in patients with a target joint associated with synovitis and recurrent bleeding, refractory to intensive treatment with clotting factor concentrates.

Given the limited evidence available on synovitis diagnosis and clinical management, we developed a modified Delphi consensus on the diagnosis and treatment of chronic synovitis in PwH. Participating AICE Haemophilia experts agreed in defining synovitis as a marker of disease activity and in recommending its follow-up. Moreover, they judged US examination more adequate than clinical evaluation, MRI, and CT for screening and detecting synovitis.

Considering therapeutic implications, AICE clinicians reached full consent on the need to switch on-demand patients to prophylaxis and to tailor the treatment schedules in subjects already under prophylaxis. No consensus was found regarding the choice of analgesic and anti-inflammatory therapies, and the indication to different orthopaedic surgical approaches.

In conclusion, we confirm that synovitis should be considered an important marker of disease activity in PwH. However, further investigations are needed to evaluate the impact of different therapeutic options for the treatment of synovitis and haemophilic arthropathy. Such studies should involve the entire comprehensive care team of haemophilia centres including haematologists, radiologists, pain management experts, physiatrists, rehabilitation specialists, and orthopaedic

surgeons. In particular, in the evolving landscape of haemophilia treatment,<sup>87</sup> characterized by an increasing use of enhanced half-life concentrates, non-replacement therapies, and gene therapy, the identification of early and subclinical signs of arthropathy can represent a major outcome to assess efficacy of therapy in PwH.<sup>88</sup>

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## Conflicts of interest

MNDDM has acted as consultant/adviser and/or speaker for Bayer Healthcare, CSL Behring, Novo Nordisk, Pfizer, Roche, Sobi and Takeda, outside of the submitted work. MN acted as consultant for Bayer, BIOVIIIx, Novonordisk and Amgen and received speaker fees from Kedrion, Octapharma, Pfizer, CSLBehring, Novonordisk, Bayer Sobi and Takeda. IR acted as consultant for Sobi, Bayer, Takeda. CM has acted as paid consultant for Pfizer, and received speaker fees from Pfizer, Sobi, Takeda, Novartis, Novo Nordisk, outside of the submitted work. AR acted as paid consultant/advisor/speaker for Bayer, CSL Behring, Kedrion, Novo Nordisk, Pfizer, Roche, Shire/Takeda and Sobi. GP has received honoraria for attending symposia/congresses and/or for speaking and/or consulting, and/or has received research funding from Bayer, NovoNordisk, Pfizer, Roche, Sobi and Takeda. All other authors have nothing to declare.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table SI.** Diagnosis of synovitis. Results of round one involving the twelve Musculoskeletal Committee Members.

**Table SII.** Clinical implications. Results of round one involving the twelve Musculoskeletal Committee Members.

**Table SIII.** Role of physiotherapy. Results of round one involving the twelve Musculoskeletal Committee Members.

**Table SIV.** Role of orthopaedic surgery. Results of round one involving the twelve Musculoskeletal Committee Members.

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## Appendix I

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