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Review

Improving assessment and management of pain in hemophilia: an Italian Delphi consensus statement☆

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ABSTRACT

Comprehensive evidence-based guidelines and well-validated assessment scales for pain in people with hemophilia (PwH) are needed. Here, we report 28 statements covering five topics on pain assessment and management in pediatric and adult PwH that were developed by 60 Italian hemophilia specialists during a Delphi consensus process. Overall, a clear consensus was achieved for 19 of the 28 statements. Consensus was reached on all statements on the topic of pain assessment and quality of life (QoL), including the need for regular pain assessment on a quantitative scale, the importance of distinguishing between different pain types, and the need to evaluate the impact of pain on patient QoL. The other four topics concerned acute and chronic pain management in adults and in children. Consensus was reached on statements regarding non-pharmacologic treatment and the use of first-line paracetamol (acetaminophen). There was a lack of consensus regarding the use of non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or opioids.

1. Introduction

Hemophilia is an X-linked bleeding disorder caused by an inherited deficiency of coagulation factor VIII (hemophilia A [HA]) or IX (hemophilia B [HB]) [1,2]. The estimated incidence of hemophilia in male live births is 1 in 5000 for HA and 1 in 30,000 for HB [3]. Hemophilia is characterized by articular bleeding episodes, or hemarthroses, mainly in the knees, ankles, and elbows [2,4,5]. Recurrent intra-articular bleeding progressively damages and eventually destroys the joint, in a process known as hemophilic arthropathy [4,5].

Prophylaxis with factor VIII/IX (FVIII/IX) replacement therapy reduces bleeding episodes and, in turn, reduces the development of hemophilic arthropathy [2]. However, subclinical bleeding episodes and hemophilic arthropathy can occur despite prophylaxis [6,7], and the optimum prophylactic regimen, which needs to be started at a very young age to prevent future arthropathy, has not been determined yet

☆ The members of the HAEMODOL Study Group are listed in the Appendix.

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[1]. Moreover, many adults have damaged joints as a result of not receiving appropriate prophylaxis as infants, and FVIII/IX replacement therapy is still not widely available in some countries. Thus, despite great advances in hemophilia treatment during recent years, the prevalence of hemophilic arthropathy and the presence of arthropathic joint changes is not negligible in persons with hemophilia (PwH) [8,9], including those with moderate hemophilia [10,11].

Joint pain, both acute (caused by hemarthrosis) and chronic (caused by hemophilic arthropathy), is a major problem in PwH, including children and adolescents [12–19]. Up to 50% of adult PwH have chronically painful joints that cause disability and impair quality of life (QoL) [10,20], and in a multinational study, 89% of PwH experienced at least one pain exacerbation episode during a 4-week observation period [21]. Chronic and acute pain are frequently experienced concurrently, which causes unique challenges in the assessment and management of pain in PwH [12,22,23].

Appropriate pain assessment and effective management strategies are essential to improve the functionality and QoL of PwH [20,24,25]. Despite being a pervasive problem, pain is often not optimally treated in PwH [15,18,19,22–27]. There are numerous evidence-based guidelines available for the management of pain in chronic joint conditions, such as osteoarthritis; however, various challenges associated with hemophilic arthropathy (different pathophysiology and demographics versus osteoarthritis, bleeding diathesis affecting the benefit:risk ratio of some medications, such as non-steroidal anti-inflammatory drugs [NSAIDs]) limit the ability to extrapolate recommendations from such guidelines to PwH. The 2020 World Federation of Hemophilia (WFH) guidelines for the management of hemophilia does contain information regarding pain management for hemophilic arthropathy. This recommends the use of clotting factor replacement to stop potential active bleeding associated with acute pain, and functional training, education on pain management (including the use of complementary pain management techniques, such as meditation, distraction, mindfulness, or music therapy) and a stepwise use of analgesics to manage acute and chronic pain [2]. Regarding the latter, paracetamol (step 1), cyclooxygenase-2 (COX-2) inhibitors, or paracetamol plus codeine, or paracetamol plus tramadol (step 2), and morphine (step 3) are suggested. There is, however, a lack of supporting evidence for these recommendations and there are no comprehensive evidence-based guidelines specifically on pain management in PwH; therefore, clinical practice is inconsistent and largely empirical [12,15,25,27,28]. Furthermore, pain assessment in PwH is not well developed [12,15,22,29,30], with only one recently validated pain assessment tool specific for use in patients with PwH currently available (the Multidimensional Hemophilia Pain Questionnaire [MHPQ]) [22].

Thus, there is an urgent need to improve and standardize both pain assessment and pain management in PwH [25]. To this end, the HAEMODOL (HAEMO = Hemophilia and DOL = "DOLore", the Italian word for 'pain') Study Group was established, a group of clinicians from multiple hemophilia treatment centers in Italy, who agreed to participate in an ongoing manner in various surveys organized by the HAEMODOL Steering Committee. Results of a prior survey from this group, investigating clinician opinion on different aspects of hemophilia-related pain [31], highlighted the need to further investigate pain in PwH, and initiate a path of scientific sharing on pain management within the community of clinicians in Italy managing patients with PwH. Here, we report recommendations on the assessment and management of pain in pediatric and adult PwH that were subsequently developed by the HAEMODOL Study Group during a Delphi consensus process.

2. Methods

Between July and October 2018, a modified Delphi consensus process was conducted among a panel of 60 clinicians (the HAEMODOL Study Group; Appendix 1) with experience in treating PwH from 35 Italian hemophilia treatment centers to generate statements on the assessment and management of pain in PwH.

2.1. Preliminary literature search

Prior to the Delphi consensus process, a multidisciplinary steering committee of 12 Italian experts in hemophilia, orthopedic complications of hemophilia, and pain therapy was established to define relevant topics concerning pain assessment and management in PwH. To gain insight into current recommendations on the treatment of pain in PwH, and to identify controversial issues before the first meeting of the steering committee, a literature search was performed of the Medline, Scopus, Web of Science and Cochrane databases using the keywords (h(*a*)emophilia OR h(*a*)emophilic) AND (pain) AND (assess* OR treat* OR prevent* OR manag* OR therap*) in the article title, with no date or language limits applied. A total of 65 papers were retrieved and analyzed. Of these, one was a retrospective study on pain management and three were randomized controlled studies on COX-2 inhibitors used for pain relief in PwH. All the other papers were editorials (n = 1), reviews (n = 5), surveys (n = 13), questionnaire/assessment tools proposals (n = 7), and case reports (n = 2), or studies on non-pharmacological approaches [acupuncture (n = 5), physiotherapy (n = 9), psychological interventions (n = 19)]. Given the relative lack of evidence on specific pharmacological treatments for pain control in PwH (as determined by the literature search; only 4 relevant studies of pharmacological treatment vs 33 studies of non-pharmacological treatments), the HAEMODOL steering committee decided to focus on pharmacological treatment of pain in PwH; non-pharmacological approaches were also considered as a secondary topic to provide a balanced and comprehensive perspective on pain management. In light of the lack of published evidence, the steering committee considered the Delphi method appropriate to reach consensus based on expert opinion [32].

2.2. Preliminary online survey

The HAEMODOL steering committee appointed a panel of five experts (2 hematologists, a physiatrist, a rehabilitation specialist and a pain specialist) to design and conduct a preliminary online survey of the HAEMODOL Study Group (Fig. 1). This was based on the results of the prior survey [31], the experts' clinical experience and the literature review, and examined issues in a more in-depth manner. The aim of the survey was to understand current practice and define the challenges

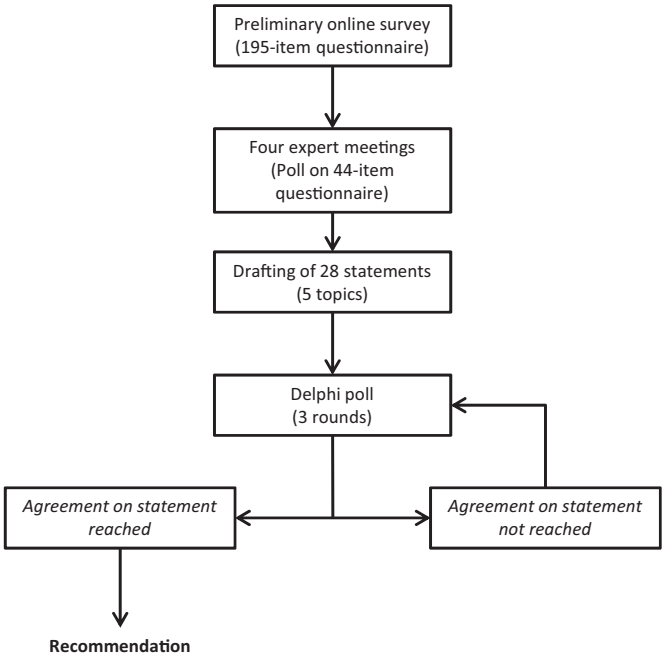

Fig. 1. Main steps of the HAEMODOL Project.

faced by healthcare providers when treating pain in PwH. The final questionnaire to be used in the survey was validated by the Steering Committee, and was comprised of 195 items grouped into eight topics: multidisciplinary approach to pain in hemophilia; assessment of pain and quality of life; non-drug therapy for the adult patient; pharmacologic therapy for the adult patient; non-pharmacologic therapy of the pediatric patient with acute pain; pharmacologic therapy of the pediatric patient with acute pain; non-pharmacologic therapy of the pediatric patient with chronic pain; and pharmacologic therapy of the pediatric patient with chronic pain. Clinicians expressed their level of agreement with each item, scored on a 5-point Likert scale, ranging from 1 (totally disagree) to 5 (totally agree). An option to choose not to respond to the item was also available.

Between January and February 2018, 42 of the 61 clinicians/specialists belonging to the HAEMODOL Study Group completed the online survey, and, in March 2018, the Steering Committee evaluated and synthesized the online survey results. The survey results were evaluated based on the following criteria: (1) items with at least 66% of responses scored 1–2 were deemed 'in disagreement'; (2) items with at least 66% of responses scored 4–5 were deemed 'in agreement'; and (3) items that did not reach the previous cut-offs or that had at least 66% of responses scored as 3 were deemed 'doubtful'.

The Steering Committee then set the objectives and agenda of four subsequent 'Expert Meetings' of the HAEMODOL Study Group (see Section 2.3), which included structured discussion of the 44 items derived from their evaluation of the online survey results.

2.3. Expert meetings and formulation of Delphi statements

Four regional meetings, each attended by ~15 members of the HAEMODOL Study Group (including members of the Steering Committee), were held between March and April of 2018. Presentations were made at each meeting, the focus of which were to present a synthesis of the of results of the 195-item online survey. At each meeting, structured 'break out' sessions were then held to evaluate, discuss and vote on each of the 44 items.

Based on the results of the four expert meetings, the Steering Committee drafted 28 statements for the Delphi consensus process at a meeting held in June 2018 (Fig. 1). The statements were grouped into five topics: pain assessment and QoL; acute pain in the adult patient; chronic pain in the adult patient; acute pain in the pediatric patient; and chronic pain in the pediatric patient. For each statement, the relevant population, management strategies in terms of diagnostic tools, and pharmacologic and non-pharmacologic treatments were defined. The steering committee validated the final statements (via email communication) to be submitted to the Delphi process.

2.4. Delphi process

The steering committee planned three consensus rounds, which were conducted online with the 60 Italian clinicians (i.e., The HAEMODOL Study Group). The clinicians expressed their level of agreement or disagreement for each statement using a Likert scale ranging from 1 (totally disagree) to 9 (totally agree), where intermediate scores of 2–3, 4–6, and 7–8 corresponded to disagreement, tentative agreement, and agreement, respectively. As previously described [33], consensus was reached when 80% of ratings for a statement fell within one of the 3-point regions of the Likert scale (1–3, 4–6, or 7–9), and consensus was not reached when 90% of ratings fell within one of the extra-wide regions (1–6 or 4–9). If consensus was not reached on a statement during the first one or two rounds, the statement was reformulated and recirculated in subsequent rounds until consensus was reached or the statement was rejected.

The steering committee validated the final results of the Delphi process presented here.

3. Results

Of the 60 clinicians, 52 completed the first Delphi round, 51 completed the second, and 51 also completed the third round. Over the five topic areas, the consensus process resulted in 19 recommendations (statements upon which agreement was reached; Tables 1–5).

3.1. Topic 1: Pain assessment and quality of life

As shown in Table 1, consensus was reached on all statements related to pain assessment and QoL in PwH. It should be noted that for statement 7 (the impact of pain on QoL as measured by the EQ-5D-5L) consensus was only reached after the original statement was reformulated to specify that it is important to evaluate the impact of pain on QoL at each check-up or in the case of significant changes in the patient's clinical condition or therapy; the original statement did not address significant changes in the patient's clinical condition or therapy.

The statements acknowledge that, in the outpatient setting, pain needs to be investigated as a symptom by the hemophilia center physician at each visit (statement 1), and that pain must be assessed on a quantitative scale that has been validated and is appropriate for the age of the patient (adult versus pediatric patients) [statement 2].

It was agreed that it is important to distinguish between different types of pain (statements 3 and 4): acute versus chronic pain, and nociceptive pain versus neuropathic pain (using the Pain Detect questionnaire used to diagnose neuropathic pain; statement 3). In chronic pain, the nature of pain should be determined, i.e. continuous and persistent versus that caused by exacerbation of arthropathy (flare-ups), with the intensity, frequency, and duration of the latter monitored (statement 5). We propose that information on pain is integrated with that on bleeding episodes, as recorded in the infusion log, to assist with monitoring the frequency of pain onset (statement 6).

Table 1
Consensus statements for recommendations concerning pain assessment and quality of life in persons with hemophilia (Topic 1).

Number	Statement	Agreement
1	Clinicians at hemophilia centers must investigate pain at every consultation with hemophilic patients.	Yes
2	Pain assessment must be carried out by using quantitative scales validated for adults (NRS or VAS) and pediatric patients (Wong-Baker or FLACC Scale). For each determination, report the finding in the patient's notes specifying the scale used, so as to be able to monitor changes in the symptom.	Yes
3	When assessing pain, it is important to distinguish between nociceptive and neuropathic pain by using the questionnaire for neuropathic pain (Pain Detect).	Yes
4	When assessing pain, it is important to distinguish between acute and chronic pain.	Yes
5	In chronic pain, a distinction must be made between pain perceived in a continuous and persistent manner and pain caused by flare-ups. In the case of flare-ups, it is necessary to measure the intensity of the pain and record its frequency and duration.	Yes
6	To monitor the frequency of pain onset, the data on the bleeding episodes contained in the infusion logs should be integrated with the data on chronic pain and episodes of acute pain, on the intensity of such episodes and the use of pain-relieving drugs, if used.	Yes
7	It is important to evaluate the impact of pain on the patient's quality of life at each check-up or in the case of significant changes in the patient's clinical condition or therapy, using the EQ-5D-5L questionnaire.	Yes[a]

EQ-5D-5L – 5-level version of the EuroQol 5 dimension, FLACC – face, legs, activity, cry, consolability, NRS – numeric rating scale, VAS – visual analog scale.

[a] Reformulation and agreement after consensus round 3.

Table 2
Consensus statements for recommendations concerning the management of *acute pain in adults* with hemophilia (Topic 2).

Number	Statement	Agreement
1	The non-pharmacologic treatment of acute joint or muscle pain is based on the RICE protocol (rest, ice, compression, and elevation), including limiting (not completely blocking) movement and load in the first 1–2 days after symptom onset, and the application of ice (or in any case cooling of the affected area) for 10–15 min several times a day for the first 1–2 days after symptom onset is also indicated, provided that the ice is not applied in direct contact with the skin.	Yes
2	Within non-pharmacologic interventions, in severe hemarthrosis of the large joints in the adult patient it may be useful to perform arthrocentesis within the first hours from the onset of the acute pain.	No[a]
3	The pharmacologic treatment of first choice for pain due to acute hemarthrosis and/or muscle hematoma in the adult patient is oral paracetamol at an effective analgesic dose of 1000 mg every 8 h. This should be combined with an opioid if the pain is severe (NRS >7) or there is no therapeutic response within 4 h.	Yes
4	In the event of pain due to acute hemarthrosis and/or muscle hematoma in the adult patient, both oral NSAIDs + PPI and COXIB may be used for short periods as a first-line pharmacologic treatment, in cases in which paracetamol is contraindicated or ineffective.	Yes
5	The second-line pharmacologic treatment of acute pain due to hemarthrosis and/or muscle hematoma in the adult patient is paracetamol or NSAID, in combination with tramadol or codeine.	No[b]
6	In the event of unsatisfactory pain control with the second-line therapy (paracetamol or NSAID, in combination with tramadol or codeine), pain due to acute hemarthrosis and/or muscle hematoma in the adult patient may be managed with third-line opioids (oxycodone, tapentadol).	Yes

COXIB – COX-2 inhibitor, NRS – numeric rating scale, NSAID – non-steroidal anti-inflammatory drug, PPI – proton pump inhibitor, VAS – visual analog scale.
[a] Aggregation of opinions in regions 7–9 (agreement) of 47.1%.
[b] Aggregation of opinions in regions 7–9 (agreement) of 60.0%.

3.2. Topic 2: Acute pain in adult PwH

Consensus was reached on four of the six statements on the management of acute pain (see Table 2).

It was agreed that, in addition to non-pharmacologic treatment strategies (i.e., the RICE protocol of rest, ice, compression, and elevation), paracetamol (acetaminophen) represents the first-line therapy for acute musculoskeletal pain in adults (statements 1 and 3). In severe cases, paracetamol can be administered in combination with an opioid (statement 3), while an NSAID plus a proton pump inhibitor (PPI) or COX-2 inhibitor can be used as a first-line treatment for short periods for cases of acute pain in which paracetamol is ineffective or cannot be used (statement 4).

Consensus was not reached with regard to statement 5, which advocated second-line therapy with paracetamol or an NSAID in combination with tramadol or codeine; however, in the event that such a regimen is ineffective, it was agreed that a stronger opioid, such as oxycodone or tapentadol, may be used as third-line therapy (statement 6). Agreement was also not reached for statement 2 pertaining to the usefulness of arthrocentesis shortly after the onset of acute pain.

3.3. Topic 3: Chronic pain in adult PwH

Consensus was reached on four of the six statements regarding the management of chronic pain in adults with hemophilia (see Table 3).

Our recommended pharmacologic approach to chronic pain is very similar to that for acute pain. Alongside non-pharmacologic treatment strategies (i.e., physical therapy), paracetamol represents the first-line therapy for chronic musculoskeletal pain in adults (statements 1 and 2). In addition to baseline therapy with paracetamol, we recommend that the management of flare-ups is mainly based on corticosteroids or NSAIDs to reduce the inflammatory component (statement 4).

In contrast to the equivalent statement for acute pain, agreement was not reached for the short-term use of NSAIDs plus proton pump inhibitors (PPIs) and COX-2 inhibitors as first-line treatment for chronic pain in which paracetamol has been previously ineffective or is contraindicated (statement 3). As with the equivalent statement for acute

Table 3
Consensus statements for recommendations concerning the management of *chronic pain in adults* with hemophilia (Topic 3).

Number	Statement	Agreement
1	The non-pharmacologic treatment of chronic joint or muscle pain (and/or peripheral neurological pain) in the adult patient consists of physical therapy (land- and water-based exercise therapy) prescribed by the physiatrist and/or orthopedic surgeon.	Yes
2	In the event of chronic arthropathic pain in the adult patient, the first-line treatment is oral paracetamol at a dose of 1000 mg every 8 h or the combination of paracetamol and tramadol or an opioid other than tramadol (codeine or buprenorphine).	Yes
3	In the event of chronic arthropathic pain in the adult patient, both oral NSAIDs + PPIs and COXIBs may be used as a first-line pharmacologic treatment, for short periods due to their side effects, in cases in which paracetamol is contraindicated or ineffective.	No[a]
4	When planning the first-line pharmacologic treatment of chronic arthropathic pain in the adult, oral cortisone, or oral NSAIDs or COXIBs may be used for short periods as anti-inflammatories in combination with paracetamol in the event of flare-ups.	Yes
5	The second-line pharmacologic treatment of chronic arthropathic pain recommended for the adult patients is paracetamol or NSAIDs in combination with tramadol or an opioid other than tramadol (codeine or buprenorphine).	No[b]
6	In the adult patient, in the event of chronic arthropathic pain negatively affecting quality of life and refractory to second-line treatment (paracetamol or oral NSAIDs or COXIBs in combination with tramadol or an opioid other than tramadol – codeine or buprenorphine) other opioids may be used as a third-line strategy (fentanyl, oxycodone, tapentadol).	Yes

COXIB – COX-2 inhibitor, NSAID – non-steroidal anti-inflammatory drug, PPI – proton pump inhibitor.
[a] Aggregation of opinions in regions 7–9 (agreement) of 54.9%.
[b] Aggregation of opinions in regions 7–9 (agreement) of 64.7%.

Table 4
Consensus statements for recommendations concerning the management of *acute pain in pediatric patients* with hemophilia (Topic 4).

Number	Statement	Agreement
1	The non-pharmacologic treatment of acute pain due to hemarthrosis or hematoma, whether spontaneous or traumatic, in pediatric patients consists of the application of ice (or in any case cooling of the affected area) for 10–15 min several times a day for the first 1–2 days after symptom onset, provided that the ice is not applied in direct contact with the skin.	Yes
2	In acute pain due to hemarthrosis and/or hematoma in pediatric patients, the first-line pharmacologic treatment is oral paracetamol at a dose appropriate for the patient's weight (15 mg/kg) every 8 h. For pediatric patients weighing >26 kg the dose is 500 mg every 8 h.	Yes
3	In planning first-line pharmacologic therapy for acute pain due to hemarthrosis and/or hematoma in pediatric patients, oral cortisone or NSAIDs may be prescribed in combination with paracetamol.	No[a]

NSAID – non-steroidal anti-inflammatory drug.
[a] Aggregation of opinions in regions 7–9 (agreement) of 61.2%.

Table 5
Consensus statements for recommendations concerning the management of *chronic pain in pediatric patients* with hemophilia (Topic 5).

Number	Statement	Result
1	Non-pharmacologic treatment of chronic pain in pediatric patients consists of physical therapy (land- and water-based exercise therapy) prescribed by the physiatrist and/or orthopedic surgeon, to be initiated as soon as possible.	Yes
2	In the event of chronic arthropathic pain in pediatric patients, the first-line treatment is oral paracetamol at a dose appropriate for the child's weight (15 mg/kg) every 8 h. For pediatric patients weighing >26 kg the dose is 500 mg every 8 h	Yes
3	In the first-line pharmacologic treatment of flare-ups of chronic arthropathic pain in a pediatric patient receiving prophylaxis, cortisone may be used for short periods in combination with paracetamol.	No[a]
4	In the first-line pharmacologic treatment of flare-ups of chronic arthropathic pain in a pediatric patient receiving prophylaxis, an oral NSAID (ibuprofen) may be used for short periods in combination with paracetamol.	No[b]
5	If the first-line strategies prove ineffective, in the pharmacologic treatment of chronic arthropathic pain in a pediatric patient receiving prophylaxis it is possible to use, as a second-line strategy, tramadol in addition to paracetamol.	No[c]
6	If the first-line strategies prove ineffective, in the pharmacologic treatment of chronic arthropathic pain in a pediatric patient over the age of 12 years receiving prophylaxis, it is possible to use the combination of paracetamol and codeine as a second-line strategy.	No[d]

NSAID – non-steroidal anti-inflammatory drug.
[a] Aggregation of opinions in regions 7–9 (agreement) of 68.1%.
[b] Aggregation of opinions in regions 7–9 (agreement) of 42.6%.
[c] Aggregation of opinions in regions 7–9 (agreement) of 50.0%.
[d] Aggregation of opinions in regions 7–9 (agreement) of 70.2%.

pain, agreement was not reached for chronic pain statement 5, supporting second-line therapy with paracetamol or NSAIDs in combination with tramadol or another opioid, such as codeine. However, it was agreed that in the event that such a regimen is ineffective, stronger opioids (i.e., fentanyl, oxycodone, and tapentadol) may be used as third-line therapy (statement 6).

3.4. Topic 4: Acute pain in pediatric PwH

Consensus was reached for two of the three statements regarding the management of acute pain in pediatric PwH (Table 4). It was agreed that, in addition to ice application, acute pain from hemarthrosis or hematoma should be treated with paracetamol as the first-line analgesic therapy of choice (statements 1 and 2). Consensus was not reached in relation to the prescription of corticosteroids or NSAIDs in combination with paracetamol as a first-line approach (statement 3).

3.5. Topic 5: Chronic pain in pediatric PwH

As for adults, it was agreed that, along with physical therapy, pediatric patients with chronic pain should receive first-line pharmacologic therapy with paracetamol (statements 1 and 2; Table 5).

Consensus was not reached for statements 3 and 4, regarding first-line paracetamol in combination with corticosteroids or NSAIDs to treat flare-ups in pediatric patients receiving prophylaxis, or for statements 5 and 6, regarding paracetamol in combination with tramadol or codeine as second-line options for chronic arthropathic pain. Agreement could not be reached on any of these four statements, despite reformulating them from two more general original statements, which proposed using corticosteroids or NSAIDs for flare-ups, and tramadol or codeine for chronic pain, respectively.

4. Discussion

Adequate assessment of pain and its causes is essential in guiding proper management of pain in PwH [2,30,34]. To our knowledge, this is the first study to use a Delphi process to reach consensus on pain management in PwH. We recruited a multidisciplinary panel of experts, including pain specialists, with clinical experience in PwH. The lack of published evidence on the management of pain in PwH means that evidence-based practice recommendations cannot be established, and that our advice is largely based on clinical experience, previously published advice on therapeutic options for pain management in PwH, and non-hemophilia-specific pain management guidelines [15,20,27,28,35].

Pain assessment should be undertaken using scales validated for use in PwH, as other assessment tools may not be sensitive to the idiosyncrasies of hemophilia-related pain, such as the co-occurrence of acute and chronic pain [12,22,29]. While the MHPQ has been developed and validated in adult PwH [22], it has not been well validated in children and teenagers and, thus, its usefulness in these latter patient populations is not clear. There is a need, therefore, to develop and validate more pain assessment tools that are appropriate for PwH of all ages, and useful in both acute and chronic pain [12,22,25]. In the meantime, we recommend that instruments validated in pain situations other than hemophilia (such as the numeric rating scale [NRS] or visual analog scale [VAS] for adults and the Wong-Baker FACES scale or FLACC [face, legs, activity, cry, consolability] scale for pediatric patients) be used [13,15,25,29].

We also recognize the importance of assessing the impact of pain on the QoL of PwH. Our recommendation is that the EQ-5D-5L be used in this regard [23,36–39]. However, it should be noted that the EQ-5D-5L assesses perceived overall general health status, mobility, functioning and presence of pain, but not specifically the impact of pain on QoL. Additional conditions (i.e. mobility issues, comorbidities, etc.) could, therefore, lead to an impaired health status regardless the presence of chronic pain. Despite these inherent limitations, and in the absence of any tools that specifically assess the impact of pain on QoL, we feel that the EQ-5D-5L can be used, although the development of more specific tools to measure the impact of pain on QoL should be a priority in future research.

In addition to assessing pain intensity and its effects on QoL, it is important to understand the underlying cause of pain [2,30]. In PwH, the first priority is to exclude bleeding as a cause of pain [30]. There is a need to clearly distinguish acute from chronic pain, but given the overlap in clinical symptoms and lack of standard diagnostic protocols, it can be difficult for patients and clinicians to distinguish between acute hemarthrosis pain and acute exacerbation of arthropathy (flare-ups), which potentially contributes to inappropriate treatment [15,19,22,23,25,30,40,41]. While the majority of PwH have nociceptive pain, a proportion demonstrate signs of neuropathic pain and/or altered central pain mechanisms [30,42], which require specific treatment with opioids, gabapentinoids and/or antidepressants [43]. Questionnaires designed to help diagnose neuropathic pain (e.g., the recommended Pain Detect questionnaire) can be helpful in this regard [30,43,44].

Treatment of acute and chronic pain in adult and pediatric PwH is based on non-pharmacologic and pharmacologic therapy [2,4,12,15,27,45–47]. The RICE protocol is recommended for acute pain in adults (ice application alone for pediatric patients) [15,47]. Physical therapy and rehabilitation, including land- and water-based exercise, as recommended in our statements, may help to ameliorate chronic pain [15,46–51]. In some cases, arthrocentesis may be useful, but the proven efficacy of the available pharmacologic approaches restricts the indications to selected patients with severe and painful hemarthroses [4] and we were unable to come to an agreement on the use of arthrocentesis for acute pain in adults.

Although there is a lack of published evidence on the pharmacologic management of pain in PwH, our approach to analgesia selection is consistent with other recommended pain management strategies for

PwH, which reflect the World Health Organization's analgesic ladder approach [2,12,15,20,25,27]. According to available expert recommendations for pain management in hemophilia, paracetamol, administered at a dose that does not affect coagulation or liver function, is the preferred first-line pharmacologic therapy for acute and chronic pain in adults and pediatric patients [2,4,12,15,20,27]. However, in the preliminary survey of our expert panel, while paracetamol was the most frequent first choice treatment for chronic and acute pain in pediatric patients, in adults first-line treatment for chronic pain was most frequently COX-2 inhibitors (41.5%) and for acute pain was paracetamol plus tramadol or codeine (37.7%) [6].

There was a lack of consensus in relation to our statements regarding first- and second-line treatment strategies involving NSAIDs and COX-2 selective inhibitors, particularly for chronic pain. It should be noted that NSAIDs are not recommended by the WFH but we included them in our recommendations because (i) these drugs are recommended in the guidelines for pain associated with other pathologies (although, as mentioned in the Introduction, their benefit:risk ratio differs in PwH); (ii) they are frequently used by patients without prescription; and (iii) it is likely that clinicians will prescribe them on occasion due to a lack of other available options. Our results are consistent with European and Italian surveys on the management of pain in PwH, in which there was relatively little consensus beyond the first-line use of paracetamol for most patients [15,18].While ibuprofen appears to be relatively safe and effective for the management of inflammatory conditions or chronic articular pain in PwH [28,46,52–55], there are major unresolved concerns regarding the safety of NSAIDs in PwH, particularly gastrointestinal bleeding risk, which limit their use to short-term control of pain associated with flare-ups [2,20,25,46]. COX-2 inhibitors have a lower risk of gastrointestinal bleeding complications than traditional NSAIDs (although both are associated with an increased risk of thrombotic events [20,28,56]) and they appear to be safe and effective in managing chronic articular pain in PwH [57–60]. Therefore, it seems reasonable to use the lowest possible dose of COX-2 inhibitor for the shortest possible time [35,46]. In the initial survey of our expert panel, COX-2 inhibitors were a more frequent first-line choice for chronic pain in adults than for acute pain (41.5% versus 18.9%), whereas NSAIDs were less frequently used (3.8% and 5.7% for chronic and acute pain, respectively) [31]. More studies comparing the relative safety of NSAIDs versus paracetamol in PwH would help guide first-line treatment decisions in these patients. The risks of adverse events with traditional NSAIDs and COX-2 inhibitors must be carefully considered, and long-term treatment with NSAIDs should be accompanied by careful patient surveillance and co-prescription of PPIs [15,35].

Clinical data guiding the use of opioids for pain management in adults and pediatric PwH are lacking. If relief can be achieved with paracetamol, opioids should be avoided but they should not be underused for patients with refractory pain [15,20,28,41]. Combination therapy with agents acting at different receptors of the pain pathway may be beneficial as a second-line approach, for example paracetamol or an NSAID plus tramadol or codeine [12,28]. Opioids are usually considered as second-line pain therapy [15,18,41], but in the preliminary survey of our expert panel, combination therapy with paracetamol and tramadol or codeine was often chosen as first-line treatment for acute and chronic pain in adults (37.7% and 39.6%, respectively) [31]. Reluctance to use NSAIDs rather than opioids may have contributed to the lack of consensus on statements recommending combination therapy with paracetamol or NSAID plus tramadol or codeine for the second-line treatment of acute or chronic pain.

The recommendations for adults reached greater consensus than those for pediatric patients. This is likely to be because finding a consensus in adults is simpler, given that all treatment options need to be considered more carefully in children due to heightened concerns about the safety of medications in children and their lack of ability to provide consent for treatment.

Our recommendations for pharmacologic therapy for pain management in PwH do not take into consideration the use of clotting factor replacement therapies.

5. Conclusions

In conclusion, based on our Delphi consensus, the management of acute and chronic pain in PwH requires an individualized approach based on multimodal non-pharmacologic and pharmacologic therapies delivered by a multidisciplinary team, which should include hematologists, pain specialists, and physiatrists. Ongoing monitoring and assessment of pain and its effects on QoL, with appropriate adjustment of treatment, is required for optimal pain management in PwH. Despite the clinical importance of the recommendations developed and reported herein, investigation of the role of additional components of the multimodal approach, such as psychological assessment and support, assessment of altered central pain processing, and the use of adjunctive medications (e.g. anticonvulsants and antidepressants) and complementary pain management techniques, would be useful to expand our recommendations further. In addition, there is some evidence of the benefit of physical therapy in the management of pain in PwH [61] and further consideration of this aspect of pain management may complement the recommendations we provide.

6. Future considerations

Several unmet needs exist in the management of pain in PwH, including the need for evidence-based clinical practice recommendations for pain management in adults and pediatric PwH, particularly with regard to the use of opioids. There is also a need for validated hemophilia-specific pain assessment scales that are appropriate for PwH of all ages and useful for both acute and chronic pain. Further research is needed regarding our understanding of the underlying causes of pain, aside from bleeding. There is no standard diagnostic protocol to differentiate between hemarthrosis and flare-ups of hemophilic arthropathy, suggesting a potential role for point-of-care ultrasound in diagnosis. Lastly, there is a need for specific questionnaires and treatments for PwH with neuropathic pain and/or altered central pain mechanisms. Addressing these important issues will help physicians to improve pain management outcomes in all PwH.

7. Practice points

- Pain should be investigated on a quantitative scale and the impact of pain on quality of life should be considered.
- It is important to distinguish between different types of pain so that the most appropriate pain management treatment is provided.
- First-line paracetamol is recommended for acute and chronic pain in adult and pediatric patients with hemophilia.
- Optimal pain management requires ongoing monitoring and assessment of pain and its effects on quality of life, as well as individualized non-pharmacologic and pharmacologic treatment strategies.
- The current management of pain in patients with hemophilia in Italy may improve by adopting these clinical recommendations.

7.1. Research agenda

- Further development of pain assessment in patients with hemophilia to tailor pain management for every patient
- Studies comparing the relative safety of non-steroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors versus paracetamol in patients with hemophilia
- Clinical studies investigating the use of opioids for pain management in adult and pediatric patients with hemophilia

Author contributions

Contribution Author(s) Study concepts: CS, MNDDM, CM, BA; Study design: CS, MNDDM, CM, BA; Data acquisition: AC, GDM, MM, MEM, ACM, EVP, AR, RCS, AT; Quality control of data and algorithms: CS, MNDDM, CM, BA; Data analysis and interpretation: CS, MNDDM, CM, BA, AC, GDM, MM, MEM, ACM, EVP, AR, RCS, AT; Manuscript preparation: CS, MNDDM, CM; Manuscript editing: CS, MNDDM, CM, BA; Manuscript review: AC, GDM, MM, MEM, ACM, EVP, AR, RCS, AT. All authors approved the final version of the manuscript for submission.

Declaration of Competing Interest

Cristina Santoro: Received honoraria for participation in speaker bureau and advisory boards from Sobi, Takeda, Bayer, CSL Behring, Roche, NovoNordisk, and Pfizer.

Matteo Nicola Dario Di Minno: Received grants and honoraria from Sobi, Pfizer, Bayer, Novo-Nordisk, Takeda, Roche and Daiichi Sankyo.

Maria Elisa Mancuso: Acted as paid consultant, advisor, and/or speaker for Bayer Healthcare, CSL Behring, Novo Nordisk, Pfizer, Roche, Sobi, Grifols, Kedrion, Octapharma, Biomarin, and Catalyst.

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Emilio Valter Passeri declare no conflict of interest.

Antonio Corcione, Marco Martinelli, Benedetto Acone, Angiola Rocino declare no conflicts of interest.

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Appendix A. Haemodol study group

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