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REVIEW ARTICLE

The evolution of physiotherapy in the multidisciplinary management of persons with haemophilia (PWH): A scoping review

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Abstract

Introduction: Haemophilia is a rare congenital bleeding disorder, and the most common manifestation is spontaneous bleeding in muscles and joints. Despite the benefits linked to recent and dramatic pharmacological advances at least in high income setting, many patients still develop musculoskeletal dysfunctions during their lifetime, which must be managed by physiotherapists in the frame of a multidisciplinary team. The aim of the scoping review is to map the available evidence by providing an overview on the past and present physiotherapy scenario in persons with haemophilia (PWH).

Materials and methods: The review was conducted according to the guidelines of the PRISMA extension for scoping reviews. Scientific articles on physiotherapy and sport interventions for PWH published from 1960 up to September 2021 have been included. Search was conducted on the e-databases PubMed and PEDro without restrictions for the study design.

Results: Sixty eight articles were included, 52 related to rehabilitation and preventive physiotherapy, 16 to sport. The results have been reported in chronological order and divided into two categories: (1) rehabilitation and preventive physiotherapy; (2) sport activities.

Conclusions: This is the first scoping review on physiotherapy in haemophilia, based on the existing evidence on this topic which allowed us to underline how the role of the physiotherapist changed over time. Historically this specialist did intervene only after an acute bleed or surgical operation, but now he has a pivotal role in the multidisciplinary team that acts to improve from birth the quality of life of the PWH. His activity is also closely intertwined with sport promotion and supervision.

KEYWORDS
haemophilia, physical therapist, physiotherapy, rehabilitation, sport activities

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1 | INTRODUCTION

Haemophilia is a rare inherited disorder characterised by the deficiency of coagulation factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B.[1] The main clinical manifestation is recurrent bleeding, resulting in different degrees of organ damage. Haemorrhagic manifestations depend largely on the degree of coagulation factor deficiency and the most common clinical signs occur in the musculoskeletal system, such as haemarthrosis, synovitis, haematomas and chronic arthropathy.[2,3]

Haemarthrosis are the hallmark of haemophilia. After the occurrence of three or more bleeds into a single joint within a consecutive 6-month period, the joint is being referred to as target joint.[4,5] Ankles, knees and elbows are those most frequently affected, followed by shoulder and hip.[6,7] The clinical signs of joint illness are reduced mobility, swelling due to synovial hypertrophy but also muscle and capsular contractures.[6] Synovitis has long been thought to be the triggering event, that evolves in parallel with cartilage damage, influencing each other and being both sustained by the presence of blood in the joint. In PWH the ability of the synovium to remove blood is thwarted by repeated haemorrhages, leading to deposits of haemosiderin and synovial hyperplasia.[7,8] The inflamed synovium is highly vascularised and friable, and thus bleeds easily even following minor trauma, resulting in a vicious circle that is difficult to break. Repeated episodes of haemarthrosis lead to joint remodelling and ultimately to arthropathy, a disabling chronic condition characterised by damage in the cartilage and bone, chronic pain and reduced quality of life.[9,10] Another frequent complication of haemophilia is the occurrence of haematomas, that typically result from traumatic events, even minor ones. They can be subdivided into subcutaneous, subperiosteal or more frequently muscular. Muscle haemorrhages occur in approximately 10%–20% of PWH and account for 10%–15% of all haemorrhagic events, causing motion limitations, disability, and impaired quality of life.[11,12] Muscle bleeding increases the risks of developing the compartment syndrome, cysts and pseudotumours.

Until 50 years ago, the pharmacological treatment of PWH was almost non-existent. Whole blood or plasma were the only available weapons of very limited efficacy, so that patient life expectancy was 15–20 years. The cases who survived adolescence had severe musculoskeletal damage and were often confined to wheelchairs or bedridden.[13] Treatment has changed over the years from an episodic therapy useful to stop acute bleeding to prophylactic regimens aimed at preventing bleeding. Many drugs are currently available, from coagulation factor concentrates with standard or extended plasma half-lives to new subcutaneous non-replacement drugs such as emicizumab and others in the pipeline. These products have made possible to improve quality of life and life expectancy in the PWH, provided there is around him a multidisciplinary team that helps to maintain what is obtained with prophylaxis.[14,15] The physiotherapist is one of the specialists who must be part of the comprehensive team and should be present throughout the PWH life: in children, for a primary action that avoids the establishment of incorrect postures and behaviours that risk to undermine the musculoskeletal structure; in adults, for post-surgical rehabilitation or to maintain the residual functional activity after chronic joint damage; in all ages, to promote and supervise exercise and sport activities.[15] With this background, the aim of this scoping review is to describe the past, present and future role of physiotherapy in the multidisciplinary management of PWH.

2 | MATERIALS AND METHODS

The PRISMA model for scoping reviews was followed.[16] Literature search included scientific articles concerning physiotherapy and sport activities for PWH published until September 2021, with the aim of analysing time trends. Three different authors, S.G., V.B. and S.P., selected the articles for inclusion based on their personal expertise, but the articles that did not obtain two thirds of approval from the authors were excluded. Electronic databases such as PubMed and Physiotherapy Evidence Database (PEDro) were consulted to identify relevant studies. Other articles, including textbooks and chapters on physiotherapy for haemophilia were also considered. For the PubMed search, the terms "haemophilia" and "hemophilia" were used, linked with the Boolean operator AND terms such as "physical therapy, physiotherapy, physical activity, sport, exercise, physical exercise, exercise programme, aquatic training, Nordic walking and rehabilitation". In the query box, these terms were searched only within the titles and/or abstracts of the articles. On PEDro, the search terms "haemophilia" and "hemophilia" were used as found in titles and abstracts of the articles. Articles that met the following inclusion criteria were selected:

- Population: included male subjects with inherited haemophilia A or B, with no age restrictions.
- Intervention: articles that described physiotherapy and/or sport programs for PWH, whether for preventive or recovery purposes.
- Language of publication: articles written in English and Italian.
- Years of publication: from 1960 to September 2021.
- Study design: no restrictions on the design of selected articles.
- Relevance to the research aim.

Exclusion criteria were failure to meet eligibility criteria, presence of topics already covered in other articles and inability to download the full text. Because two clearly defined phases can be identified in the care of PWH, that is, the time until the 1990s prior to the use on a large scale of prophylaxis and the subsequent 30-year period characterized by dramatic therapeutic progress, articles were selected based on this time division. In the post-1990 phase, our selection was split into 5-year periods, because a much larger number of articles was available. A total of 68 articles were ultimately considered. The entire process is reported in the flow-diagram of the PRISMA Statement 2020 (Figure 1).

3 | RESULTS

A total of 68 articles were included in the scoping review.[1,15,17-82] Of them, 30 dealt with the role of physiotherapy and rehabilitation, 22

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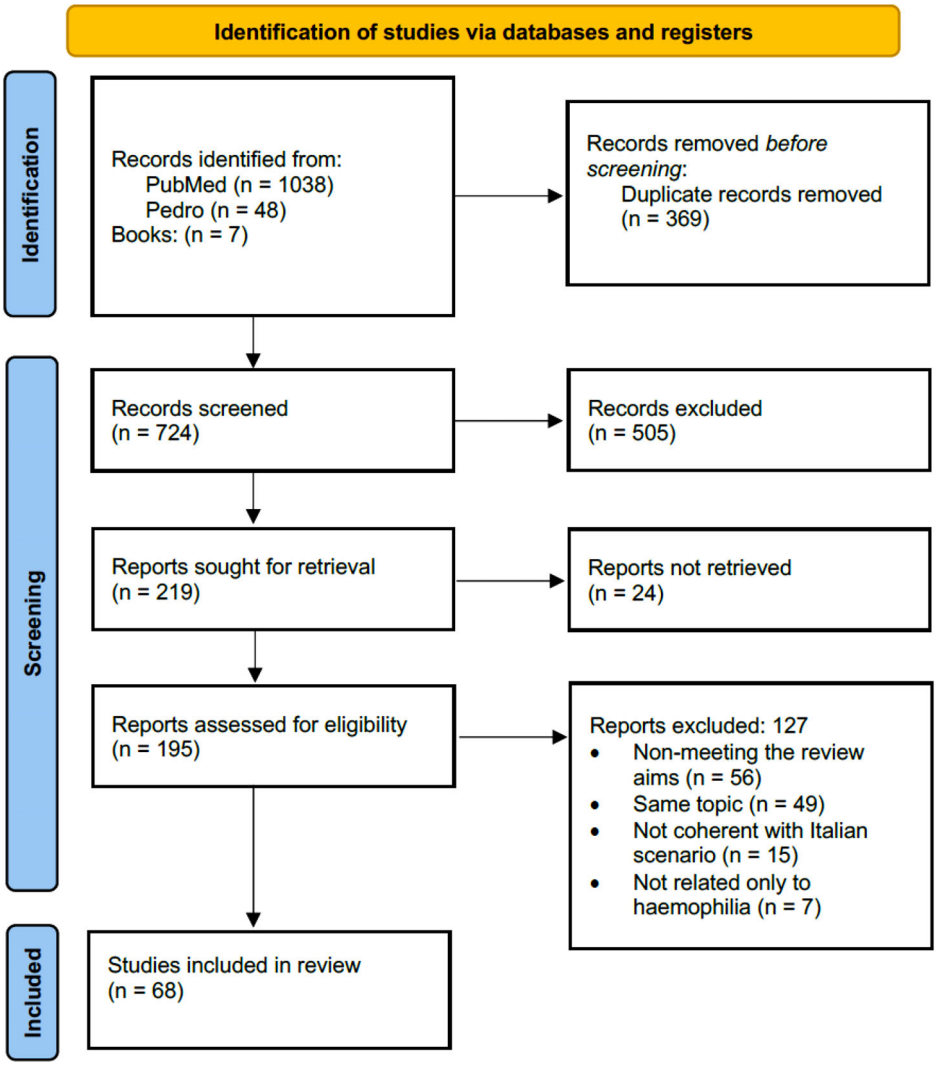


FIGURE 1 Flow-chart of selected studies (PRISMA 2020 statement)

with exercise protocols or specific types of intervention and 16 with sport. The results of studies selected according to the eligibility criteria are presented herewith divided into two sub-sections according to their topic: (1) rehabilitation and preventive physiotherapy; (2) sport activities. Table 1 summarizes all the included articles, highlighting which intervention was described in each.

3.1 | Rehabilitation and preventive physiotherapy

Fifty-two articles[1,15,17–66] dealt with rehabilitation and preventive physiotherapy. Most of them aimed to map the options for the management of PWH or demonstrate the role of physiotherapy, not only in the presence of clinical problems but also for preventive purposes and to allow a healthy growth. Several studies examined a specific physiotherapy intervention, proposed an exercise programme, or evaluated its efficacy. Narrative reviews concerning rehabilitation physiotherapy amount to 13, clinical trials to 16, systematic reviews and textbook chapters both to 5.

In the articles before the year 2000, focus was almost exclusively on rehabilitation following surgical interventions. It was only in the first two decades of the current century that rehabilitation started to be featured both pre- and post-surgery and that physiotherapy gradually took a key role in the comprehensive management of PWH.

In the 60s and 70s of the last century only chapters of textbooks dealt with physiotherapy describing it exclusively as a rehabilitative weapon following an acute bleeding event,[17–22] and we have to wait until 2005 when Stephensen[29] first published an article that emphasizes the role of physiotherapy not only after surgery but also pre-operatively, with the goal to allow a faster post-operative recovery. In the 90s, first Heijnen[23] and then Buzzard[24] developed the concept of preventive physiotherapy in PWH, aimed at maintaining or improving joint and motor function. This concept was subsequently dealt with in all the remaining selected articles. In some of them, physiotherapy was seen as an active intervention, characterized by muscle strengthening sessions meant to increase endurance and overall performance, both as a start-up activity and a path to sports.

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TABLE 1 All manuscripts included in this scoping review are summarized here, highlighting which Physiotherapy intervention was described in each

References (*n*)	Author	Year	Study/Article type	Physiotherapy intervention/ role described
17	Neumark E	1966	Textbook (chapter)	Rehabilitation post-acute event
18	Polli E et al.	1970	Abstract book	Rehabilitation post-acute event
19	McCollough NC	1973	Textbook	Rehabilitation post-acute event
20	Panicucci F	1974	Textbook	Rehabilitation post-acute event
21	Boone DC	1976	Textbook	Rehabilitation post-acute event
22	Pelletier JR	1987	Single-case experimental study	Nonsurgical rehabilitative techniques
23	Hejinen L	1993	Review	Prevention of muscoloskeletal problems
69	Buzzard BM	1996	Review	Prevention of sport injuries
25	Ribbans WJ et al.	1997	Review	Rehabilitation after acute hematroses
26	Battistella LR	1998	Review	Rehabilitation post-acute event
54	Buzzard BM	1998	Review	Rehabilitation and proprioception
24	Buzzard BM	1999	Review	Prevention of articular contractures
27	Buzzard BM & Beeton K	2000	Textbook	Comprehensive overview of the physiotherapy strategy
28	Santavirta N et al.	2001	Clinical trial	Rehabilitation post-acute event
51	Tiktinsky R et al.	2002	Pilot study	Progressive resistance training
70	Mulder K et al.	2004	Review	Exercise and physical activity
29	Stephensen D	2005	Single-case review	Pre-rehabilitation for total knee arthroplasty
71	Mulder K	2006	Exercises guide	Exercises for rehabilitation post-acute event
50	Wittmeier K et al.	2007	Review	Progress rehabilitative or physical activity programme
30	Hejinen L	2008	Review	Rehabilitation and physical activity programme
49	Engelbert RHH et al.	2008	Clinical trial	Aerobic exercise capacity
32	D'young AI	2009	Case study	Conservative non-surgical physiotherapy
47	Gomis M et al.	2009	Systematic review	Regular exercise and rehabilitation
72	Ross C et al.	2009	Clinical trial	Coaching and supervision for athletics
42	Blamey G et al.	2010	Review	Rehabilitation and physical activity programme
55	Hill K et al.	2010	Pilot study	Home exercises programme
56	Vallejo L et al.	2010	Systematic review	Hydrotherapy for hemophilic artropaty
33	Kawaji M et al.	2011	Clinical trial	Physical activity to prevent chronic joint disease
31	Forsyth A & Zourikian N	2012	Review	Rehabilitation after orthopedic surgery
34	Broderick CR et al.	2012	Case-crossover, prospective cohort study	Physical activity and bleeding risk
43	Souza JC et al.	2012	Review	Physical exercises to improve quality of life
57	Von Mackensen S et al.	2012	Non-randomized, interventional, prospective, bi-centre cohort study	Benefits of hydrotherapy and aqua-training
73	Khair K et al.	2012	Multicentre study	Physical activity in children to improve quality of life
74	Schved JF et al.	2012	Clinical trial	Scubadiving programme
75	Czepa D et al.	2012	Clinical trial	Physical performance evaluation
35	Negrier C et al.	2013	Systematic review	Benefits of physical activity programmes
52	Eid MA et al.	2014		Resistance and aerobic exercises
59	Mazloum V et al.	2014	Randomized-controlled trial	Hydrotherapy in addition to rehabilitation training for joint disease

(Continues)

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TABLE 1 (Continued)

References (*n*)	Author	Year	Study/Article type	Physiotherapy intervention/ role described
60	Al-Sharif FA et al.	2014	Randomized-controlled trial	Aerobic walking exercise training
62	Cuesta-Barriuso R et al.	2014	Randomized-controlled trial	Physiotherapy interventions for ankle arthropathy
63	Boccalandro E et al.	2014	Clinical trial	Tailored physical or rehabilitation programme.
78	Stemberger M et al.	2014	Case report	Climbing programme
76	McGee S et al.	2015	Retrospective single-centre cohort study	Organized sport programmes
37	Lobet S et al.	2016	Review	Exercise therapy and nutrition in chronic musculoskeletal diseases
40	Schäfer GS et al.	2016	Systematic review	Physical activity for musculoskeletal improvement
44	Strike K et al.	2016	Review	Physical exercises programmes
48	Salim M et al.	2016	Clinical trial	Nordic walking programme
77	Runkel B et al.	2016	Randomized controlled trial	Physical fitness training
39	De Kleijn P et al.	2017	Guidelines	Physiotherapy management
80	Howell C et al	2017	Review	Organized sport activities
38	Stephensen D et al.	2018	Narrative review	Advances in musculoskeletal physiotherapy
45	Boccalandro E et al.	2018	Single-centre study	Multidisciplinary team activity
46	Hilberg T	2018	Review	Sport activity programmes
64	Mateo F et al.	2018	Pilot study	Sport activity programmes
81	Farrugia A et al.	2018	Review	Benefits of sport activities
58	Passeri EV et al.	2019	Non-randomized trial	Water rehabilitation after orthopedic surgery
61	Neelapala YVR et al.	2019	Systematic review	Hydrotherapy for rehabilitation
66	Boccalandro E et al.	2019	Review	Telemedicine and tele-rehabilitation
82	Wagner B et al.	2019	Clinical trial	Online physical exercise programmes
1	Srivastava A et al.	2020	Guidelines	Physiotherapy management
15	Wells AJ & Stephensen D	2020	Review	Multidisciplinary team activity
36	Lobet S et al.	2020	Editorial	Multidisciplinary team activity
53	Wagner B et al.	2020	Systematic review	Resistance exercises on strength
68	O'Donovan M et al.	2020	Review	Telemedicine
41	Lobet S et al.	2021	Review	Counselling and physically coaching
65	Tat NM et al.	2021	Randomized pilot study	Manual therapy activities
67	Boccalandro E et al.	2021	Letter to editor	Intelligent game engines for home exercises
84	Mulder K et al.	2021	Guidelines	Role of physiotherapist in the multidisciplinary team

The specific role of the physiotherapist as a healthcare professional is evaluated in five articles.[15,36,37,41,50] Initially, the physiotherapist was seen as a specialist who comes into action only in the post-trauma or post-surgery recovery phase, but since the 2000s this professional acquired a much wider role and responsibilities.[23] From the beginning of the 2000s until now this role, in synergy with such other specialists of the multidisciplinary team as orthopaedists and haematologists, has been to support and encourage physical activity, to perform rehabilitation interventions aimed at maximizing the physical potential and abilities of the individual, as well as to evaluate and intervene on dysfunctions not strictly related to the acute bleeding episode.[15,36] Therefore, the physiotherapy intervention has progressively developed a proactive goal, aimed at optimizing biomechanics, preventing bleeding, and facilitating physical activity.

The importance of physiotherapy for the primary prevention of joint damage in PWH was first emphasised by Lobet et al.[37] and subsequently reiterated by Stephensen et al.[38] Furthermore, the role of preventive physiotherapy acquired a prominent position within the most recent third edition of the World Federation of Haemophilia Guidelines.[1] De Kleijn et al.[37] published in 2017 an essay on the physiotherapy management of PWH. In it, a first part dealt with the importance of the multidisciplinary management and the role of the

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physiotherapist within the comprehensive care team. A second part dealt with the musculoskeletal consequences of haemophilia, with a discussion on the options for management of an acute bleeding episode, treatment of chronic sequels, outcome of orthopaedic surgery, pain control, sport activities and physiotherapy in developing countries. The last part of the text described and evaluated the scores to be used by physiotherapists for the functional analysis of patients. More recently, Lobet et al.[41] addressed the role of physiotherapy in the treatment of PWH and pointed out that, despite recent and dramatic pharmacological advances and related great clinical benefits, physiotherapy is still insufficiently included and implemented in the frame of the comprehensive management of haemophilia.

The type and duration of physiotherapy are among the topics most widely discussed in selected articles. In 2006 Mulder[71] first published a programme tailored for PWH, thus marking a turning point in their management. The guide is targeted at all physiotherapists, especially those with little experience in treating people with bleeding disorders, to other health professionals who act when no physiotherapist is available, as well as to PWH and their families. Blamey et al.[42] did precisely describe the basic elements for creating for PWH an effective exercise programme, emphasizing that this first requires a deep understanding of the objectives to be achieved with the chosen exercises.

In 2011, Souza et al.[43] published a systematic review on physical activity for PWH. The authors highlighted that the PWH from an early age often chooses to limit the performance of any physical activity. Developing a specific exercise programme that can be easily and consistently done is therefore of pristine importance. In 2018, Boccalandro et al.[45] published the results of a study on the effectiveness of a multidisciplinary physical activity programme tailored for older PWH born before 1975, that is, at time when replacement therapy was still in its infancy and arthropathy was inevitable.

Very important is also resistance training. Engelbert et al.[49] showed that a lower aerobic capacity in children with haemophilia than in healthy controls is associated with lower levels of performed physical activity. Furthermore, a systematic review published in 2020[53] investigated the effects of resistance training in PWH and demonstrated that this is a safe approach when appropriately monitored, tailored, and performed under adequate anti-haemorrhagic cover.

Until recently all physiotherapy activities took place in presence in the frame of professionals' offices but nowadays, they can also be carried out online at distance. This new frontier was described for the first time in 2018 by Mateo et al.[64] and subsequently by Boccalandro et al.[66] Furthermore, tele-rehabilitation was a fundamental tool to ensure to PWH continuity in their therapeutic path during the Covid-19 pandemic, as emphasized by O'Donovan et al.[68]

3.2 | Sport activities

We identified 16 articles dealing with the performance of sports by PWH supervised by a physiotherapist.[67–82] In 1996, Buzzard[69] published for the first time a review dealing with sport in PWH. The review highlighted the need for PWH to start physical activity as soon as possible, encouraging them to continue it regularly. This strategy was at variance with that previously prevailing, that is, to limit motion as much as possible in PWH to reduce the bleeding risk. Among the sports identified as suitable for PWH were swimming, golf, table tennis, walking and fishing, whereas contact sports such as soccer, rugby, karate, wrestling, or skateboard were not recommended or discouraged.[69] A complete musculoskeletal evaluation is required for all PWH before starting any sport, according to Mulder et al.[70] In 2009, Ross et al.[72] published the results of a study in adolescent PWH and showed that the risk of trauma or bleeding complications did not increase among participants who performed high or low impact physical activities while on prophylaxis.

The classification of sports more suitable for PWH according to the American Paediatric Society was reported by Gomis et al.[47] Sports were divided into three groups based on the patient risk: high, medium, or low. The authors also highlighted that in more recent years this subdivision is being less and less used, being replaced by a more individualized choice according to individual patient characteristics.

An inactive lifestyle affects both the health and physical performance of the general population, as well as those of PWH. In them, Khair et al.[73] reported that sport practice followed by an improvement in the health-related quality of life, with no an increased risk of bleeding nor development of target joints.

Physiotherapy programmes carried out in water have long been employed, as reported by von Mackensen et al.,[57] Passeri et al.[58] and Mazloum et al.[59] It appears that hydrotherapy helps PWH to improve resistance, physical strength and more generally the quality of life.[57–59] Physiotherapy in water has always been a rehabilitation cornerstone, as witnessed by the fact and deed that when PWH were advised to start a sport the first recommended choice was swimming, a sport considered to have a low bleeding risk.[49,67] But among the water sports there is not only swimming. In 2012, Schved et al.[74] showed that PWH performed a scuba-diving programme without complications or adverse events.

Indoor or outdoor gym and fitness are among the sports that can be easily practiced by everyone. Several studies[45,75–77] have shown that if these sport activities are practiced by PWH under the supervision of an experienced physiotherapist, the rate of bleeding does not increase. Nordic walking is becoming an increasingly popular outdoor activity classified midway between rehabilitative physiotherapy and sport. In 2016, a pilot study[48] investigated the effects of a Nordic Walking programme lasting 3 months in PWH older than 40 years. All participants reported significant improvements in their physical abilities, with no increase in the number of bleeds or drug consumption.

Over time, many other sports are being practiced by PWH under the supervision of a physiotherapist, and in 2014 it was the turn of such a demanding sport as climbing.[78] Even though all the cited studies refer to amateur activities, Gonzalez-Porras et al.[79] did report the case of a severe haemophilia A patient who became a professional cyclist, thanks to the activity of a multidisciplinary team that constantly followed him during his professional sporting career. Like him, other top athletes with haemophilia have shown that by following specific programmes it is possible to practice sports at a high level without an increasing

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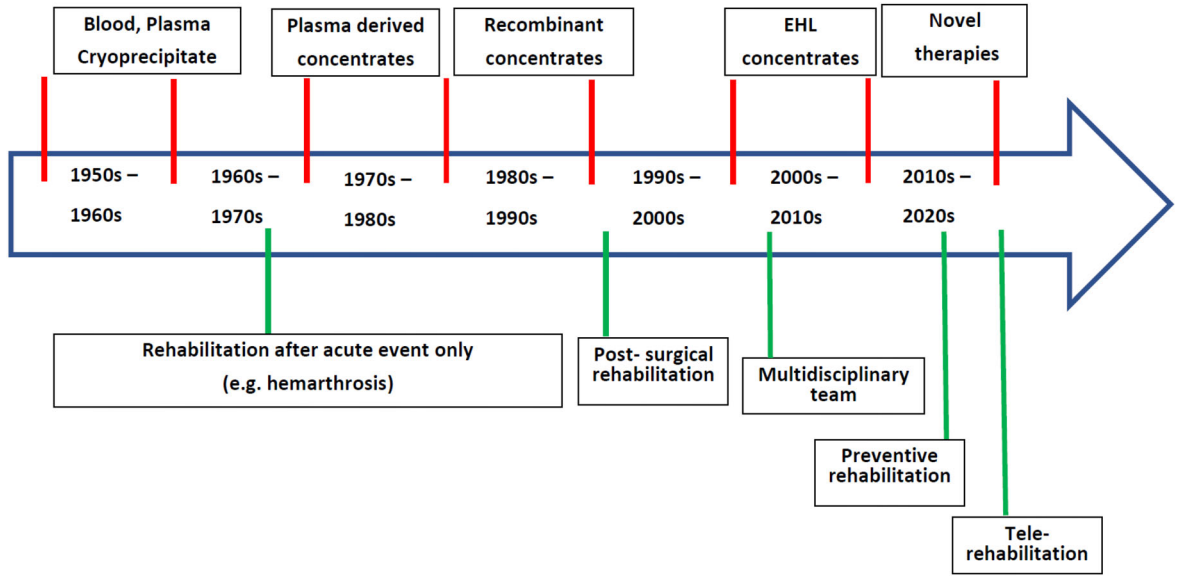


FIGURE 2 The timeline of the physiotherapy evolution in parallel with the evolution of haemophilia treatments

risk, thus encouraging to practice sports also the PWH who are not professional athletes. Other studies and reviews have emphasized and summarized the multiple benefits that sport can bring to PWH if practiced with appropriate recommendations and programmes.[80–82] The timeline of physiotherapy evolution compared to the evolution of the haemophilia treatments is represented in Figure 2.

4 | DISCUSSION

4.1 | Conclusive remarks

This scoping review on haemophilia and physiotherapy and has allowed us to underline how the role of the physiotherapist changed over the years. Until the 1970s, children and adult PWH hardly had any opportunity for treatment and were thus discouraged from all forms of physical activity for the fear of bleeding. With the introduction first in the 1970s of efficacious therapies with plasma-derived coagulation factors, more emphasis started to be placed on rehabilitation and exercise. Thus, in the years between 1970 and 1990, there was a shift in focus towards the use of rehabilitation not only following a bleeding episode and surgical intervention.[17–26] The possibility for PWH to undergo prophylaxis with factor replacement while on physiotherapy was a significant step forward, but the 1980s marked a period of discouragement due to the development of drug-related infectious diseases such as HIV and hepatitis.[83] Many PWH became ill, and many of them abandoned replacement therapy and thus the possibility of reducing haemorrhagic episodes and their consequences. Fortunately, these years were overcome thanks to the development of viral inactivation methods and recombinant factors. Accordingly, PWH began to be treated more safely and were thus encouraged to resume physiotherapy, sports and physical activity. The concept of preventive physiotherapy emerged for the first time and was seen as fundamental to avoid or reduce the onset of bleeding and maintain joint and muscle function if are practised. Admittedly, this favourable scenario was and still is far from being implemented in many middle- and low-income countries, in which poor access to therapies goes in parallel with a very limited role for physiotherapy.

During the first two decades of the 2000s, the drugs available for treatment of underwent further improvements, so that a more comprehensive and multidisciplinary management of PWH involved the orthopaedist, physiotherapist, and haematologist together.[27–66] The importance that the physiotherapist has acquired in the comprehensive management of the PWH within the multidisciplinary team has been more and more recognized, so that nowadays this professional is playing a pivotal role in the management of haemophilia.[15,23]

The improvement of therapies and the multidisciplinary management of PWH have also favoured an increase in prosthetic surgery, in turn leading to a greater need for post-operative rehabilitation targeted and tailored to the individual patient, together with the newly added concept of pre-rehabilitation that, mentioned for the first time by Stephensen,[29] contemplates physiotherapy interventions applied to PWH before surgery.

Physical exercise and sports have been more and more frequently shown to be a safe and necessary approach to improve overall health in PWH, prevent bleeding, and improve the perceived quality of life. Several studies highlighted the physical and psychological benefits of exercise and sport and demonstrated their protective effect against disease manifestations. Exercise guidelines have also been proposed aimed at both patients and professionals. One of the most important of them, being the first of its kind, is the Mulder's exercise protocol.[71]

More recently, specific physiotherapy interventions, from strength and endurance training to hydrotherapy[56–59] and telerehabilitation,[66–68] were introduced, ultimately demonstrating that exercise and sport offer many benefits to the individual, in

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biomechanical and psychological terms but also with a positive impact on quality of life.

The practice of sport is nowadays much more accessible than in the past but requires an accurate and individual prescription based upon a complete evaluation of each PWH, and a supervision carried out not only by the haematologist but also by the physiotherapist. These and other professionals in the team work together with the goal to obtain more and more information on the clinical picture from their different points of view, and thus to guarantee to patients the best possible care and quality of life. This new role of the physiotherapist has been extensively developed in the recently published Canadian guidelines,[84] which emphasize how the figure of this specialist is involved in all the aspects of the PWH management, from the evaluation and treatment of acute and chronic events toward health promotion, education, and multidisciplinary collaboration.

Sport has always been a debated topic. Early articles did highlight its importance, but also emphasized difficult implementation in PWH, because many physicians avoided to prescribe sports and patients themselves were afraid. In the articles reviewed up to 2009, sports were divided into three categories according to the risk of bleeding.[47] Today, this distinction is no longer used in favour of a more individualised choice, after several studies have shown that sports, when carried out, tailored, and supervised according to the individual's ability, manage to improve movement and physical performances without increasing the bleeding incidence and trauma in comparison to the sedentary haemophilia patient. Even niche and demanding sports such as scuba diving, climbing, and mountain biking are currently mentioned among those practised with positive outcomes.[48,74,78,79] Therefore, sport is not only possible but essential, thus creating a direct link with physiotherapy. Physiotherapists have the primary task of assessing the patient and directing him to the sport most suited for him and for his needs. They also prepare and assist him in practising sport with a tailored programme and through continuous education and supervision.

Today, the many new therapies for the treatment of haemophilia guarantee greater efficacy of anti-haemorrhagic coverage together with a reduced need for intravenous infusions/subcutaneous injections. The PWH, thanks to the combined efficacy, safety, and practicality of these treatments, feels more and more like a person without bleeding problems and truly behaves as such. This new normality, which gives to the patient the opportunity to practice even demanding physical and sport activities, has also inevitably led to the emergence of pre-existing dysfunctional problems, kept hidden by previous inactivity. By dysfunctional problems we mean the motion alternatives that the musculoskeletal system uses to maintain its function. When this reversible situation is prolonged over time, the original function is substituted by a dysfunction that will primarily affect other joints and that over time will irreversibly compromise motion, thus initiating a full-blown pathology. Only a preventive physiotherapy intervention, established before the dysfunctional damage becomes irreversible, is likely to allow the maintenance of the original functionality of the musculoskeletal system. A complete functional analysis of the musculoskeletal system is required before any rehabilitation intervention, because nowadays evaluation scores used in the musculoskeletal field, such as the Haemophilia Joint Health Score (HJHS) 2.1,[85] are no longer able to identify the dysfunctions highlighted by the new dynamics of the patient, nor to explain them. Through an accurate functional analysis, the reversible biomechanical compensations that the patient puts in place to compensate for the compromised functional motion must therefore be identified. The physiotherapist should intervene in this new context and follow the patient step by step, teaching him how to move safely and how to best use his musculoskeletal system.

4.2 | Future developments

Recently the "European Haemophilia Consortium and EAHAD Physiotherapy Committee[86]" published eight principles that outline the standards that the physiotherapists dealing with haemophilia should follow. These professionals will need to collaborate with other specialists in the management of PWH, who in turn must have easy and consistent access to rehabilitation treatments.

The innovative therapies that became available in the last 10–20 years are a definite benefit for PWH, through the attainment and maintenance of consistent levels of haemostatic competence and the avoidance of the peaks and troughs that characterized the traditional therapeutic approaches. This situation is a bonus also for the physiotherapist, who can handle these patients with much more confidence. The efficacy of these therapies makes patients much more independent from the specialist in the treatment centre. Thus, we envisage the increasing development of telemedicine approaches, designed to allow home rehabilitation and exercising but also allowing a supervision at distance by the physiotherapist.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

This is a scoping review, all data here described are present in published reports and are available at: https://pubmed.ncbi.nlm.nih.gov/, https://pedro.org.au/, or upon request.

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REFERENCES

1. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020;26:1-158.
2. den Uijl IEM, Mauser Bunschoten EP, Roosendaal G, et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? *Haemophilia*. 2011;17(6):849-853.
3. Di Minno MD, Ambrosino P, Franchini M, et al. Arthropathy in patients with moderate hemophilia A: a systematic review of the literature. *Semin Thromb Hemost*. 2013;39(7):723-731.
4. Valentino LA, Hakobyan N, Enockson C, et al. Exploring the biological basis of haemophilic joint disease: experimental studies. *Haemophilia*. 2012;18(3):310-318.
5. Manco-Johnson M, Nuss R, Geraghty S, et al. Results of secondary prophylaxis in children with severe hemophilia. *Am J Hematol*. 1994;47(2):113-117.
6. Lobet S, Hermans C, Lambert C. Optimal management of hemophilic arthropathy and hematomas. *J Blood Med*. 2014;5:207-218.
7. van Vulpen LFD, Holstein K, Martinoli C. Joint disease in haemophilia: pathophysiology, pain and imaging. *Haemophilia*. 2018;24(6):44-49.
8. Blobel C, Haxaire C, Kalliolias G, et al. Blood induced arthropathy in hemophilia: mechanisms and heterogeneity. *Semin Thromb Hemost*. 2015;41(8):832-837.
9. Roosendaal G, Vianen M, Wenting M, et al. Iron deposits and catabolic properties of synovial tissue from patients with haemophilia. *J Bone Joint Surg Br*. 1998;80(3):540-553.
10. Mantovani A, Biswas SK, Galdiero MR, et al. Macrophage plasticity and polarization in tissue repair and remodeling. *J Pathol*. 2013;229(2):176-185.
11. Rodriguez-Merchan EC. Management of musculoskeletal complications in patients with hemophilia: literature review and expert recommendations. *Cardiovasc Hematol Disord Drug Targets*. 2021;21(3):162-166.
12. Rodriguez-Merchan EC. Complications of muscle hematomas in hemophilia. *Cardiovasc Hematol Disord Drug Targets*. 2020;20(4):242-248.
13. Mannucci P. Hemophilia therapy: the future has begun. *Haematologica*. 2020;105(3):545-553.
14. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*. 2016;388(10040):187-197.
15. Wells AJ, Stephensen D. The role of the physiotherapist in the management of people with haemophilia: defining the new normal. *Br J Hosp Med (Lond)*. 2020;81(8):1-8.
16. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467-473.
17. Neumark E. Rehabilitation in hemophilia. *Bibl Haematol*. 1966;26:202-203.
18. Polli E, Morosini C, Cortellaro M, Praga C. Trattamento e riabilitazione globale degli emofilici. *Atti del Convegno su problemi clinici e sociali della Emofilia*. 1970.
19. McCollough NC. Comprehensive management of musculoskeletal disorders in hemophilia. *National Academy of Sciences*. 1973. editor.
20. Panicucci F, Il trattamento globale dell'emofilico. 1974
21. Boone DC, Comprehensive management of hemophilia. F A Davis Co; 1976
22. Pelletier JR, Findley TW, Gemma SA. Isometric exercise for an individual with hemophilic arthropathy. *Phys Ther*. 1987;67(9):1359-1364.
23. Heijnen L. Rehabilitation and the role of the physical therapist. *Southeast Asian J Trop Med Public Health*. 1993;24(1):26-29.
24. Buzzard BM. Physiotherapy for the prevention of articular contraction in haemophilia. *Haemophilia*. 1999;5(1):10-15.
25. Ribbans WJ, Giangrande P, Beeton K. Conservative treatment of hemarthrosis for prevention of hemophilic synovitis. *Clin Orthop Relat Res*. 1997:12-18.
26. Battistella LR. Rehabilitation in haemophilia - Options in the developing world. *Haemophilia*. 1998;4(4):486-490.
27. Buzzard BM, Beeton K. *Physiotherapy management of haemophilia*. Blackwell Science; 2000.
28. Santavirta N, Solovieva S, Helkama O, et al. Musculoskeletal pain and functional ability in haemophilia A and B. Physiotherapy and rehabilitation in haemophilia patients. *Rheumatol Int*. 2001;21(1):15-19.
29. Stephensen D. Rehabilitation of patients with haemophilia after orthopaedic surgery: a case study. *Haemophilia*. 2005;11(S1):26-29.
30. Heijnen L. The role of rehabilitation and sports in haemophilia patients with inhibitors. *Haemophilia*. 2008;14(S6):45-51.
31. Forsyth A, Zourikian N. How we treat: considerations for physiotherapy in the patient with haemophilia and inhibitors undergoing elective orthopaedic surgery. *Haemophilia*. 2012;18(4):550-553.
32. Al D'young. Conservative physiotherapeutic management of chronic haematoma and haemophilic pseudotumours: case study and comparison to historical management. *Haemophilia*. 2009;15(1):253-260.
33. Khawaji M, Astermark J, Åkesson K, Berntorp E. Physical activity and joint function in adults with severe haemophilia on long-term prophylaxis. *Blood Coagul Fibrinolysis*. 2011;22(1):50-55.
34. Broderick CR, Herbert RD, Latimer J, et al. Association between physical activity and risk of bleeding in children with hemophilia. *JAMA*. 2012;308(14):1452-1459.
35. Negrier C, Seuser A, Forsyth A, et al. The benefits of exercise for patients with haemophilia and recommendations for safe and effective physical activity. *Haemophilia*. 2013;19(4):487-498.
36. Lobet S, Hermans C, Stephensen D. The emerging clinical and scientific role of the physiotherapist in haemophilia care. *Haemophilia*. 2020;26(4):560-562.
37. Lobet S, Lambert C, Hermans C. Stop only advising physical activity in adults with haemophilia…prescribe it now! The role of exercise therapy and nutrition in chronic musculoskeletal diseases. *Haemophilia*. 2016;22(5):e462-4.
38. Stephensen D, Bladen M, McLaughlin P. Recent advances in musculoskeletal physiotherapy for haemophilia. *Ther Adv Hematol*. 2018;9(8):227-237.
39. De Kleijn P, Mauser-Bunschoten EP, Physiotherapy management in haemophilia. Background and practical guidelines, 2017
40. Schäfer GS, Valderramas S, Gomes AR, et al. Physical exercise, pain and musculoskeletal function in patients with haemophilia: a systematic review. *Haemophilia*. 2016;22(3):e119-29.
41. Lobet S, Timmer M, Königs C, et al. The role of physiotherapy in the new treatment landscape for haemophilia. *J Clin Med*. 2021;10(13):2822.
42. Blamey G, Forsyth A, Zourikian N, et al. Comprehensive elements of a physiotherapy exercise programme in haemophilia - a global perspective. *Haemophilia*. 2010;16(S5):136-145.
43. Souza JC, Simoes HG, Campbell CSG, et al. Haemophilia and exercise. *Int J Sports Med*. 2012;33(2):83-88.
44. Strike K, Mulder K, Michael R. Exercise for haemophilia. *Cochrane Database Syst Rev*. 2016;2016(12):CD011180.
45. Boccalandro E, Mancuso ME, Riva S, et al. Ageing successfully with haemophilia: a multidisciplinary programme. *Haemophilia*. 2018;24(1):57-62.

13652516, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.14661 by CochraneItalia, Wiley Online Library on [18/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

46. Hilberg T. Programmed Sports Therapy (PST) in People with Haemophilia (PwH) "sports therapy model for rare diseases. *Orphanet J Rare Dis*. 2018;13(1):1-9.
47. Gomis M, Querol F, Gallach JE, et al. Exercise and sport in the treatment of haemophilic patients: a systematic review. *Haemophilia*. 2009;15(1):43-54.
48. Salim M, Brodin E, Spaals-Abrahamsson Y, et al. The effect of Nordic Walking on joint status, quality of life, physical ability, exercise capacity and pain in adult persons with haemophilia. *Blood Coagul Fibrinolysis*. 2016;27(4):467-472.
49. Engelbert RHH, Plantinga M, Van der Net J, et al. Aerobic capacity in children with hemophilia. *J Pediatr*. 2008;152(6):833-838.
50. Wittmeier K, Mulder K. Enhancing lifestyle for individuals with haemophilia through physical activity and exercise: the role of physiotherapy. *Haemophilia*. 2007;13(2):31-37.
51. Tiktinsky R, Falk B, Heim M, Martinovitz U. The effect of resistance training on the frequency of bleeding in haemophilia patients: a pilot study. *Haemophilia*. 2002;8(1):22-27.
52. Eid MA, Ibrahim MM, Aly SM. Effect of resistance and aerobic exercises on bone mineral density, muscle strength and functional ability in children with hemophilia. *Egypt J Med Hum Genet*. 2014;15(2):139-147.
53. Wagner B, Krüger S, Hilberg T, et al. The effect of resistance exercise on strength and safety outcome for people with haemophilia: a systematic review. *Haemophilia*. 2020;26(2):200-215.
54. Buzzard BM. Proprioceptive training in haemophilia. *Haemophilia*. 1998;4(4):528-531.
55. Hill K, Fearn M, Williams S, et al. Effectiveness of a balance training home exercise programme for adults with haemophilia: a pilot study. *Haemophilia*. 2010;16(1):162-169.
56. Vallejo L, Pardo A, Gomis M, et al. Influence of aquatic training on the motor performance of patients with haemophilic arthropathy. *Haemophilia*. 2010;16(1):155-161.
57. Von Mackensen S, Eifrig B, Zäch D, et al. The impact of a specific aqua-training for adult haemophilic patients - results of the WATERCISE study (WAT-QoL). *Haemophilia*. 2012;18(5):714-721.
58. Passeri EV, Martinelli M, Gatteri V, et al. Standard and water rehabilitation: an analysis of over 14 years' experience in patients with haemophilia or other clotting factor disorders after orthopaedic surgery. *Haemophilia*. 2019;25(4):699-707.
59. Mazloum V, Rahnama N, Khayambashi K. Effects of therapeutic exercise and hydrotherapy on pain severity and knee range of motion in patients with hemophilia: a randomized controlled trial. *Int J Prev Med*. 2014;5(1):83-88.
60. Al-Sharif FA, Al-Jiffri OH, El-Kader SMA, Ashmawy EM. Impact of mild versus moderate intensity aerobic walking exercise training on markers of bone metabolism and hand grip strength in moderate hemophilic A patients. *Afr Health Sci*. 2014;14(1):11-16.
61. Neelapala YVR, Attal R, Tandale S. Aquatic exercise for persons with haemophilia: a review of literature. *Complement Ther Clin Pract*. 2019;34:195-200.
62. Cuesta-Barriuso R, Gómez-Conesa A, López-Pina JA. Manual therapy in the treatment of ankle hemophilic arthropathy. A randomized pilot study. *Physiother Theory Pract*. 2014;30(8):534-539.
63. Boccalandro E, Pasta G, Mannucci PM, et al. Integrated postural analysis in children with haemophilia. *Haemophilia*. 2014;20(2):263-267.
64. Mateo F, Soria-Olivas E, Carrasco JJ, et al. HemoKinect: a microsoft kinect V2 based exergaming software to supervise physical exercise of patients with hemophilia. *Sensors (Basel)*. 2018;18(8):2439.
65. Tat NM, Can F, Sasmaz HI, Tat AM, Antmen AB. The effects of manual therapy on musculoskeletal system, functional level, joint health and kinesiophobia in young adults with severe haemophilia: a randomized pilot study. *Haemophilia*. 2021;27(2):e230-e238.
66. Boccalandro EA, Dallari G, Mannucci PM. Telemedicine and telerehabilitation: current and forthcoming applications in haemophilia. *Blood Transfus*. 2019;17(5):385-390.
67. Boccalandro EA, Begnozzi V, Mannucci PM. Intelligent game engines for home exercises (exergames) in boys with haemophilia. *Haemophilia*. 2021;27(1):e151-4.
68. O'Donovan M, Buckley C, Benson J, et al. Telehealth for delivery of haemophilia comprehensive care during the COVID-19 pandemic. *Haemophilia*. 2020;26(6):984-990.
69. Buzzard BM. Sports and hemophilia: antagonist or protagonist. *Clin Orthop Relat Res*. 1996:25-30.
70. Mulder K, Cassis F, Seuser DRA, et al. Risks and benefits of sports and fitness activities for people with haemophilia. *Haemophilia*. 2004;10(4):161-163.
71. Mulder K. *Exercises for people with Hemophilia. World Federation of Hemophilia*. 2006.
72. Ross C, Goldenberg NA, Hund D, MJ Manco-Johnson. Athletic participation in severe hemophilia: bleeding and joint outcomes in children on prophylaxis. *Pediatrics*. 2009;124(5):1267-1272.
73. Khair K, Littley A, Will A, von Mackensen S. The impact of sport on children with haemophilia. *Haemophilia*. 2012;18(6):898-905.
74. Schved JF, De Haro M, Drapeau M, Schved M. Scuba diving is possible and safe for patients with haemophilia. *Haemophilia*. 2012;18(1):75-79.
75. Czepa D, Von Mackensen S, Hilberg T. Haemophilia & Exercise Project (HEP): subjective and objective physical performance in adult haemophilia patients - results of a cross-sectional study. *Haemophilia*. 2012;18(1):80-85.
76. Mcgee S, Raffini L, Witmer C. Organized sports participation, and the association with injury in paediatric patients with haemophilia. *Haemophilia*. 2015;21(4):538-542.
77. Runkel B, Czepa D, Hilberg T. RCT of a 6-month programmed sports therapy (PST) in patients with haemophilia – improvement of physical fitness. *Haemophilia*. 2016;22(5):765-771.
78. Stemberger M, Schmit E, Czepa D, et al. Climbing therapy under PK-tailored prophylaxis. *Hamostaseologie*. 2014;34:S13-8.
79. Gonzalez-Porras JR, Lopez-Cadenas F, Alberca I, Bastida JM. Top-level sport in athletes with severe haemophilia A. *Haemophilia*. 2017;23(4):e391-3.
80. Howell C, Scott K, Patel DR. Sports participation recommendations for patients with bleeding disorders. *Transl Pediatr*. 2017;6(3):174-180.
81. Farrugia A, Gringeri A, von Mackensen S. The multiple benefits of sport in haemophilia. *Haemophilia*. 2018;24(3):341-343.
82. Wagner B, Seuser A, Krüger S, et al. Establishing an online physical exercise program for people with hemophilia. *Wien Klin Wochenschr*. 2019;131(21-22):558-566.
83. Lee CA. Transfusion-transmitted disease. *Baillieres Clin Haematol*. 1996;9(2):369-394.
84. Mulder K, McCabe E, Strike K, Nilson J. Developing clinical practice guidelines for physiotherapists working with people with inherited bleeding disorders. *Haemophilia*. 2021;27(4):674-682.
85. Ribeiro T, Abad A, Feldman BM. Developing a new scoring scheme for the Hemophilia Joint Health Score 2.1. *Res Pract Thromb Haemost*. 2019;3(3):405-411.
86. de Klejin P, Duport G, Jansone K, et al. the European Haemophilia Consortium and EAHAD Physiotherapy Committee. European principles of care for physiotherapy provision for persons with inherited bleeding disorders: perspectives of physiotherapists and patients. *Haemophilia*. 2022;28(4):649-655.

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