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REVIEW ARTICLE

Hemophilia A in children: prophylaxis, physical activity and rehabilitation in the prevention of hemophilic arthropathy

a literature review

HIGHLIGHTS

- Hemophilia A is an X-linked deficiency of factor VIII whose main long-term complication in children is hemophilic arthropathy caused by recurrent intra-articular bleeding.
- Early replacement therapy with factor VIII concentrates, non-factor therapies such as emicizumab and emerging gene-therapy options markedly reduce the frequency of joint bleeds.
- Regular low-impact physical activity (swimming, cycling, walking) builds dynamic joint stabilization through muscle strengthening, core stability and proprioception training.
- Progressive resistance training and balance/biofeedback rehabilitation are safe in children on prophylaxis and improve HJHS scores and lower-limb muscle torque.
- Objective monitoring with HJHS 2.1, 6MWT, TUG, goniometry, pedobarography and digital dynamometry allows early detection of subclinical joint changes and individualisation of care.

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ABSTRACT

BACKGROUND: Hemophilia A is a rare X-linked genetic disorder characterised by deficiency of coagulation factor VIII. In children, the dominant clinical problem is recurrent joint bleeding (hemarthrosis), which drives chronic synovitis and progressive hemophilic arthropathy — the leading cause of long-term disability in this population.

AIM: To summarise the role of contemporary bleeding prophylaxis, systematic physical activity and physiotherapy in preventing musculoskeletal complications in children with hemophilia A.

MATERIALS AND METHODS: A narrative review of current literature and guidelines on factor VIII replacement, non-factor therapy (emicizumab) and emerging gene therapy was performed, together with an appraisal of functional diagnostic tools — the Hemophilia Joint Health Score (HJHS 2.1), 6-minute walk test (6MWT), Timed Up and Go (TUG), goniometry and modern objective methods of muscle strength and postural assessment.

RESULTS: Early bleeding prophylaxis substantially reduces the number of joint bleeds. Low-impact physical activity (swimming, cycling) builds dynamic joint stabilization by strengthening the muscular corset and improving proprioception. Contemporary physiotherapy based on progressive resistance training and biofeedback is safe and essential for preserving musculoskeletal function, while objective diagnostics enable early detection of subclinical joint changes.

CONCLUSIONS: Effective prevention of hemophilic arthropathy in children requires an integrated interdisciplinary approach. Combining modern pharmacological treatment with regular physical activity and functional rehabilitation allows pediatric patients to achieve functional capacity comparable to their peers and minimises the risk of permanent disability.

KEYWORDS hemophilia A; hemophilic arthropathy; bleeding prophylaxis; pediatric physiotherapy; physical activity; HJHS scale.

GRAPHICAL ABSTRACT

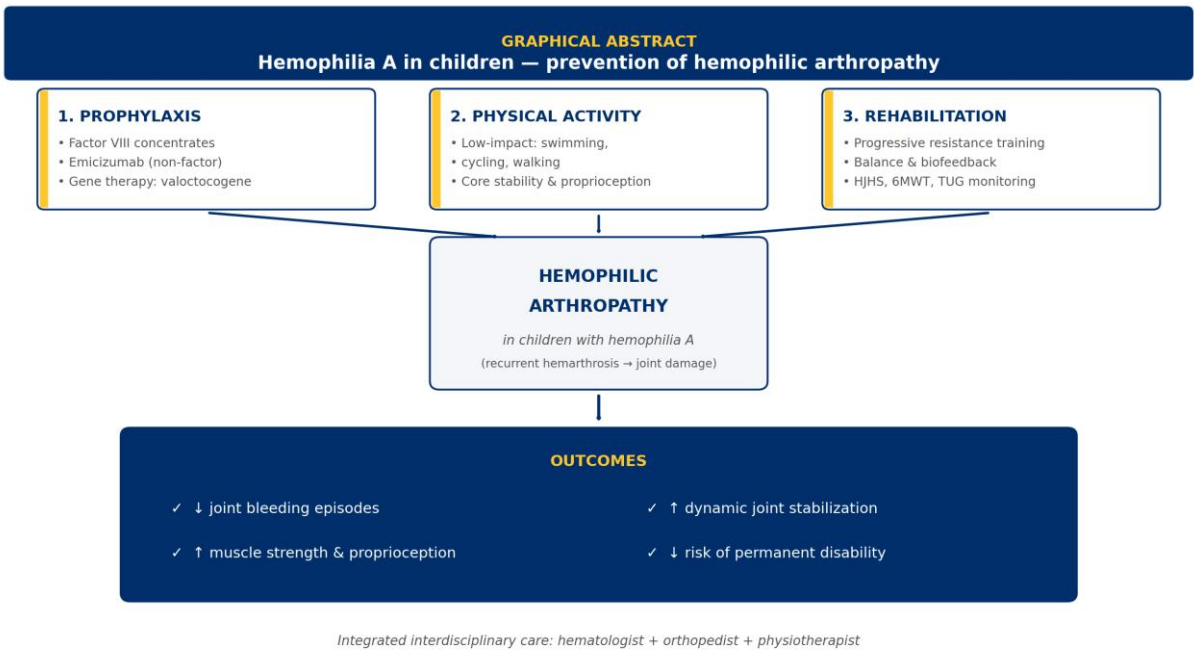

Figure 1. *Graphical abstract — integrated prevention of hemophilic arthropathy in children: bleeding prophylaxis, low-impact physical activity and targeted rehabilitation.*

1. INTRODUCTION

Hemophilia is a rare, genetically determined disorder of blood coagulation resulting from mutations in genes encoding clotting factors. It primarily affects males, as it is inherited in a sex-linked recessive manner on the X chromosome; the disease may also be secondary to spontaneous mutations, although this is relatively uncommon.

The introduction of replacement therapy with factor VIII concentrates and prophylactic administration of clotting factors has significantly altered the natural course of the disease, enabling a reduction in bleeding episodes and improvement in patients' quality of life [1]. In recent years, new therapeutic strategies have emerged, including non-factor therapies that further increase the effectiveness of bleeding prophylaxis [4]. A characteristic clinical feature of hemophilia is recurrent bleeding into muscles and joints — particularly the knees, elbows and ankles. Repeated intra-articular bleeding leads to chronic synovitis, damage to articular cartilage and progressive hemophilic arthropathy, one of the main causes of disability in this patient group [1,3].

In children, early initiation of prophylaxis and appropriately conducted rehabilitation and physical activity are of particular importance, as they can significantly limit the development of musculoskeletal complications. The aim of this study is to present the importance of bleeding prophylaxis, physical activity and rehabilitation in preventing musculoskeletal complications in children with hemophilia.

2. EPIDEMIOLOGY AND PATHOMECHANISM OF HEMOPHILIA

Hemophilia describes a group of genetic disorders that lead to dysfunction of proteins involved in the clotting cascade. Three distinct forms of congenital hemophilia exist (hemophilia A, hemophilia B and hemophilia C); the most common are hemophilia A (HA) and hemophilia B (HB). The genes for both factor VIII and factor IX are located on the long arm of the X chromosome. Hemophilia A is caused by mutations in the F8 gene (encoding coagulation factor VIII), whereas hemophilia B results from mutations in the F9 gene (encoding coagulation factor IX). The most common form is hemophilia A, with an estimated incidence of approximately 1 case per 5,000 male births worldwide [1,2]. Hemophilia B is caused by deficiency of factor IX; according to the 2024 WFH report, it affects approximately 45,600 patients worldwide and is 6–7 times less common than hemophilia A [1,2].

The severity of clinical manifestations depends on the residual activity of FVIII or FIX in plasma and is classified as severe (<1%), moderate (1–5%) or mild (>5–<50%) [2]. Depending on the type of mutation, there may be a complete absence of the protein or its significant deficiency. The most severe form of hemophilia A is most commonly associated with null mutations such as intron 22 inversion, multi-exon deletions or nonsense mutations, which result in a complete lack of functional factor VIII [5]. Factor VIII plays a key role in the coagulation cascade as a cofactor in the intrinsic tenase complex (FIXa + FVIIIa + calcium ions + phospholipids), participating in activation of factor X and thrombin generation. In hemophilia B, point mutations in the F9 gene predominate, with deletions, polymorphisms, duplications and insertions occurring less frequently, mainly in exons 2 and 8. Factor IX is produced in the liver as a precursor of a vitamin K–dependent serine protease. Activation of FIX occurs via the intrinsic pathway in the presence of calcium ions or via the extrinsic pathway through factor VIIa, calcium ions and lipoproteins. Deficiency of either factor results in impaired clot formation and an increased bleeding tendency [3,4,6].

Diagnosis of hemophilia is suspected in patients with a prolonged activated partial thromboplastin time (aPTT) that corrects upon 1:1 mixing with normal plasma. Definitive confirmation is achieved through factor assay analysis. In children with severe hemophilia, the first symptoms usually appear in the first years of life and are often associated with bleeding into joints and muscles. Recurrent hemarthrosis leads to hemosiderin

deposition in the synovium, chronic inflammation and synovial hypertrophy. Over time, this results in degradation of articular cartilage and degenerative changes — collectively referred to as hemophilic arthropathy [1,3].

3. TREATMENT

The cornerstone of hemophilia A treatment is early prophylaxis and replacement therapy with factor VIII concentrates to prevent or treat bleeding episodes. Contemporary therapeutic strategies focus primarily on bleeding prophylaxis, which involves regular administration of clotting factor to maintain a minimum plasma level and prevent spontaneous bleeding [1]. Regular prophylaxis initiated in early childhood can significantly prevent arthropathy. In long-term prophylaxis of patients without factor VIII inhibitors, efanesoctocog alfa is used — a single-molecule factor VIII product lacking the B domain and fused with two von Willebrand factor domains, two Fc fragments of immunoglobulin and two XTEN polypeptides. It is referred to as an ultra-long-acting preparation, as a single intravenous dose of 50 IU/kg maintains normal plasma factor VIII activity for 3–4 days [7].

In recent years, novel treatment methods independent of factor VIII have also been introduced. An example is emicizumab — a bispecific antibody that mimics activated factor VIII and enables thrombin generation independently of endogenous FVIII. This therapy significantly reduces bleeding frequency in patients with and without FVIII inhibitors. Among agents available in the European Union, the European Medicines Agency has also included concizumab — a monoclonal antibody directed against tissue factor pathway inhibitor (TFPI) used in hemophilia complicated by inhibitors — and marstacimab, a human IgG1 monoclonal antibody targeting TFPI used in hemophilia without inhibitors [8]. Clinical trials in Europe are currently evaluating both agents in pediatric patients [9,10].

Gene therapy, whose application in the treatment of hemophilia has been extensively studied recently, offers promising prospects. In August 2022 the first gene therapy product for hemophilia A — valoctocogene roxaparvovec — was approved in Europe. Etranacogene dezaparvovec, a therapeutic option for hemophilia B, is currently under regulatory evaluation [1]. In 2024 the FDA approved fidanacogene elaparvovec; however, Pfizer discontinued its production in 2026 due to limited demand [28,29]. These therapies are based on a single administration of a modified adeno-associated virus (AAV) designed to deliver the FVIII or FIX gene to the liver, enabling continuous endogenous synthesis and secretion of the missing factor [30,31]. Treatment is intended for patients without neutralising antibodies against the vector. Current observations indicate sustained clinical benefits for over five years without long-term or delayed toxicity, although an asymptomatic, self-limited increase in alanine aminotransferase (ALT) activity has been observed within the first year after transfer, which may lead to destruction of transduced hepatocytes if immunosuppressive therapy is not applied. Potential risks include infusion-related reactions, liver injury and adverse effects of immunosuppression [30].

4. MUSCULOSKELETAL COMPLICATIONS

Bleeding disorders such as hemophilia and their treatment impact patients' quality of life (QoL) and can affect the everyday life of both patients and their families. The most common complication of hemophilia is joint bleeding, which leads to progressive damage to joint structures. The knee, ankle and elbow joints are most frequently affected. Even a single bleeding episode may trigger an inflammatory response in the synovium; recurrent bleeding leads to chronic synovial hypertrophy and increased susceptibility to further hemorrhagic episodes. Additionally, this process results in progressive damage to articular cartilage, degenerative changes and joint deformities. Consequently, hemophilic arthropathy develops, which may cause pain, reduced range of motion, muscle weakness and gait disturbances [1,3].

The underlying mechanism is associated with hemoglobin breakdown within the joint, producing hemosiderin, which constitutes the mechanical and biochemical basis of hemarthrosis. The accumulation of iron — a product of hemoglobin degradation — leads to increased synthesis and proliferation of fibroblasts and ultimately synovial thickening. Patients with hemophilia and joint complications often present with generalised osteoporosis and localised bone damage. Chondrocytes are damaged through oxidative stress induced by accumulation of free radicals, ultimately reducing their regenerative capacity. Studies by Bordbar et al. have shown that the likelihood of these complications is higher in patients with severe hemophilia than in those with milder forms [11,12].

Another musculoskeletal complication is bleeding into muscle tissue, which may occur as a result of trauma or sudden muscle stretching. Characteristic features include myalgia, swelling and impaired muscle function. When bleeding is located in areas at risk of compressing adjacent neurovascular structures, permanent damage may occur [1].

Musculoskeletal complications significantly affect patients' quality of life and may lead to permanent disability, especially if the disease is not adequately controlled during childhood. Children with hemophilia, owing to fear of muscle and joint bleeding and the resulting synovitis and arthropathy, are at risk of developing hypokinesia and limited mobility. They often choose passive leisure activities, either independently or at their parents' urging. As a result, children with hemophilia exhibit reduced muscle performance and functional endurance in the lower and upper limbs. Muscle weakness reduces mechanical loading on bones, leading to demineralisation, osteopenia and even osteoporosis. Children with hemophilia who are less physically active than their healthy peers often experience acute or chronic orthopedic injuries, which may further limit physical activity. Reducing physical activity, particularly resistance exercise, leads to decreased muscle strength, impaired coordination and reduced postural stability, thereby increasing the risk of joint overload and further muscle atrophy. This is particularly important in the developmental age group given the potential of kinesiotherapy and sports-based interventions.

Reports also indicate the need to monitor adolescent patients with hemophilia for arterial hypertension, obesity, dyslipidemia and HOMA-IR, given higher central diastolic blood pressure (cDBP), arterial stiffness and myocardial performance index compared with age-matched healthy controls — a significant increase in coronary artery disease risk in this population.

5. THE ROLE OF PHYSICAL ACTIVITY

The contemporary model of care for a child with hemophilia has undergone a fundamental transformation, evolving from a restrictive approach based on immobilisation and injury avoidance toward active rehabilitation supported by modern clotting factor prophylaxis. A key challenge in the pediatric population remains the prevention of hemophilic arthropathy resulting from recurrent joint bleeding. In this context, physical activity should not be perceived as a risk factor but rather as an essential element stimulating proper musculoskeletal development. Regular movement induces a range of beneficial physiological adaptations that directly correlate with a reduced frequency of bleeding episodes and improved stability of peripheral joints [13,14].

The primary mechanism by which physical activity protects joints is the development of dynamic stabilization through strengthening of muscle tissue. Skeletal muscles — by virtue of their appropriate mass, strength and resting tone — enable effective absorption and dissipation of mechanical loads. Particular importance is attributed to strengthening the muscular corset (core stability). Trunk muscles, including the transversus abdominis, multifidus and pelvic floor muscles, provide the foundation for force generation and control of limb movements [15]. In children with hemophilia, in whom bleeding most frequently affects the

elbow, knee and ankle joints, adequate muscular efficiency is essential for protecting joint capsules and preventing pathological compensations [16].

Recurrent intra-articular bleeding damages not only the cartilage structure but also the joint capsule and ligaments. Impaired afferent signalling leads to delayed activation of stabilising muscles, creating a vicious cycle of instability and secondary injuries. This results in significant proprioceptive deficits — impaired sense of joint position. In children, this manifests as gait instability and frequent balance disturbances [17].

6. REHABILITATION IN HEMOPHILIA

Proprioception-oriented training allows for a significant improvement in neuromuscular control. Regular exercises on unstable surfaces, using rehabilitation balls or sensory discs, train the child's nervous system to respond more rapidly to external stimuli. This is crucial in preventing ankle sprains — one of the most common sites of bleeding in young patients [18].

The selection of a sports discipline must take into account the severity of arthropathy, the frequency of bleeding episodes and the current prophylactic regimen. The National Bleeding Disorders Foundation (NBDF) in the United States classifies activities according to risk level, promoting low-impact sports. In the table below, activities are organised from low to high risk, providing a practical tool to support safe planning of physical activity. The low-risk category includes exercise forms such as swimming, walking and stationary cycling, which are considered the safest and most recommended for children with coagulation disorders. Swimming, due to buoyancy, reduces joint load almost to zero, allowing safe increases in range of motion and improvement of cardiorespiratory fitness. Stationary cycling is a valuable component of aerobic training, enabling precise control of exercise intensity (e.g. through heart rate monitoring) and eliminating sudden rotational movements within the knee joints typical of team sports classified in higher risk categories.

Such classification and interpretation of physical activities not only help reduce the risk of injury and bleeding but also enable conscious development of the child's physical fitness, adapted to functional capacity and clinical condition. The moderate-risk group includes disciplines requiring greater coordination and generating higher joint loads, which may be undertaken conditionally — provided good disease control and appropriate functional preparation. The moderate-to-high risk category includes activities with an increased risk of injury, often associated with physical contact or high speed. The final category — high risk — comprises activities with a significant probability of trauma and bleeding and is generally not recommended in this patient population [19].

Table 1. *Injury-risk categories associated with physical activity [20].*

Low risk	Low-to-moderate risk	Moderate risk	Moderate-to-high risk	High risk
Walking	Cycling	Running	Contact sports (basketball, soccer)	Trampoline jumping
Swimming	Circuit training	Rock climbing	Horseback riding	Electric scooter riding
Frisbee	Resistance training	Tennis	Ice / roller skating	Motocross
Elliptical training	Fishing	Jump rope	Skiing	Ice hockey
Stationary cycling	Rowing	Aerobics	Martial arts	Skatepark

Incorporating these activities into the daily routine supports the cardiovascular system, has a beneficial effect on bone mineralisation and stabilises peripheral joints. Stabilisation training, based on exercises performed on safe, unstable surfaces, helps the child develop body awareness and reduces the risk of falls.

A key component of physiotherapy in children with hemophilia is strengthening exercises and systematic balance training. Functional physiotherapy involves transferring acquired skills to specific activities of daily living, enabling children to participate more safely in peer-related activities.

The foundation of contemporary kinesiotherapy is progressive resistance training. Although in the past there were concerns that resistance exercises might provoke bleeding, recent studies demonstrate that appropriately dosed resistance is safe and essential in patients receiving prophylaxis. Resistance exercises improve muscle strength without inducing hemarthroses. In children under 14 years of age, exercises using body weight or elastic bands are recommended, while extreme free weights should be avoided. Systematic training leads to a reduction in HJHS scores (indicating improved joint status) and an increase in lower-limb muscle torque [21].

An important component is the inclusion of biofeedback, which allows the child to visualise shifts in the centre of gravity, increasing motivation and the effectiveness of learning new postural strategies. Functional physiotherapy emphasises task-specific activities such as standing up from chairs of varying heights or climbing steps, which facilitates faster adaptation to real-life mechanical loads [22].

7. FUNCTIONAL DIAGNOSTICS AND OBJECTIVE TOOLS

Objective assessment of the musculoskeletal system is the foundation for therapy planning. The gold standard in clinical evaluation in children (4–18 years) is the Hemophilia Joint Health Score (HJHS 2.1). It allows detection of even subtle changes in the elbow, knee and ankle joints. The scale assesses eight domains, including swelling, muscle atrophy, pain and range of motion. A score above 25 points represents a threshold indicating significant functional impairment [23].

The 6-minute walk test (6MWT) and the Timed Up and Go (TUG) test in patients with hemophilia are crucial for monitoring aerobic capacity and dynamic balance, deficits of which are directly associated with an increased risk of falls and, consequently, joint bleeding. Regular goniometric measurements are equally important, allowing early detection of flexion contractures; failure to identify these changes leads to a cascade of biomechanical gait disturbances that irreversibly damage the articular cartilage of previously unaffected joints [24,25].

Modern methods such as pedobarographic assessment enable objective analysis of centre of pressure (CoP) displacement. In children with hemophilia, this is an essential tool for identifying postural defects such as plano-valgus foot, which — if untreated — generate pathological force vectors in the ankle and knee joints, predisposing to further bleeding episodes [26].

In the assessment of muscle strength, it is crucial to move away from subjective methods toward digital dynamometers and isokinetic systems (e.g. Con-Trex). Their advantage in pediatrics lies in ensuring maximum safety — constant angular velocity eliminates the risk of sudden, uncontrolled overload that could induce bleeding during the assessment itself.

A multidimensional, objective evaluation enables comprehensive understanding of the child's clinical condition. As a result, rehabilitation becomes a targeted medical intervention, allowing young patients to safely achieve functional capacity comparable to their peers [27].

8. CONCLUSIONS

The implementation of regular replacement therapy and modern non-factor therapies (e.g. emicizumab) in children with hemophilia constitutes the foundation for protecting the musculoskeletal system. Properly conducted prophylaxis maintains a minimal plasma clotting factor level, which significantly reduces the frequency of joint bleeds and minimises the risk of developing irreversible hemophilic arthropathy.

Advances in hematology have enabled a shift from on-demand to preventive treatment approaches in children. By stabilising coagulation parameters, pediatric patients can avoid chronic pain and functional limitations, which translates into improved psychosocial functioning and physical capacity comparable to their peers.

Physical activity, especially low-impact types, should not be restricted but rather promoted as an essential element of dynamic joint stabilization. Regular exercise increases muscle mass and improves proprioception, creating a natural protective barrier against injuries and secondary bleeding episodes.

Physiotherapy is an indispensable component of comprehensive care. Systematic monitoring of the musculoskeletal system using objective tools such as the HJHS scale and functional tests allows early detection of changes and personalisation of rehabilitation programmes.

Effective prevention of hemophilia-related complications requires close and continuous collaboration within an interdisciplinary therapeutic team, including a hematologist, an orthopedic specialist and a physiotherapist. Only an integrated approach combining optimal factor replacement with targeted rehabilitation enables preservation of full musculoskeletal function in children with hemophilia.

DISCLOSURE

Author Contributions

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There are no supplementary data connected with this article.

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