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Update on Patophysiology and Management of Complication in Children With Haemophilia: A Literature Review from 2020-2025

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Abstract: Background: The high prevalence of death in children with haemophilia is often associated with its complications. The complications can worsen the quality of life of children and pose a high economic threat. This emphasizes the need for early detection and good management of complications. **Aim**: This literature review aims to discuss the pathophysiology and management of complications that can present in paediatric patients with haemophilia. **Method**: A literature search of *original research, case reports, systematic reviews*, and *meta-analyses* was conducted through *Google Scholar*, *ProQuest*, and *Wiley*. The included articles met the following criteria: year of publication 2020-2025, in English or Indonesian, and must at least have a complete article section. **Results & Discussion**: The total number of articles reviewed was 20 articles. The types of complications that often occur in paediatric patients with haemophilia are haemophilic arthropathy, inhibitor, bleeding, and psychosocial disorders. Management options given for each complication vary, but in general consist of prophylactic transfusion of coagulation factor replacement, physical rehabilitation therapy, pain management, surgery, bypassing agents, gene therapy, and monoclonal antibodies. Each type of management has its own goals and procedures, and modifications of the mode of therapy administration have the potential to provide better outcomes for the severity and disability of the patient. **Summary**: Complications of haemophilia in children require more attention from health workers. Acute therapy and prophylaxis remain the main options, with a number of new regimens being developed that are expected to be more widely used and available for people from various social strata.

Keywords: arthropathy; children; complication; haemophilia; management

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Introduction

Based on a study in 2020 in Korea, congenital bleeding disorders have a prevalence of around 47.8% in children population (Yoon et al., 2020). Based on that prevalence, in other study, haemophilia is the most common disease with a prevalence of haemophilia type A of 1/5.000-10.000 males or equivalent to 56.3% of all congenital bleeding diseases—in addition to *clotting disorder* and *platelet disorder* (Kannan & Mohan, 2016; Owaidah et al., 2018). Haemophilia is one of the causes of mortality in both paediatric and adult patients, with a death incidence rate of 0,2/100 patients/year based on a 2019 study (Hay et al., 2020). In 26% of cases of death in children (aged <10 years) with haemophilia, the most likely main cause is late diagnosis. This is due to spontaneous mutation of the haemophilia gene without any hereditary history. Other causes include the lack of understanding from children about their haemophilia and the risk of complications, leading to a high incidence of trauma that causes massive bleeding and cannot be compensated properly (Mansouritorghabeh et al., 2017).

Besides being a direct cause of mortality in paediatric haemophilia patients, various complications also contribute to a poor quality of life and significant

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economic risks. This is evident in the limitations of children with haemophilia to carry out their daily activities as freely as other children in their age. From an economic perspective, repeated hospitalizations are unavoidable if complications are not properly managed. This situation illustrates the importance of proper management of complications that can arise in paediatric haemophilia patients. Even better, these complications can be prevented and detected early, leading to more targeted treatment.

To date, the targeted management for paediatric haemophilia patients is generally the same as for adults: prophylaxis and acute management of bleeding, pain management, and physical rehabilitation. Regarding potential complications, several approaches and treatment modifications are available. These include the use of gene therapy, bypassing agents, joint replacement surgery, and monoclonal antibodies. A 2023 study demonstrated that subcutaneous injection of emicizumab 3 mg/kg every 2 weeks for 52 weeks with follow-up up to 7 years reduced the rate of morbidity caused by intracranial haemorrhage and joint damage. This therapy regimen is particularly beneficial for infants who are at high risk for receiving factor replacement therapy using central venous access or postponing prophylactic therapy until later in life (Pipe et al., 2024).

In various healthcare settings, managing children with haemophilia complications remains a challenge that must be addressed as quickly as possible. This situation is particularly acute in the emergency department and is crucial to prevent unintended, fatal consequences. To support a more systematic understanding of the recognition and integrated management of haemophilia complications in children, this article aims to broadly discuss these issues. The author includes an introduction to haemophilia in children—which differs in some aspects from haemophilia in adults—and then proceeds to discuss a series of haemophilia complications that can occur, explaining their pathophysiology, and treatment approaches that can be attempted to achieve patient recovery.

Materials and Methods

The author conducted a literature review by collecting published research results to explore various complications that can occur in paediatric patients with haemophilia along with the comprehensive management available. The main problem formulations in the literature search were "What is the pathophysiology of complications in haemophilia in children?" and "What is the current management of these complications in haemophilia in children?" The literature search was conducted through *Google Scholar*, *ProQuest,* and *Wiley* domains, conducted from June 1-30, 2025. Some of the search terms included: haemophilia in children; complications; haemophilic arthropathy; inhibitors; management; pathophysiology; prognosis; bleeding; and mortality. All literature results obtained were manually reviewed with the following inclusion criteria: year of publication of the article, namely 2020-2025; articles in English or Indonesian; relevant to the topic presented in this article; type of article, namely *original research*, *case reports, systematic reviews,* and *meta-analyses*; subjects are human; and must at least have a complete article section.

This review aims to describe and evaluate pathophysiology and current management of complication of haemophilia in children. Each included literature was assessed for its research methods, findings, and potential for future research. The articles on the management of complications of haemophilia in children presented in this paper was reviewed by the author for data quality and clinical relevance to the community, especially for children population with the disease from various clinical background.

Result and Discussion

The results of literature selection based on inclusion and exclusion criteria are presented in a simple *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) chart as follows (Figure 1). The total number of articles reviewed further was 20 articles.

The presentation of the literature review results begins with a brief discussion of haemophilia, especially in the paediatric population. The following paragraphs will focus on each of the complications found.

Haemophilia

Haemophilia refers to hereditary and non-hereditary diseases associated with bleeding episodes due to gene mutations and deficiencies and/or damages to blood coagulation factors. Haemophilia is a rare, recessive X-linked disease. Deficiency of the coagulation factor FVIII causes haemophilia type A, and FIX deficiency causes haemophilia type B. Haemophilia type A has the largest number of patient in the world with a prevalence of 1/5.000 male population (Bordbar et al., 2023; Gualtierotti et al., 2022). Furthermore, haemophilia can be classified based on its severity as seen from the percentage of remaining coagulation factors (Cuesta-Barriuso et al., 2022). In a cross-sectional study conducted in Yogyakarta, Indonesia, the number of haemophilia patients in children aged 8-16 years was 44 children, with a frequency of spontaneous bleeding episodes of 13.5 times/year previously (Maimon et al., 2024). In another study in Solo, it was found that 24% of paediatric patients had haemophilia and 10% of them

having poor quality of life scores (Jaelani & Utama, 2023).

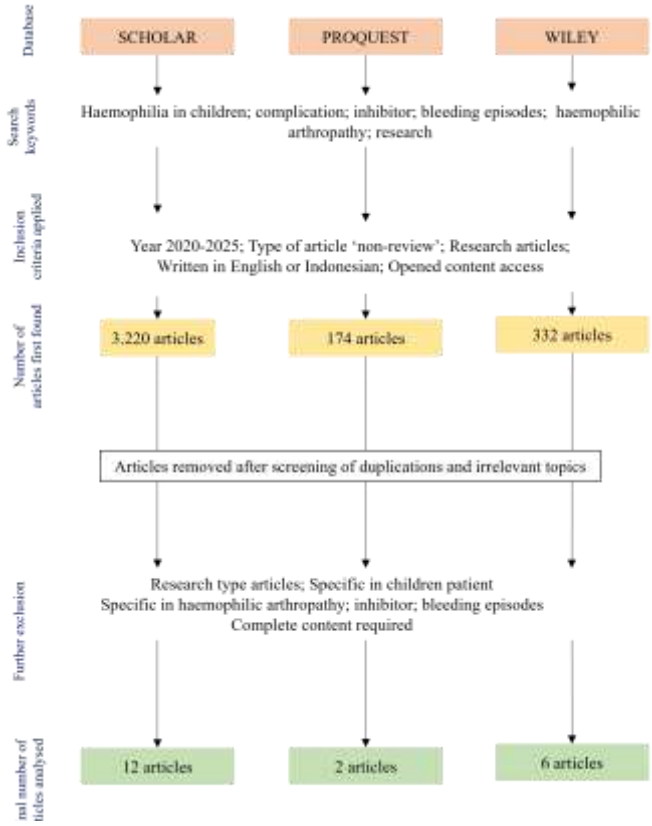

Figure 1 PRISMA chart of selection of articles reviewed (total n = 20 articles)

Meanwhile, genetic factors play an important role in the pathophysiology of the disease. In the Centre for Disease Control and Prevention (CDC) chart on the inheritance of the haemophilia gene, in parents with a carrier mother and a normal father, a 25% chance of having a boy with haemophilia can be found. Meanwhile, in parents with a haemophiliac father and a normal mother, there is a 50% chance of having a girl who will be a carrier. Research showed that 82% of infants aged up to 2 years are diagnosed with haemophilia type A, with 70% of them diagnosed in the first month after birth. The average diagnosis is based on the mother's status as a carrier, a positive family history of haemophilia, and bleeding episodes (Kulkarni et al., 2017).

Until now, the standard method for establishing the diagnosis of haemophilia is the assessment of FVIII or FIX activity through 2 parameters: *activated partial thromboplastin time* (aPTT) and *chromogenic substrate assay* (CSA). In addition to these methods, the *Nijmegen-Bethesda Assay* can also be performed to assess the presence of inhibitors in plasma that inhibit the action of FVIII and/or FIX (Muller et al., 2022).

The literature stated that the manifestation of paediatric patients with haemophilia is in the form of spontaneous bleeding and occurs repeatedly, especially in the musculoskeletal system. This bleeding can occur even though it is only caused by minor trauma (Gualtierotti et al., 2022). The main management of haemophilia patients consists of prophylaxis and symptomatic (Daffunchio et al., 2023). In Indonesia, based on a cross-sectional study in 8 provinces, the most frequently used management model is prophylaxis and replacement factor therapy either with (17.3%) or without a combination with recombinant products (75.5%) (Chozie et al., 2022).

Other literature summarizes a list of treatments that can be selected according to the condition and preferences of patients with haemophilia. These options include: gene therapy (Azhar et al., 2021); extended half-life therapy (Azhar et al., 2021); non-clotting factor concentrate product (Azhar et al., 2021); recombinant therapy (Khair, 2019); prophylactic therapy to minimize bleeding and disability (Khair, 2019); *desmopressin* and *tranexamic acid*, especially for paediatric patients with mild haemophilia type A (Khair, 2019); bypassing agents used to control bleeding in cases of children with inhibitors, accompanied by routine administration of high-dose clotting factors to eliminate inhibitors (Khair, 2019); and monoclonal antibodies, such as emicizumab (Khair, 2019), especially indicated in haemophilia patients with inhibitor formation (Castet et al., 2025).

Gene therapy in haemophilia patients has gained more popularity in the recent years (Azhar et al., 2021). Gene therapy works by transferring specific genes to induce the synthesis of endogenously defective or missing coagulation factors in the plasma of haemophilia patients. One of the gene-carrying vectors used in gene therapy is *adeno-associated viral* (AAV). To date, seven types of drugs containing AAV have entered clinical use, two of which are for haemophilia: Roctavian and Hemgenix. One advantage of AAV vectors over other viral vectors is their non-pathogenic nature and weak immunogenicity, so they do not trigger an immune reaction in the body. Research indicates that gene therapy with AAV has been tested in patients with haemophilia type B and has shown increased plasma FIX concentrations (Chernyi et al., 2024).

In addition to choosing the appropriate treatment for haemophilia patients based on their clinical manifestations, doctors must also consider the patient's and family' perceptions and experiences regarding the type of treatment that provided. A qualitative study was conducted on 13 patients with haemophilia, two of whom were children aged 8-10 years. Patients and caregivers (for children) were interviewed about their experiences and perceptions of haemophilia management. Most patients received emicizumab

therapy, which is considered more effective as a prophylaxis, maintaining high levels of coagulation factors in the body for up to 6 months compared to therapy that must be administered every few weeks. However, the majority of patients and caregivers continued to complain about the intravenous route required for drug delivery—which they found embarrassing when seen by others—and also about the limited availability of replacement factors in some areas or limited to central cities (Castet et al., 2025). The interview results indicate the need for greater attention for patients with haemophilia, including a compassionate and understanding approach to care, equitable distribution of therapy at the appropriate time, and patient education regarding the prognosis of their diseases. Family members and communities also need to be educated about the health threats posed by haemophilia patients and the concrete support they can provide.

Although haemophilia symptoms can be well-controlled through regular medication follow-up, most paediatric patients still experience significant psychosocial impacts from their condition. These impacts include decreased school productivity, poor relationships with friends and family, mobility difficulties, chronic pain, mental health issues, dependency on caregivers, and a lack of psychological support from healthcare professionals and the community (Fornari et al., 2024).

Like a number of other chronic diseases such as diabetes mellitus, intracranial infections, and tumours, haemophilia has a different clinical spectrum in paediatric and adult patients. This difference can be seen in the manifestations of bleeding that occur. In children, particularly those up to 2 years of age, bleeding is more common in the intracranial area, the oral cavity, and in genital after circumcision. Meanwhile, hemarthrosis is more common in older children and adults (Han et al., 2024). This difference emphasizes the importance of understanding the risk factors for spontaneous bleeding in children according to their age group and providing regular, uninterrupted prophylactic therapy.

Bleeding in various organs is a major complication of haemophilia. This is a leading cause of high mortality in paediatric patients. Complications discussed further below include haemophilic arthropathy, inhibitor formation, and impaired quality of life. Other complications will also be briefly discussed.

1. Haemophilic Arthropathy

The musculoskeletal system is a predilection for complications in haemophilia patients. Recurrent bleeding, accompanied by pain, deformity, and joint damage, is termed haemophilic arthropathy (HA) (Bordbar et al., 2023). HA results from recurrent hemarthrosis and is the most common complication in haemophilia (Azhar et al., 2021). Hemarthrosis tends to occur in 50% of children with haemophilia. The most common locations for hemarthrosis are the knee (60%), elbow (47.5%), and ankle (40%) (Vantaku et al., 2023). Hidden joint is a term used to describe joint damage secondary to recurrent hemarthrosis in haemophilia patients (Daffunchio et al., 2023). A cross-sectional analytical study found a higher frequency and degree of arthropathy in paediatric patients with haemophilia aged 11 years and older (Daffunchio et al., 2023). If not treated adequately, HA can lead to long-term joint deformities that are difficult to repaired (Khair, 2019).

Clinical manifestations reported in patients with HA are related to the effects of inflammation on the joints. Those manifestations included specifically pain, skin discoloration, swelling, stiffness and limitations in mobility, and functional disability (Cuesta-Barriuso et al., 2022; Hassab et al., 2022). If joint damage is severe, particularly in the ankles, it can lead to postural disturbances in children (Elnaggar, 2019).

The gold standard for screening joint conditions in haemophilia patients is *Magnetic Resonance Imaging* (MRI). However, because its use is limited, other methods are needed that are more affordable and dynamic. One of the concepts developed is HEAD-US (*Early Detection of Haemophilia Arthropathy with Ultrasound*). HEAD-US introduces the use of ultrasound to assess the integrity of cartilage, synovial fluid, and subchondral bone (Daffunchio et al., 2023).

A cross-sectional study of 28 male patients aged 5–17 years with haemophilia analysed the potential role of *MRI-T2 mapping* diagnostic tools in assessing the structural condition of joint cartilage in the course of haemophilia. The study demonstrated a significant negative correlation between the child's age and cartilage T2 relaxation times in both the knee and ankle joints (Majeed et al., 2020). This suggests that HA is more common in younger haemophilia patients, with longer T2 relaxation times indicating disorganization of the collagen network within the joint. This is concerning because younger children are at high risk of various types of traumas during their growth period. Therefore, continuous monitoring of children's activities beyond the vulnerable age interval is crucial to reduce the incidence of HA in children from an earlier age.

Other studies have assessed the role of biomarkers in assessing the degree of joint damage in the early stages before the development of HA. Two biomarkers known to significantly correlate with joint space narrowing on X-rays are *urinary C-telopeptide fragments of type II collagen* (CTX-II) and *serum chondroitin sulphate epitope 846* (CS846) (Pasta et al., 2020). In haemophilia patients, the level of CS846 is known to be

increased significantly after occurrence of a joint bleeding (Vulpen et al., 2015).

Due to the high incidence of HA in paediatric patients with haemophilia, early detection of joint health decline is essential. This screening can be performed using the *Haemophilia Joint Health Score* (HJHS) questionnaire. Meanwhile, in paediatric patients with haemophilia who have undergone therapy, regular assessments of their quality of life are necessary. This assessment can be done using questionnaires such as the *Haemo quality of life* (Haemo-QoL) (Hassab et al., 2022).

A correlation analysis between the HJHS score and Haemo-QoL in both paediatric patients and their parents revealed a significant association across several domains, including haemophilia severity, disease duration, number of bleeding episodes in the past year, and number of joints involved (Hassab et al., 2022). This underscores the need for closer attention to paediatric haemophilia patients as they age (as disease duration increases), including anticipating the development of HA if the child has a history of bleeding in the joint area. If a child is suspected of having HA in one joint, medical teams need to exclude the possibility of involvement of other joints, which may not yet be symptomatic, so that prevention can be implemented earlier.

Studies have also shown a relationship between the Haemo-QoL score of patients with a history of anaemia and previous hepatitis C infection (Hassab et al., 2022). Since haemophilia is more common in boys and anaemia is rare in boys, the discovery of anaemia in boys may lead to suspicion of haemophilia, especially at higher levels of severity due to unknown bleeding of internal organs.

Pathophysiology

A cross-sectional study in Iran showed that HA occurred in 22.3% of patients (age range 2-76 years) with haemophilia. Based on this prevalence, 93% of patients with HA occurred in more than 1 joint with the majority of HA occurring in haemophilia type A. Various factors were associated with the occurrence of HA as a complication of haemophilia, including: high severity of haemophilia (OR = 10.12); history of infection such as previous hepatitis C infection (OR = 3.67); and the number of bleeding episodes more than 3 times per year (Bordbar et al., 2023).

HA can be caused by various factors, such as recurrent inflammation of the synovial lining of the joint (synovitis), narrowing of the joint cavity, and cartilage damage. This recurrent inflammation is associated with hemosiderin deposition during haemolysis during bleeding into the joint (Bordbar et al., 2023; Hassab et al., 2022). Exposure of blood products to the joint facilitates an inflammatory reaction by innate immune cells. Inflammation is also facilitated by the formation of destructive oxygen metabolites catalysed by iron (Fe) release. This recurrent inflammation can be manifested by synovial hypertrophy caused by hypervascularization in the joint (Cuesta-Barriuso et al., 2022). Inflammation results in apoptosis of chondrocytes and damages the cartilage matrix structure. The resulting joint damage begins with intra-articular hemosiderin deposition, followed by chronic synovial inflammation, inflammation of the joint capsule surface, and the entire joint structure (Pasta et al., 2020). Furthermore, the inflammatory reaction is accompanied by the release of destructive enzymes and cytokines (Cuesta-Barriuso et al., 2022; Pasta et al., 2020).

Damage to these joint components can worsen the quality of life of paediatric patients with haemophilia, especially at the growing age that still requires bone and joint development (Bordbar et al., 2023). In addition to joint damage, HA can also manifest as bone damage after significant impact on cartilage and synovial fluid damage (Daffunchio et al., 2023).

Management

Pediatric patients with haemophilia should receive screening to detect early joint involvement in the disease process. Studies have shown that structural joint changes can even occur in patients on prophylactic therapy, indicating the possibility of subclinical bleeding without obvious symptoms (Daffunchio et al., 2023).

The management of HA that remains effective today is the administration of a prophylactic regimen combined with recombinant or plasma factor concentrates (Bordbar et al., 2023). Other studies have shown a significant improvement in patient well-being after synovectomy (Hassab et al., 2022). Synovectomy can be indicated in children with repeated joint bleeding and do not respond to conservative treatment. Procedure option that available included *arthroscopic synovectomy* and *radio synovectomy*. According to the research, patients who undergo synovectomy showed improved joint bleeding frequency and pain degree (Zhang et al., 2018).

A cross-sectional study was conducted with 50 male patients aged 4–16 years who suffered complications of HA. In this study, the majority of HA occurred in the knee joint (72%). Treatments included plasma transfusion, cryoprecipitate transfusion, and clotting factor transfusion—either one or a combination of the three (Hassab et al., 2022).

A systematic review summarizes the management of joint hemarthrosis in patients with haemophilia. Acute bleeding should be treated immediately with clotting factor replacement and maintained for several days after the onset of bleeding. The expected therapeutic targets for bleeding are also outlined. Coagulation factor replacement is

administered at doses starting at 25 IU/kg body weight in haemophilia A and can be increased, especially in patients who have developed inhibitor complications. Along with pharmacological therapy, conventional strategies, including elevation and ice packs, can still be employed to reduce bleeding, inflammation, and pain (Gualtierotti et al., 2022).

In joint bleeding that has progressed chronically to HA, prophylactic therapy is necessary to prevent recurrent bleeding. Prophylactic therapy involves administering replacement clotting factors 2-3 times per week until adequate target factor concentrations in plasma are achieved. That factors concentrations target should be plasma factor levels of 40–60 UI/dl (Gualtierotti et al., 2022).

Further rehabilitation is recommended immediately after the child receives prophylactic or curative therapy for an acute attack. Rehabilitation programs include physiotherapy, isometric and isotonic physical activity, and stretching exercises. The desired goal of rehabilitation is to strengthen the muscles surrounding the joint to maintain movement stability and reduce the risk of subsequent bleeding episodes (Gualtierotti et al., 2022). In addition to its direct benefits for bleeding episodes, a rehabilitation program incorporating various forms of physical activity should help balance the patient's well-being, increase confidence in the consistency of therapy and disease control, and improve daily productivity.

The effectiveness of rehabilitation programs has been demonstrated by other studies. A study of 13 male patients aged 13–61 years showed improvements in joint function after receiving kinetotherapy and engaging in recreational sports. Recreational sports that could be considered such as ping-pong and soccer (Trăilă et al., 2023).

Pain management in HA can be achieved with analgesics such as paracetamol and selective non-steroid anti-inflammatory drugs (such as *celecoxib* and *etoricoxib*). Medication selection is based on a gradual progression. If pharmacological therapy is no longer effective, then surgery may be an option (Gualtierotti et al., 2022).

Lastly for this section, a case-control study with 20 children each with haemophilia type A aged 8-16 years in the control and treatment groups tested the effect of pulsed *Nd:YAG laser* therapy on HA manifestations in patients. The treatment group was given laser therapy 3 times/week accompanied by a physical activity program for 4 weeks, while the control group received a placebo laser and physical activity program. The results of the study showed that pulsed *Nd:YAG laser* is considered to have the potential to be an effective therapy to control pain and improve postural control in children with HA (Elnaggar, 2019).

2. Inhibitor Development

Inhibitors are another important complication in paediatric haemophilia patients, characterized by the formation of autoantibodies against the replacement coagulation factors used as therapy (Cuesta-Barriuso et al., 2022). Research showed that inhibitors were quite common in paediatric patients, with a prevalence of 22.8%, with 82.1% occurring within the first 20 days after the starting of factor replacement therapy (Thornburg et al., 2025). The formation of these inhibitors renders factor replacement therapy ineffective, complicating bleeding control efforts and, in the long term, can lead to degenerative damage due to recurrent, untreated hemarthrosis (Cuesta-Barriuso et al., 2022).

Pathophysiology

The formation of these inhibitor antibodies is usually caused by exposure to long-term replacement clotting factor therapy. Factor VIII or IX inhibitors occur in one-third of paediatric patients with haemophilia, emphasizing the importance of early screening for this complication (Khair, 2019). Other studies suggest that inhibitors form in 20% of infants with haemophilia, which also increases the risk of intracranial haemorrhage (Kulkarni et al., 2017). The formation of inhibitors can increase the burden of medical costs for haemophilia patients due to the ineffectiveness of each acute or prophylactic therapy undergone. It can be said that inhibitors are the form of complications that most suppress the welfare of life for patients, families, and medical teams involved.

The pathophysiology of inhibitor formation involves the initiation of an immune response to exogenous coagulation factors acting as antigens. The interaction between antigens and immune cells is thought to occur in the spleen, although lymph nodes and bone marrow are also likely involved. Immune cells functioning as *antigen-presenting cells* (APCs) carry antigens (coagulation factors) and induce the activation of adaptive immune cells in the form of *T cells* and *B cells*. The next process is the production of neutralizing antibodies in the form of *immunoglobulin G* (IgG) specific for both FVIII and FIX. Because haemophilia type A tends to have a higher prevalence, the incidence of FVIII inhibitor formation is also more frequent than for other coagulation factors (Tieu et al., 2020).

Case-control studies have shown an association between increased *granulocyte colony-stimulating factor* and *interleukin 6* (IL-6) cytokines with the formation of FVIII inhibitors in patients with haemophilia type A. This condition can also be observed in decreased IL-10 levels (Fan et al., 2025). This indicates a high incidence of inhibitor formation in patients with a history of chronic

inflammation, including long-term coagulation factor therapy-induced inflammation. Meanwhile, biomarkers that have been associated with inhibitor formation have the potential to be diagnostic strategies in monitoring the risk of inhibitor formation in haemophilia patients.

Management

Therapy in patients with inhibitors can use *bypassing agents* (BPA). BPA can be in the form of *activated prothrombin complex concentrate* (aPCC) *and recombinant activated human factor VII* (rFVIIa) with product types *eptacog alfa* and *eptacog beta* (Escobar et al., 2021). aPCC can be given at a dose of 50-100 IU/kg and rFVIIa can be given at a dose of 270 µg/kg single dose (Gualtierotti et al., 2022). In general, BPA works by increasing thrombin production to control bleeding or through activation of the extrinsic coagulation pathway without involving FVIII or FIX (Escobar et al., 2021).

A clinical trial evaluated the safety of rFVIIa eptacog beta in 60 patients with haemophilia. The results showed that eptacog beta was well tolerated without signs of hypersensitivity, thrombosis, or the formation of anti-eptacog beta autoantibodies (Escobar et al., 2021). Another similar study showed that eptacog beta was safe and effective as a bleeding control therapy at doses of 75 and 225 µg/kg in paediatric patients aged <12 years (Pipe et al., 2022). Eptacog beta was also found in another study to be effective in reducing the risk of recurrent bleeding at doses starting at 75 µg/kg in 465 patients with haemophilia (Dunn et al., 2025).

Another therapy that can be used for haemophilia patient with inhibitor formation is administrating of recombinant FIX Fc fusion protein (rFIXFc). A clinical trial was conducted to test the efficacy of rFIXFc prophylaxis in paediatric patients <18 years of age diagnosed with haemophilia type B who had never received FIX prophylaxis before. The study revealed that rFIXFc prophylaxis can reduce the risk of bleeding and slow the duration until spontaneous bleeding occurs again after prophylaxis is administered. This difference is significant compared to patients who only received on-demand prophylaxis (Nolan et al., 2024). The clinical implications of the study's results include the importance of providing prophylaxis to patients with haemophilia type B, especially starting as early as possible.

Another treatment option that deserves attention is the use of the monoclonal antibody *emicizumab*. Emicizumab works by replacing the lost FVIII function in haemophilia type A to facilitate FX activation in the coagulation cascade (Schmitt et al., 2023). Furthermore, a study comparing the effectiveness of emicizumab with BPA found emicizumab to be more economical as a prophylactic therapy, especially in patients with haemophilia type A who got inhibitors (Polack et al., 2021). A study of 88 paediatric patients with haemophilia type A aged 1-15 years reported significant improvements in patients' quality of life after prophylactic therapy with emicizumab. Improvements were particularly evident in aspects of physical health, exercise, and school attendance following successful control of bleeding episodes (Mancuso et al., 2020). Overall, studies have consistently shown that emicizumab can be an effective prophylactic therapy for paediatric patients with haemophilia type A. Further discussion could shed light on the potential use of emicizumab and similar compounds for patients with haemophilia type B.

Finally, another clinical trial assessed the safety of emicizumab dose titration in patients with haemophilia A with suboptimal bleeding control at the initial dose. Generally, emicizumab is administered at a dose of 1,5 mg/kg/week. However, the study showed that increasing the dose to 3 mg/kg/week was well tolerated by patients without significant side effects (Schmitt et al., 2023). This opens the possibility of a new management algorithm to try increasing the drug dose if the previous dose does not provide optimal results. Furthermore, as an alternative, further research is needed to determine the safety and effectiveness of increasing the frequency of emicizumab administration at the same dose.

Other Complications

Bleeding is both the most common and the main manifestation of haemophilia also the complication from the disease. Severe bleeding episodes including intracranial haemorrhage generally occur in populations with limited health resources so that paediatric patients do not receive adequate factor replacement therapy and supervision (Azhar et al., 2021). Research shows that intracranial haemorrhage occurs in 7% of infants with haemophilia (Kulkarni et al., 2017). Other studies show that the prevalence of intracranial haemorrhage is 17.5% and is the most common complication found in paediatric patients (Vantaku et al., 2023).

Conventional therapy with clotting factors that has been carried out to date can have the disadvantage of a short half-life regimen. This has implications for increasing the frequency of drug administration needed by patients. Recent developments have found FVIII/FIX concentrates with a longer half-life, or so-called *extended half-life* (EHL) which can reduce the frequency of infusions by 30-35% (Cuesta-Barriuso et al., 2022). The use of this therapy will be very beneficial for paediatric patients who are at risk of mental trauma due to the frequency of frequent hospital visits to receive treatment.

Disturbance in psychosocial aspect of children is another complication from haemophilia that needed to be addressed. Various psychosocial impacts on

haemophilia patients can reduce their quality of life (Azhar et al., 2021). A cross-sectional study of 50 male haemophilia patients aged 6-18 years assessed the association between haemophilia and mental and behavioural disorders. Examples of mental and behavioural disorders that can occur include thought disorders, depression, aggressive behaviour, and attention deficit disorders. Research shows that the occurrence of mental and behavioural disorders in children with haemophilia is significantly related to factors such as the patient's age and disease severity. Paediatric haemophilia patients with haemophilia who manifest as HA are also associated with the development of mental and behavioural disorders, which are related to the duration of HA and the number of joints involved (Elsakka et al., 2022).

Since haemophilia is a long-term disease, mental health disorders in paediatric patients must be detected as early as possible and receive immediate medical assistance. Uncontrolled mental disorders can hinder the regularity of prophylactic therapy, which ultimately worsens the disease and causes a repeat cycle. Paediatric patients should also receive support and positive affirmation that the haemophilia they suffer from will not interfere with their activities if the routine treatment schedule is followed. In addition, they also need to be convinced that the more compliant the prophylactic treatment is carried out as early as possible, the greater the possibility that the child will receive a lower frequency of injections as the degree of bleeding control increases in the future.

Other reported complications, which are also indirectly the result of other complications, include compartment syndrome (2.5%) and limited mobility or partial paralysis (5%) (Vantaku et al., 2023). A case report reported complications such as septic arthritis of the knee in a 9-year-old child diagnosed with haemophilia type A in India (Das et al., 2021). Infections can also occur, transmitted haematogenously through blood transfusions or clotting factors during haemophilia treatment, including *human immunodeficiency virus* (HIV) and *hepatitis C* infections (Azhar et al., 2021; Hay et al., 2020).

Further Discussion

Despite its relatively low prevalence, the complications and severity of haemophilia can pose a serious health threat, particularly to children worldwide. Most cases of haemophilia are diagnosed late or undiagnosed, at least until irreversible bleeding and death occur. This underscores the importance of public awareness of clinical manifestations that suggest haemophilia. Several issues remain unanswered in the literature and could be topics for future publications. The role of the community in establishing a supportive community for haemophilia patients is an ongoing plan, particularly focusing on their mental health. Furthermore, it is important to review the implementation of simple screening methods for bleeding disorders in all children from an early age, including tracing the family history of similar diseases. For communities living in areas with limited healthcare resources, telemedicine technology can be used to facilitate monitoring and consultation between paediatric patients, families, and medical personnel. However, this certainly requires further study regarding its potential implementation amidst difficulties with smartphone and internet access, as well as the misuse of telemedicine for inadequate consultations. The various new therapies that have been introduced can be assessed for their application in developing countries with a high prevalence of haemophilia, including Indonesia (Danisa et al., 2025). The government plays a crucial role in distributing coagulation factor products to all healthcare facilities to ensure easier access for all levels of society. Current and potential future challenges and obstacles must be investigated early to minimize significant impacts on ongoing therapy programs. Finally, this literature review does not address further efforts to monitor patient progress following the administration of specific therapies for each haemophilia complication.

Conclusion

Haemophilia is one of the highest causes of mortality in children, so it needs serious attention regarding the complications that accompany it. Complications in the musculoskeletal system, the formation of inhibitors to the therapy regimen, and implications for psychosocial aspects contribute to the majority of causes of disability in paediatric patients with haemophilia. Early screening for possible complications needs to be done in all children who have been diagnosed with haemophilia. Diagnosis of complications at a milder degree of severity can lead to better therapy management and prognosis. So far, the types of therapy used are divided into acute therapy and prophylaxis. Various new regimens have been introduced and have begun to be used clinically, including algorithms for increasing the dose of therapy that have proven effective for patients. All therapies are expected to help reduce morbidity and improve the quality of life of paediatric patients with haemophilia. A number of further questions need to be explored to broaden understanding, especially regarding the identification and comprehensive management of haemophilia complications in paediatric patients.

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