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Review Article

The key complications of hemophilia and recent advancements in their management: an update

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ABSTRACT

Hemophilia A is an X-linked recessive disorder which is due to factor VIII deficiency. It is a life-threatening coagulation disorder leading to complications including hemophilic-arthropathy, development of inhibitors, transfusion-related infections and profound psychosocial impact on the life of the patients. The aim of this study is to analyze the challenges in complications and the latest advancements in managing those complications. A thorough and systemic literature review was done to fulfill the objective of this study. The emergence of hemophilic arthropathy due to repeated symptoms of hemarthrosis is the most frequent complication found in haemophiliacs. Another critical complication, mainly seen in resource-poor settings is the development of lethal and severe bleeding episodes including episodes of intracranial hemorrhage. The development of inhibitors is another major challenge which often adds profoundly to the financial burden faced by hemophilia patients. Another major challenge is acquiring various transfusion-transmitted infections which was particularly more common few decades back. Studies also have revealed that there are myriads of significant psychosocial effects affecting the quality of life of hemophiliacs. Emerging treatments such as gene therapy, non-clotting factor concentrate products and extended half-life therapy can usher a new era in the management and the quality of life in hemophilia patients.

Keywords: Hemophilia, Bleeding disorders, Factor VIII, Complications, Inhibitors, Prophylaxis, Management, Arthropathy, Psychosocial

INTRODUCTION

Hemophilia is a coagulation disorder where the factors in the intrinsic cascade of coagulation are defective.[1] The types of haemophilia that are common include haemophilia A and haemophilia B with factor VIII and factor IX deficiency. Hemophilia A and B are X-linked recessive traits where males are affected and females are carriers. Females can be affected in cases of compound heterozygosity, skewed lyonization and X chromosome loss. Hemophilia affects 1.2 million individuals worldwide with Hemophilia A occuring in approximately 1 in 4000 to 5000 male births and haemophilia B occurring in 1 in 15,000 to 30,000 live births.[2] Based on the report of the Annual Global Survey 2018 by World Federation of Hemophilia, the prevalence of people with haemophilia in Malaysia is 1,075, with the cases of hemophilia A and B are 900 (83.7%) and 172 (16%) respectively with the age range of 19-44 years-old.

Table 1: Types of bleeding disorders

Bleeding disorder	Factor deficiency	Traits
Hemophilia A	Factor VIII	X-linked recessive
Hemophilia B	Factor IX	X-linked recessive

Hemophilia A occurs due to failure of production of functional factor VIII protein which may be due to genetic mutations. The severity of haemophilia is characterized as mild, moderate or severe based on factor activity level measured in international units (IU)/ml.[3]

Table 2: Severity of hemophilia.

Severity of hemophilia	Factor activity level (IU/ml)
Mild hemophilia	>0.05 and <0.40
Moderate hemophilia	≥0.01 and ≤0.05
Severe hemophilia	<0.01

Laboratory result shows prolonged activated partial thromboplastin time which corrects when mixed with normal plasma. Diagnosis is confirmed with reduced levels of factor VIII activity. Uncorrected mixing studies suggest the presence of an autoantibody (inhibitor).

Manifestations seen in hemophilia ranges from fatal hemorrhagic CNS events to superficial ecchymosis. Infants with severe hemophilia usually presents with easy bruising, hemarthrosis, oral bleeding due to injury or after an invasive procedure within the first two years of life.

In the absence of a known family history of hemophilia, a person with mild hemophilia may go undiagnosed for a long period of time unless if a critical hemostatic challenge (eg,trauma, surgery) happens. The common sites of bleeding include joints, muscles, central nervous system, oral and gastrointestinal tract. These symptoms might be recurrent and may lead to further complications such as haemophilic arthropathy, chronic pain, contractures etc. These complications interfere with patient's daily activities and it can cause decrease in health-related quality of life.[4]

Treatment of hemophilia A involves replacement therapy of factor VIII with plasma-derived factor (pdF). Concentrates or recombinant factor concentrates which is either prophylactically or on-demand.[5]

Eighty per cent of global population of haemophiliacs live in resource poor settings. Due to haemophilia being a rare disease with high cost, therapy is limited to the majority of patients in developing countries. With no proper treatment, this will lead to further complications which can affect patient's health and quality of life.

Therefore, appropriate management and control of haemophilia is essential to prevent long-term problems and to improve the patient's health-related quality of life. Early management and awareness to people with haemophilia from a young age would give a good treatment outcome.

Health knowledge since adolescent age would give a good treatment outcome and effectiveness on individuals.[6] The aim of the study was to discuss the challenges in complications of hemophilia patients and the advancements in managing those complications.

METHODS

The focus of the study was to review the challenges in complications of hemophilia and advancements in managing the complications. The search strategy included published studies in the last 10-15 years which focuses on relevant data which applies to the challenges arising in the complications of hemophilia and the advancement in management. The papers were reviewed through searches such as pubmed, uptodate, clinicalkey and google scholar. The search terms included 'hemophilia A', 'hemophilia B', 'complications', 'arthropathy', 'hemorrhage', 'inhibitors', 'infections', 'psychosocial', 'emerging therapy'. Other publications were reviewed from reference list including research studies and review papers.

Table 3: Complications of hemophilia.

Complications of haemophilia
Hemophilic arthropathy
Development inhibitors
Transfusion transmitted and other infection related to complication
Hemorrhage
Psychosocial impact on hemophilia patients

Hemophilic arthropathy

Arthropathy is a common complication of hemophilia that occurs primarily due to chronic hemarthrosis in the elbows, knees and ankles due to the absence of the coagulation factors. Multiple hemorrhages in the joint can make it a target joint, rendering it more vulnerable to bleeding than a typical joint.[7] Target joints often advance towards hemophilic arthropathy, and is distinguished by joint deformities, synovial hypertrophy, cartilage and bone destruction, an impairment that has a detrimental influence on physical activity and quality of life. Patients generally perished during the last century at a relatively early age; hence age-related comorbidities were of limited concern.[8] If left unabated, more than 30 hemarthroses per annum could arise in patients with severe hemophilia.

Bleeding incidence and locations tend to differ depending on a patient's age.[9] The far more frequently identified joints are the knees, elbows, and ankles, whereas hips, shoulders, and subtalar joints are less common.[7] Hemophilic arthropathy could be further categorized into three classes. Hemarthrosis is the first occurrence of a joint bleed, which also contributes towards arthropathy with recurrent bleeding in the same joint. The three classes are acute hemarthrosis, subacute hemarthrosis and the final class is chronic arthropathy.

The clinical presentation for acute hemarthrosis is the onset of pain and immediate distress. If replacement intervention is performed in time after the onset of joint

bleeding, hemarthrosis could progress rapidly within a few hours, leading to transient functional dysfunction. It will further turn into a joint that is sore, hot and swollen. Subacute hemarthrosis occurs in the same joint after numerous episodes of hemarthrosis. Incomplete healing of the involved joint makes it become a trigger joint. Reduced mobility, swelling of the joints owing to joint effusion or synovial hypertrophy. Chronic arthropathy indicates repeated episodes of hemarthrosis that elicit a proliferative and debilitating chronic synovitis with gradual joint damage, termed hemophilic arthropathy.[9]

The pathogenesis of hemophilic arthropathy essentially includes two main mechanisms which are synovitis and degeneration of cartilage. Joint bleeding is responsible for synovitis, resulting in synovial hypertrophy and vascular remodeling. The inflamed synovium develops plasmin, matrix metalloproteinases (MMPs), and pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and factor-alpha tumor necrosis (TNFα) that affects the cartilage. Synovial and pro-inflammatory are blood-derived cytokines that facilitates the production of hydrogen peroxide by chondrocytes. In the presence of erythrocyte-derived iron (Fe2+), hydrogen peroxide (H_2O_2) is able to react, resulting in the production of very toxic hydroxyl radicals (OH•) that induce chondrocyte apoptosis. Inflammation also stimulates the NF-nB Ligand (RANK-L)-RANK-osteoprotegerin (OPG)-pathway receptor activator, resulting in osteoclastic bone resorption. OPG guards the bones from excessive resorption by binding to RANK-L instead of RANK.[10]

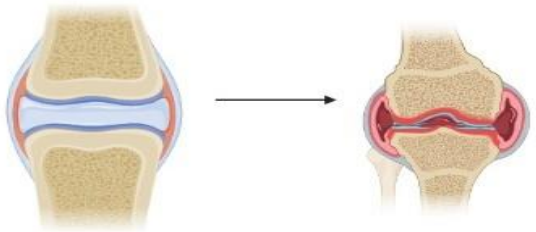

Figure 1: Progression of a normal joint to arthropathy.

A complete musculoskeletal assessment needs to be done in every patient with hemophilia, with an assessment of the joints in children every 6 months and annually in adults. The clinical scores used for diagnosis are the Gilbert score and The Hemophilia Joint Health Score (HJHS). The Gilbert score was initially used to assess the function and structure of affected joints. The HJHS then became the clinical score of choice due to the advancement in noticing significant early changes when assessing joint health. Moving on to the diagnostic modalities, several classifications are used to manage haemophilic arthropathy on the basis of medical findings, and radiological tests. The classifications used for conventional radiological finding systems are the Petterson ranking which classifies the joint disease as dependent on the developmental stage and the Arnold-Hilgartner scale, where the joint is scored on the basis of a radiological shift description. Magnetic resonance imaging (MRI) has recently been identified as the gold standard in diagnosis because of its advantages in identifying changes that traditional radiographs do not visualise. In assisting with the diagnosis, ultrasound has also shown positive results as it is capable of assessing the level and degree of inflammation of soft tissue and identifying the involvement of intra-articular fluid with easy usage in the paediatric population.[11]

Development of inhibitors

The formation of inhibitors, an alloantibody that forms in response to the infused factor, is onthe complications of c lotting-factor use in hemophilia patients. This occur when the immune system generates neutralizing antibodies when it identifies the infused component as foreign.[12]

The incidence of development of inhibitor in severe and mild or moderate haemophilia A is 20-30% and 5-10% respectively and <5% in hemophilia B.[13] Inhibitors are more common in hemophilia A than in hemophilia B with the prevalence in Malaysia for haemophilia A is 60 out of 900 patients (6.67%) and for hemophilia B, 6 out of 172 patients (3.49%).

Inhibitors are polyclonal antibodies of high affinity which is primarily immunoglobulin G (IgG) which direct against A2 and/or C2 factor protein domains. The antibodies neutralize the clotting factor function and reduce the concentration of factor infusion.[14] The major challenge in treating people with hemophilia with clotting factor is the increased risk of inhibitor development.

Inhibitors are typically detected after a median of 9 to 12 clotting factor exposures in childhood. The use of factor VIII treatment for extreme bleeding or surgery has been suspected of affecting inhibitor formation due to significant tissue damage and inflammation that can cause an extravascular FVIII antibody response.[15] It was also found that genetic context influences the development of inhibitors. An elevated risk is associated with a family history of inhibitors and the occurrence of null gene mutations.16 The same study by Santagostino et al also found that prophylaxis patients have a lower chance of developing inhibitors in relative to those treated on demand.

Inhibitor development remains a major complication of haemophilia treatment, which also makes it difficult to give prophylaxis and to treat bleeding problems. It is also associated with high rates of hospitalization, cost and death of haemophilia patients.

The titer of inhibitor, which is time and temperature dependent is expressed as Bethesda units (BU) whereby 1 BU neutralizes 50% of clotting factor activity. ≥5 BU shows a high titer inhibitor and <5 BU is a low titer inhibitor. The development of both low and high titer

inhibitors greatly interfere with the treatment of bleeding and in achieving adequate hemostasis. This happens when exogenous replacement factor binds to high titer inhibitors and prevent hemostasis from occurring.

The bypassing agents used for prevention of acute bleeds in patients with inhibitor development are activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII (rFVIIa). The use of bypassing agents as prophylaxis in a patient w ith inhibitors also prevents bleeding episodes such as hem arthrosis and target joint bleeding.[17] The same review paper also stated that Immune Tolerance Therapy (ITI) is the first choice of treatment in patients who does not respond to prophylaxis or on demand treatment. However, patient with inhibitors is associated with 3 times higher cost of treatment that causes a financial burden to individual, healthcare and then those without inhibitors.[18]

Table 4: Annual Global survey 2018 by World Federation of Hemophilia shows the percentage of patients on prophylaxis.

Country	Age below 18 years (%)	Age more than 18 years (%)
Malaysia	85	65
Singapore	88	54
Indonesia	0	0
Thailand	20	5
Philippines	2	0
Cambodia	5	0

Emicizumab prophylaxis was found to be associated witha significantly lower risk of bleeding and increased quality of life compared to no prophylaxis in patients with haemophilia A with inhibitors.

Emicizumab (ACE910) is a humanised, recombinant bisp ecific monoclonal antibody that replaces the activated fac tor VIII role in coagulation, thereby decreasing bleeding r ates. A study reported shows treatment with once-weekly subcutaneous administration of emicizumab decreases the bleeding episodes among haemophilia A patients with or without inhibitors.[19] Emicizumab prophylaxis shown to reduce the occurrence of spontaneous bleeding seen in a study of annualized bleeding rate of patients with and without emicizumab prophylaxis.[20]

The Annual Global survey 2018 by World Federation of Hemophilia shows a total of 6 patients with the use of Hemlibra (Emicizumab) from Malaysia, which is 0.5% out of the total number of people with haemophilia. Other south east Asian countries with the use of hemlibra are Singapore and Thailand with a total of 2 (0.78%) and 3 (0.18%) patients respectively. A lower risk of inhibitor production is associated with routine prophylaxis than on demand treatment. The study reported by Oldenburg et al shows that prophylaxis with emicizumab shows a significantly reduced bleeding rate, which was 79% lower than the rate with the usage of bypassing-agent prophylaxis.[20] This result in a major advantage in the quality of life related to the wellbeing of the patient.

Transfusion transmitted and other infection related complications

Overall most patients with hemophilia were infected with viruses which complicated by factor VIII and IX concentrates therapy. In the 1980s and early 1990s, clotting factor products causes the transmission of hepatitis B, hepatitis C and HIV, which resulted in high deaths.[13] Advancement of treatment equivalent to plasma-derived clotting factor and home administered replacement has started within the 1970s.[21] The culprit for this manifestation was by thousands of blood donors in which the concentration coagulation factors originate did not undergo viral inactivation.[22] On the contrary, an issue has been raised in Malaysia as a study shown that the community did not participate in blood donation which resulted a rapid multiply request for blood in medical settings. Malaysian National Blood Centre expected at least 10% of Malaysian engagement but only came to conclusion of 3% contribution. The community indeed have knowledge and attitude but still lack in practice.[23] Therefore, preventive measures are taken by fulfilling varied non-invasive steps incorporating standard screening plasma and selection of donors, constructive viricidal cycle and sensitive diagnostic measures so as to observe miscellaneous pathogens. These methods have improved to minimize the probable transmission of HIV and HCV to concerning one in a pair of million blood units.[13]

In this current era, the modern therapy towards patients with hemophilia has better treatment with a lesser chance to be infected through concentrates, thus improve their quality of life. Take Malaysia and South Africa to illustrate the use depletion of freeze-dried and virus-inactivated cryoprecipitates fabrication to their patients.[24] Patients with hemophilia found to be positive of 3.8% for HIV and 6% for Hepatitis B and 23.9% for HCV as a result study in western India in 2000.[25] Roughly 80% hemophilia patients develop antibodies against the surface antigen of hepatitis B virus (HBsAg) while the other 10% becomes chronic carriers. HIV antibodies were found in 77% of middle aged and elderly patients with hemophilia A and 42% with hemophilia B but incidence was lower correlating the used amount of FVIII concentrates.[22] Haemophilia patients are afflicted by hepatitis C and HIV of 50% in advanced countries. The prevalence of hepatitis C is closely related with the frequency of exogenous FVIII and FIX concentrated administered. Therefore, the prevalence is dependent on the number of doses as it directly increases the risk of acquiring an infective agent[13]. In 1976-1991, the highest mortality rate due to haemophiliac patient was HIV infection compared to bleeding with only 5%. In those days, an estimated 90% of those with severe haemophilia were infected with HIV and many developed AIDS with thousands of deaths. After 1985, the method of factor VIII concentrates preparation and laboratory donor's examination has reduced the risk requiring HIV

infection.[24] The rate of HIV infection has dropped further as plasma products become safer.[26]

Peripheral vein is the top pick of venous access required during treatment but central venous line is favourable in many cases. Children with haemophilia usually associated with infectious complication by venous line thus implementing an embedded apparatus such as port-a-cath may lower the rate of infection.

Factors relating to infection must be bound by aseptic measure, quality of education and compliance of the users.[27] The best way in managing bacterial infection is to control the source of infection which is vital in people with haemophilia.[13]

Hemorrhage

Hemarthrosis (hemorrhage into a joint) represents up to 80 % of hemorrhages in hemophilia. One joint is usually affected at a time but bleeding episodes can affect a variety of joints particularly the major weight bearing joints. The most commonly affected in children are the ankles, and in adolescents and adults are the knees, elbows and ankles.[28]

The major cause of disability in hemophilia is the muscle hematoma which it may compromise the neurovascular structures. Bleeding into muscles includes 10 to 25% of hemorrhagic episodes in severe hemophilia and hematoma formation is common. Leg muscles (eg. quadriceps, iliopsoas) and arm muscles are often affected.[29]

Oropharyngeal bleeding can occur from numerous sites such as the nose, oral mucosa, and gingiva. Moreover, this type of bleeding usually follows minor trauma or dental procedures. Bleeding into the abdominal wall is often misdiagnosed as an acute abdomen due to the presence of severe pain.

A total 13 out of 1190 deaths were caused by upper GIB based on a report in United Kingdom that evaluated the causes of death.[29] The frequency of gastrointestinal bleeding will be increased with the presence of helicobacter pylori infection in hemophiliac patients.[29]

Intracranial hemorrhage (ICH) is relatively rare compared with other sites of bleeding, but it is one of the most serious events that can occur in hemophiliacs resulting in high rates of mortality and disability.[30] The percentage of ICH causing death nowadays is about 30% compared to 75 % which was the time before new therapeutic options were introduced. The incidence of ICH has declined since the 1960s, likely due to earlier diagnosis and greater use of prophylactic factor administration.[31]

Psychosocial impact on hemophilia patients

People with hemophilia (PWH) as well as their caregivers have their lives immensely impacted by psychosocial issues related to hemophilia.[32] Hemophilia's psychosocial effect was recently explored in the Hemophilia Experiences, Results and Opportunities (HERO) study. The results showed that hemophilia affected adults with moderate to severe hemophilia and their caregivers. The effect on hemophilia on PWH and caregivers is primarily due to complications of the disease which is pain from hemophilia-related bleedings (joint bleeds).[32] The pain and bleeding cause PWH difficulty in completing their studies or performing activities. Baumann et al 2017 showcased in his study that 41% of adults and 49% of children with hemophilia B had stopped their past activities due to risk of bleeding and bruising.[33] Further adding to the fact that PWH has their education and work-life obstructed due to absenteeism by hemophilia related issues.[32] In Portugal, 42.4% of working adults with hemophilia reported absenteeism due to hemophilia.[34] When it comes to how hemophilia affects relationships, a research found that PWH reports negative experiences when telling friends about hemophilia and being bullied by peers due to hemophilia.[35] This was proven with reduced overall health and physical function and increased pain scores results from the study. Furthermore, 37% of young adults with hemophilia (YA-PWH) has impacted their ability to build intimate relationships with a partner or future partner and 36% of YA-PWH experienced negative outcomes upon telling their friends about having hemophilia.[36] PWH is also financially affected, as shown in Portugal which indicates that 54.6% of adults had negative impacts on their financial income.[34,18] People with lower income uses more of Complementary and Alternative Medicine (CAM) due to the high cost of treatments of hemophilia in Europe.[37]

Mental health concerns were substantial in young adults with hemophilia (YA-PWH), 42% reporting moderate to extreme anxiety or depression but more commonly as moderate.[36] Unfortunately, PWH might suffer more mental stress and deteriorating mental health specifically this year partly due to the quarantine happening in Malaysia due to COVID-19 pandemic. The increased in period of quarantine directly influences the increase in prevalence of psychological distress and signs of posttraumatic stress disorder. The breakdown of these coping mechanisms over time due to low psychological, emotional and social support makes severe comorbid anxiety and depression exacerbating the disease.[37] One of the reasons could be that 28.7% YA-PWH struggle in the crucial time of transition from staying at home with parental support to becoming independent young adults. Another reason could be due to the relationship issues of YA-PWH with their friends or partners.[35,36] More than 50% of adult respondents reported of mild or worse depression. Adults with hemophilia reported with 41% of moderate to severe depression/anxiety.[35] There are significant percentages of PWH having mental health issues which should be addressed appropriately during treatments by providing counseling and therapy sessions.

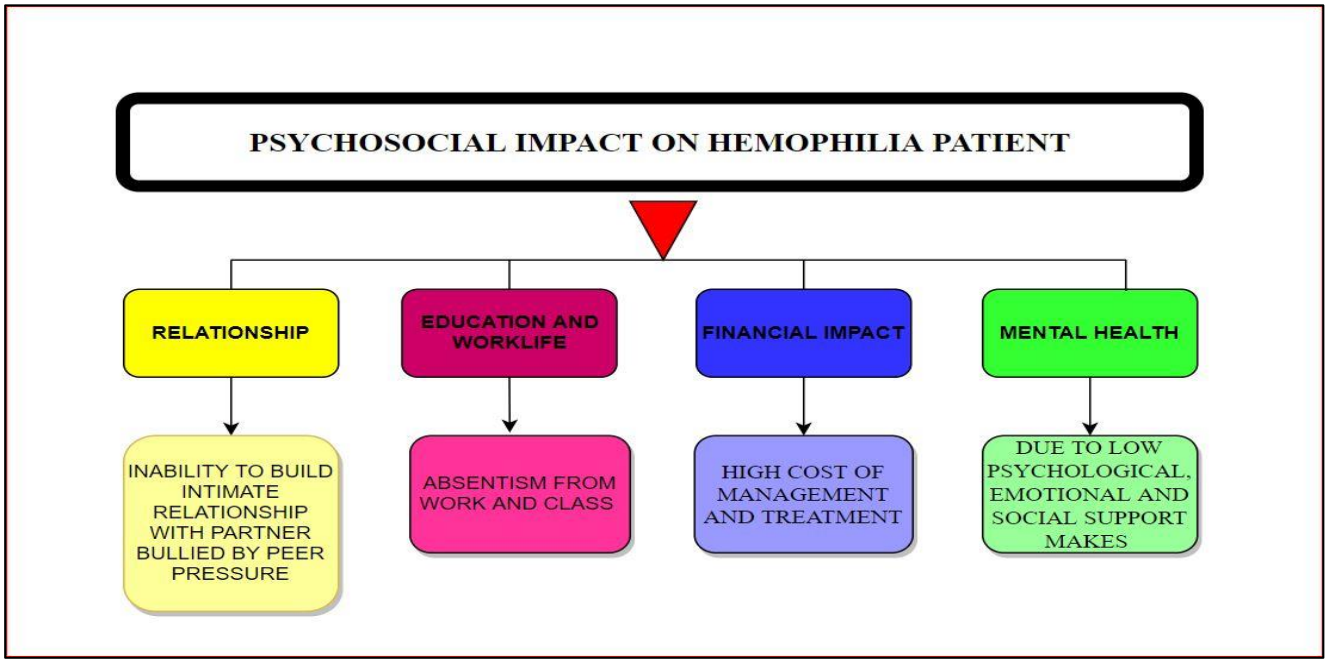

Figure 2: Psychosocial impact on hemophilia patient.

Management and advancements of complications in hemophiliacs

Immediate management of acute bleeding episodes in hemophiliac patients is important to avoid risk of lethal bleeding. Good bleeding control, treatment of underlying cause of bleeding and eradication of inhibitors has a significant impact on the prognosis.[38] Immunosuppressive agents such as steroids, rituximab, cyclophosphamide and intravenous immunoglobin are used to eliminate the inhibitor from the body. Furthermore, the recent treatment line includes corticosteroid with or without cyclophosphamide or rituximab. For patient with mild bleeding, desmopressin is administered, while factor VIII or IX concentrate is given in cases of severe bleeding. Patients with hemophilic arthropathy that have received primary prophylaxis at a younger age have manifested with lesser bleeding joint episodes. Acute hemarthrosis requires aggressive haematological intervention and joint aspiration, till total absence of the intraarticular haemorrhage. Joint status should be assessed from an ultrasonography point of view. Radio-synovectomy can control chronic synovitis. More severe surgical procedures may be expected in cases of joint degeneration.[7,11]

In terms of transfusion-transmitted infections, the principle management of transfusion transmitted complications for hepatitis B virus infection in haemophilia is to screen for hepatitis B antigen and anti-hepatitis B at least 6 to 12 monthlies. The current treatment for the Hepatitis C virus is pegylated interferon (PEG-INF and ribavirin). Other than that, immunization has shown a correlation in the safety of the patients' treatment thus they should be given hepatitis A and B vaccination.[13]

The management of haemophilia patients with inhibitors include inhibitor eradication via factor replacement with immune tolerance induction (ITI), treatment of bleeds using bypassing agents (rFVII or aPCC) and emicizumab prophylaxis.[12] Prophylaxis treatment has shown long-term effectiveness thus reducing the potential of long-term disability.

Other emerging therapies include treatment with extended half-life clotting factor concentrates (EHL CFC), EHL FVIII and FIX products show to be efficacious consistently above 90% for treating and preventing bleeding episodes in haemophilia patients. Novel drugs are currently in trials that focuses on non-factor replacement therapy. The three novel drugs which are most advanced in this group are emicizumab, RNA interference (RNAi) therapy (fitusiran), and monoclonal antibody (concizumab).[39] These drugs may imitate coagulation factors that make them immune to degradation and interact with anti-coagulant protein that occurs naturally, thus compensating for the deficiency of procoagulants.[39] In the same study, emicizumab (ACE910) showed a significant reduction of bleeding rates per annum even with inhibitors present. Although these drugs provide the most desirables advantages, there are still issues about long-term safety and efficacy. More clinical trial findings would be needed to provide valuable details. In current clinical development, a study shows gene therapy is an effective investigational treatment of hemophilia A.[9] A study showed that hemophilia A and B can be corrected by hepatic in vivo gene transfer method with adeno-associated viral (AAV) vectors.[40] The result from this study shows sustained production of endogenous clotting factors with the use of gene therapy; thus, this eliminates the need for coagulation factors infusion.[40] This approach

can also be used to reduce the production of inhibitors against clotting factors. Based on this study, AAV gene therapy may be a potentially curative therapy for haemophilia. However, there are still limitations in paediatric and those with liver disease hence further research and trials are being done for those patients.[38]

CONCLSION

In conclusion, there are various complications that can arise in patients with hemophilia such as hemophilic arthropathy, infection from plasma-derived products such as human immunodeficiency virus (HIV) and hepatitis C, development of inhibitors which causes decrease response to factor infusion and also the psychosocial impact of the disease to an affected individual. The number of challenges that can arise in hemophilia patients requires appropriate management to avoid further complications and to improve patient's health-related quality of life.

The new advancements in the management for instance extended half-life therapy, non-clotting factor concentrate, and gene therapy together with discovery and development of innovative products further enhance the management of the patient with hemophilia. Non-governmental organizations are also playing a pivotal role in providing holistic care and support to the hemophilic patients in countries like Malaysia. For example, The Hemophilia Society of Malaysia (HSM) works in collaboration with World Federation of Hemophilia, healthcare providers and governments to deliver necessary support for the patient. This is achieved through the introduction of psychosocial assistance, marriage therapy and workshops to disseminate information and understanding for individuals with haemophilia.

It is important for various bodies to take part in the advancement of treatment options by mobilizing funds and expertise to improve the overall well being of people with hemophilia and managing the complications.

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