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Clinical aspects, management, and management-related complications
of hemophilia (A) in children in Khartoum state

A thesis
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قالوا سبحانك لا علم لنا إلا ما علمتنا إله أن الطيم الحكيم
صدق الله العظيم
سورة البقرة
آية رقم (32)
Dedicated To.....

My family

with love
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Admirations for hemophilic children & their parents for their patience and co-operation.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>APPT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AZT</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>BT</td>
<td>Bleeding time</td>
</tr>
<tr>
<td>CJD</td>
<td>Creutzfeldt-Jacob disease</td>
</tr>
<tr>
<td>DDAVP</td>
<td>1, 8-Desamino-D-arginine vasopressin</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EACA</td>
<td>Epsilon aminocarpoic acid</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbant</td>
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<tr>
<td>IAMP</td>
<td>Intra-articular methylprednisilone</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>ITI</td>
<td>Immune tolerizing induction</td>
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<tr>
<td>HBV</td>
<td>Hepatitis-B-virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis-C-virus</td>
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<tr>
<td>HBcAg</td>
<td>Hepatitis-B-core antigen</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis-B-surface antigen</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immune deficiency virus</td>
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<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>RFLP</td>
<td>Restricted fragment length polymorphism</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
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<tr>
<td>RIA</td>
<td>Radio-immune assay</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>vWF</td>
<td>Von Willibald factor</td>
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<td>VII</td>
<td>Coagulation factor seven</td>
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<td>VIIa</td>
<td>Activated factor seven</td>
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<td>VIII</td>
<td>Coagulation factor eight</td>
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<tr>
<td>IX</td>
<td>Coagulation factor nine</td>
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<tr>
<td>X</td>
<td>Coagulation factor ten</td>
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<tr>
<td>Xa</td>
<td>Activated factor ten</td>
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Abstract

Hemophilia “A” is the commonest inherited coagulation disorder (factor VIII deficiency). Though inherited as X-linked pattern yet, the disease may manifested in females if a male hemophiliac marries to a female carrier or if there is an imbalanced X-inactivation. The disease has a significant mortality and morbidity most commonly in the form of joints damage and contraction of blood-borne infections.

The objectives of this study were, to determine the clinical features of hemophilia “A,” to study the complications of the disease and its treatment (mainly hepatitis “B”& HIV infections and factor VIII inhibitors) and to evaluate practice of managements compared to the international trend.

The study was a descriptive cross-sectional and hospital-based. It was conducted in the pediatric wards of Khartoum State Hospitals and the Hemophilia Clinic in Khartoum Teaching Hospital during the period from December 2003 to June 2004. A total of 71 patients (98.6% were males & 1.4% were females) aged 0-16 years who have factor VIII level of less than 40% of normal, were enrolled in this study.

Moderate hemophilia (factor VIII level 1-5% of normal with mean of 3.57 +/- 1.32 SD) was the principal type, contributed for 54.9% followed by the mild type (factor VIII level >5 % and < 40% of normal with mean of 11.8+/-5.44 SD) contributed for 42.3% while 2.4% were
with severe type (factor VIII level <1% of normal). Family history of bleeding disorders was found in 65.3% of them.

The commonest presenting complaint was muscles and joints bleeding in 49.3% followed by mucous membranes bleeding in 33.8 %. 56.3% presented during infancy, half of them were diagnosed during the same period. The frequency of bleeding was less than ten times per year in 60.5% of patients; the frequency of bleeding was significantly correlated with factor VIII level (0.02).

Arthropathy developed in 45% of patients, increasing age (P=0.03) & initial presentation with joints& muscles hemorrhages (P=0.01) were found to be risk factors. The knee joint was commonly affected (52 % out of those with arthropathy).

The prevalence of factor VIII inhibitors was found to be 14% .the severity of the disease (P=0.01) and frequent exposures to factor VIII concentrates (P=0.04) were found to be risk factors.

The prevalence of hepatitis B was found to be 1.4%.

No hemophiliac was reactive to HIV.

The principal factor administered was dried factor VIII concentrate interchanged with plasma products (69%) for acute bleeding (on demand therapy).

A comprehensive hemophilia care, advocating unified protocol for management is therefore recommended.
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نحو أن تكن أنثى آخر خاصة حددت مكانة أولية 
نحو أنثى آخر خاصة حددت مكانة أولية 
نتيجة علامة أنثى أخرى (A). إنما كان النتائج أكثر مباينية في التعبير عن مكونات الأعشاب 
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الذكور يصيبونها فهناك أنثى أخرى (A) .

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نحو أنثى أخرى (A) .

/1.4\% (أنثى، 98.6\%)

(2) (أرجأ 8 أصلي أنثى أصلية حددت مكانة أولية 
نحو أنثى أخرى (A) .

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(3) (أرجأ 8 أصلي أنثى أصلية حددت مكانة أولية 
نحو أنثى أخرى (A) .

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(4) (أرجأ 8 أصلي أنثى أصلية حددت مكانة أولية 
نحو أنثى أخرى (A) .

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(5) (أرجأ 8 أصلي أنثى أصلية حددت مكانة أولية 
نحو أنثى أخرى (A) .

/60(\%.)

) P=0.02.
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Chapter One

Introduction and Literature Review

1.1. Historical Background:

1.1.1. Hemophilia (A):

Hemophilia has been recognized as a clinical entity since biblical times when Talmudic writing permitted the avoidance of circumcision when there was repeated history of deaths from circumcisional bleeding in male siblings\(^1\).

Sex-linked hemophilia recognized in the second century, when rabbi correctly deduced that sons of hemophilic carriers were at risk of bleeding following circumcision\(^2\).

In the eleventh century the Arab physician Abucasis Zahrrwi wrote about a family in which males died of excessive bleeding from minor injuries\(^3\).

In 1828, the word hemophilia first appeared in description of a bleeding disorder at the University of Zurich\(^4\). The disease has been often called the disease of Royals, the disease was passed to several royal families from Queen Victoria, Queen of England (1937 – 1901) who was a carrier\(^5\).

In the nineteenth century, several authors ascribed the hemorrhagic episodes to delayed blood coagulation\(^6\). In 1911, Addis demonstrated that thrombin formed more slowly in hemophiliac blood than the normal blood, however, he incorrectly theorized that hemophilia was due to prothrombin deficiency\(^7\).

In 1930, Brinkhous demonstrated that the basic defect in hemophilia was delayed conversion of prothrombin to thrombin. The defect may be corrected by a fraction of normal plasma that contained the anti-hemophilic factor, later named factor VIII\(^3\).

In 1964 a proposal was put forth to organize the growing numbers of coagulation factors into a cascade\(^8,9\). In this Scheme both factor VIII and factor IX considered as proenzymes, later it was shown that they are rather co-factors for factor Xa\(^9\).

1.1.2. Factor VIII:

In 1950s with the development of basis of coagulation the only treatment for bleeding episodes was the infusion of frozen plasma, which was limited by the volume required, elective surgery was not feasible\(^11,10\). In 1964, Pool and co-workers discovered that factor VIII is concentrated in the plasma cryoprecipitate, which was initially lymphilized and pooled\(^12,13\).

The preparations had relatively low specific activity, primarily composed of plasma proteins especially fibrinogen. The pooled cryoprecipitate was then processed in steps led to intermediate purity concentrates with higher specific activities. In 1980s, more development in viral in activation procedures and high purity concentrates\(^14\).
In 1990s non – plasma – derived concentrate was prepared by recombinant DNA technology with more sensitive viral markers screening test using molecular biology techniques (15).

1.2. Prevalence:

Hemophilia (A) is the commonest – hereditary coagulation disorder, however, is still rare. It accounts for 85% of hemophilias. Hemophilia (A) is a disease without ethnic or geographical limitations, the international prevalence differs as per reporting country from 5.4 – 14.5 per 100,000 male. In the US and Europe the prevalence is 20.6 per 100,000 male with annual incidence of 1 per 5000 male, with 60% of those having severe disease (16).

A study of the pattern of bleeding disorder in children in Khartoum State carried out in 2003 concluded that 50% of the bleeders were hemophiliacs (17).

1.3. Etiology, pathogenesis and classifications:

1.3.1. Etiology:

Hemophilia (A) is a heterogeneous disorder resulting from defects in factor VIII gene that leads to a reduction in the circulating level of factor VIII. The reduction in activity can be due to decreased amount of factor VIII protein, the presence of a functionally abnormal protein, or a combination of both (18).

1.3.2. Pathogenesis:

Factor VIII is synthesized in the liver and secreted into plasma, circulates in a non-covalent complex with vWF, the normal half life of factor VIII is eight to twelve hours when associated with vWF, the half-life is markedly reduced in the absence of vWF (19).

Blood coagulation normally proceeds through a series of sequential enzymatic reactions in which protein cofactors (factor V and VIII) have an essential role (20). A very low concentrations of factor VIII (0.2mg per milliter of plasma) ensures adequate procoagulant function in normal person; a substantial (>80%) reduction in or absence of the factor leads to a bleeding disorder. Factor VIII circulates in the plasma as a complex with von Willebrand factor, a property that enhances factor VIII synthesis, protects it from proteolysis, and concentrates it to the site of hemostasis (21). The role of factor VIII in hemostasis is to accelerate the cleavage of factor X by activated factor IX (Xa) associate on the surface of activated platelets to form a functional factor X-activating complex (“tenase” or “Xase”). Factor VIII cannot become part of the “tenase” complex until it is released from von Willebrand factor, because it inhibits it is binding to phospholipids surfaces (22). The subsequent separation from von Willebrand factor requires the cleavage of factor VIII light chain by thrombin or factor Xa, release of von Willebrand factor, enabling factor VIII to bind to the phospholipids surfaces of damaged cells and adherent activated platelets (23). Clot formation is delayed in patients with hemophilia because thrombin generation is markedly reduced, the clot that is formed is friable, and easily dislodged leading to excessive prolong bleeding (24).

1.3.3. Classifications:
Hemophilia A is classified according to the patient baseline level of factor VIII into severe, moderate and mild forms, with 1 unit of factor defined as the amount in 1 ml of normal plasma (25).

- Severe hemophilia is characterized by having less than 1% (1.0 m/dl) of factor VIII, usually diagnosed in the first year of life (25).
- Moderate hemophilia is characterized by having 1-5% (1-5 u/dl) of the factor; patients seldom have spontaneous bleeding, however they do have prolonged or delayed oozing after minor trauma, it is usually diagnosed before the age of five to six years (26).
- Mild hemophilia is characterized by having more than 5% (more than 5 u/dl) usually bleeds after surgery, tooth extraction, and major injuries (26).

1.4. Genetics:

Hemophilia A is an X-linked recessive disorder that occurs almost exclusively in males, about 30 percent of the mutations arise de novo (27). Factor VIII gene lies on X chromosome at q28, it is a very large gene, about 186 kb, with 9 kb of exons, mature factor VIII contains 2332 amino acids, the size and complexity of the gene made it difficult to pinpoint specific mutations that result in hemophilia. Factor VIII now has been cloned and sequenced and numerous specific mutations have been described, including re-arrangements; missense; nonsense mutations; abnormal splicing; deletions of all or portion of the gene or insertion of genetic elements (27).

One of the most common mutations, accounting for 40 to 50 percent of patient, is combined gene inversion and crossing – over that disrupt the factor VIII gene. Many of the patients with an inversion are susceptible to the development of anti-factor VIII inhibitors antibodies, most insertions result in severe hemophilia, large deletions are almost always associated with severe hemophilia (28). Some patients with factor level compatible with severe hemophilia, may exhibit mild symptoms, because of co-inheritance of factor V leiden mutation (R 50 60) with the hemophilic gene (29). Hemophilia (A) in females is extremely rare, it may occur in females with X-chromosomal abnormalities such as turner’s, X mosaicism or if a carrier mother married to affected father, a carrier female may has factor VIII level sufficiently low to cause bleeding manifestation if she has imbalanced X-inactivation. A female may also manifest the disease if an affected father marries a carrier mother (30).

1.5. Prenatal diagnosis:

Can be carried out almost routinely, if a carrier female has a fetus that can be identified as a male, by chromosomal analysis of cell obtained by amniocentesis (16th week) or by chorionic villous sampling (10th week) and DNA
analysis using Restriction Fragment length polymorphism (RFLP) or direct sequencing (24).

1.6. Diagnosis of hemophilia:

Patients with hemophilia (A) characteristically have prolonged activated partial thromboplastin time (APTT), the prothrombin time (PT), and bleeding time (BT) are normal, although minor increase in BT have been reported by some investigators (24).

The APTT may be only slightly or at the upper limb of normal, especially if factor VIII activity is at or above 20 percent of normal (24).

The APTT is corrected when, hemophilic plasma mixed with an equal volume of normal plasma and, not corrected by factor VIII deficient plasma (24). Definitive diagnosis of hemophilia A should be based on specific assay for factor VIII activity.

- Functional factor VIII coagulant activity is measured by one stage clotting assays based on APTT (31).
- Factor VIII antigen is measured by immunological assay, which still detect normal and most of abnormal factor VIII molecules (32).
- Factor VIII activity is expressed as percent of normal or as units per milliter of plasma, by definition 1 unit of factor VIII is equal to the amount in 1ml of pooled fresh normal human plasma also by definition, 1 unit of factor VIII/ml is 100 percent of normal (24).

1.7. Clinical features:

The clinical hallmarks of hemophilia (A) are joints and muscles hemorrhage, easily bruising and prolong, potentially fatal hemorrhage after trauma or surgery (people with hemophilia does not bleed faster, they bleed longer) (33). Factor VIII does not cross the placenta; thus bleeding symptoms may be present from birth or may occur in the fetus (1).

1.7.1. Hemarthrosis:

Eighty percent of hemorrhages in hemophilia occur within the joints, hinge joints are more likely to be involved than ball and sockets joints. The joints most frequently involved in decreasing order of frequency are knees, elbows, shoulders, wrists and hips, the ankles joints are more frequently involved in toddlers because of lack of stability and that toddlers assume an upright posture, in older children the knee joints are most often involved (34,35). Hemarthrosis are sometimes heralded by an aura of mild discomfort becomes progressively painful over minutes to hours, the joint becomes swollen, warm and tender with limitation of movement occasionally associated with mild fever (24). Hemophilia has been
reported as a cause of single swollen joint with no family history of bleeding tendency (36).

1.7.2. Hematomas:

Hemorrhage into subcutaneous connective tissue or into muscle with or without known trauma is characteristic of blood clotting factors deficiency. Once hematoma formed, it slowly resolves with treatment. However, in severely affected patient, it may enlarge progressively and dissect in all directions (37). Retroperitoneal hematomas have been known to dissect through the diaphragm, into the chest and into the soft tissue of the neck result in airway compromise (24). Hemorrhagic episodes in the abdomen simulate abdominal surgical emergencies, small bowel hematoma in the terminal ileum many mimic appendicitis (38, 39). Hematomas usually occur into calf, thigh, buttck and forearm in order of frequency. While most hematomas are visible, in iliopsoas bleeding, patient losses large amount of blood with only average area of referral pain in the groin, frequently with flexion hip contracture (35,37). It may present with frank femoral neuropathy when the occult bleeding impinges on the nerve root or it may present with drop in hemoglobin concentration a compartment syndrome in the brachium following venipunture in the anticubital fossa has been reported (40,41).

1.7.3. Central nervous system bleedings:

Although very rare intracranial bleeding is the most dangerous hemorrhagic event in hemophilia patients, intracranial bleeding accounted for almost 25 percent of deaths in-patient with hemophilia before the AIDS epidemics, and antecedent trauma was recognized in approximately half these patients (42, 43). Hemophilics patients with unusual headaches, hemorrhages into the brain parenchyma, subdural or epidural hematomas should always be suspected (42). Occasionally neonate with hemophilia may sustained intracranial hemorrhage, it was suggested by some authors that, the increase incidence of cerebral hemorrhage following traumatic delivery, may be due to underling bleeding disorder in some neonates and concluded by others, in any neonate of normal gestation who develops intracerebral hemorrhage should be evaluated for hemostatic disorder (44,45,46). Intra spinal bleeding especially in the form of subdural hematoma is rare but can result in paraplegia; sub- arachnoid’s hemorrhage with signs of meningial irritation and bulging fontanels has been reported (47).

1.7.4. Mucous membranes hemorrhage:

Mucous membranes hemorrhage in form of epistaxis hemoptyisis is common in hemophilia, usually precipitated by trauma or allergic reaction. Peptic ulcer disease occurs about five times more frequently in adult hemophilic population than in the general population (48). Hematemesis is virtually rare presenting symptoms of hemostatic disorders, but hemostatic disorders may exacerbate hematemesis due to anatomic abnormalities; it may be precipitated by ingestion of NSAID. Repeated episodes of melena may occur with hemostatic disorder (49).

1.7.5. Hematuria:

Hematurea is very rare if ever, a presenting symptom of hemostatic disorder, while virtually all severely affected patients with hemophilia experience episodes of hematuria (24).
1.7.6. Dental bleeding:

Loss of deciduous teeth is seldom the cause of excessive bleeding, but extraction of permanent teeth may result in excessive hemorrhage that can persist for several days or weeks if untreated, mild to moderate hemophilia may present first time after dental extraction (24).

1.7.7. Circumcision:

Thirty percent of severe type do not bleed excessively following circumcision and most mild hemophiliacs completely escape excessive bleeding, even with circumcision (50).

1.7.8. Umbilical stump bleeding:

Umbilical stump bleeding is a feature of fibrinogen stabilizing factor deficiency (51).

1.8. Complications of Hemophilia (A):

1.8.1. Chronic arthropathy:

Historically, chronic arthropathy is the major long-term disability of hemophilia A, after joints hemorrhage, proteolytic enzymes are released by (WBC) into the joint space and heme iron induces macrophage proliferation, all of which contribute to inflammation in the synovium. The synovium thickens and develops frond like projections into the joint, these are susceptible for being pinched, and may induce further hemorrhage. The cartilaginous surface become eroded and even exposes raw bone, leaving the joint susceptible to articular fusion (52). When the child first bleeds from a joint, the joint is elastic and can accommodate a large amount of blood so that the swelling is more than the pain. In contrast with advanced arthropathy, there is little space for bleeding giving rise to pain much greater than the swelling of the joint, which is known as the target joint, became target for repeated bleeding and later arthritic (53).

1.8.2. Pseudo tumors (Blood cysts):

Pseudo tumors are blood cyst that occur in soft tissues or bone, they one rare but dangerous complication of hemophilia, they tend to increase in frequency because of improved therapeutic measures and increased life longevity of hemophiliacs (54). Most pseudo tumors are not associated with pain unless there is rapid growth or nerve compression. They have tendency to increase over a period of several years, eventually become multiloculated, they may erode the surrounding tissues or penetrate into the viscera (24).

Pseudo tumors develop primarily in the lower half of the body, usually in the thigh, buttock, or pelvis, but may occur anywhere, pseudo tumor of the temporal bone and the mandible has been reported (55).

1.8.3. Growth and development:

Children with moderate to severe hemophilia have low neuropsychological performance, attributable to the deleterious effect of chronic illness, those with an
abnormal physical growth or those with delayed pubertal development were HIV positive (56).

1.8.4. Transfusion transmitted diseases:

This has been dramatically reduced by the use of heat-treated, immunopurified and chemically treated plasma derived products up to 1980s (HIV) infection devastate hemophilic patients, chronic hepatitis C and B remain a problem for many older patients. Parvovirus and hepatitis A are non-enveloped viruses, which may escape solvent detergent and heat treatment, so plasma derived produce may continue to transmit these infectious agents (57).

Transmission of prions, which are infectious agents devoid of a nucleic acid genome, by blood products has been suggested, although no conclusive data are available. Prions are resistant to all currently available viral inactivation techniques. Prions are responsible for several neurodegenerative disorders including Creutzfeldt – Jacob Disease (CJD) in humans, especially the new variant (58, 59).

1.8.5. CD4+ T-lymphocytopenia:

An AIDS like syndrome has been reported in patients with hemophilia, with CD4 + T-lymphocytopenia unexplained opportunistic infections without evidence of HIV of infection, whether the disease is transmissible or not is debatable (60).

1.8.6. Factor VIII inhibitors:

These specific inhibitor antibodies (IgG4) neutralize factor VIII (61). There is current debate about the time frequency of anti factor VIII inhibitors in severe hemophilia A patients, they occur at a young age (<50% by 10 yrs). However, in one study the frequency of inhibitors in a large groups of patients after 18 years of follow up, was 20% (62).

The presence of inhibitors can be suspected on clinical grounds, as when a patient does not respond to conventional doses of factor VIII (63).

1.8.7. Psychological:

Chronic illness has a pervasive influence on a child’s daily life, the frequent interactions with the medical care system, occasional hospitalization, and greater dependence on the parents and health care providers characterize their lives. This may create a series of (different ness) of being unable to do things that other children can do (64).

Chronic illnesses create additional stresses and demands on families and children. Children with hemophilia have frequent psychological and behavioral problems than normal population, and the level of severity correlate poorly with psychological status (65). Approximately 25% of children with severe hemophilia aged
6-18 yrs exhibit below normal performance in regards to their cognitive skills and have a more emotional and behavioral problem\(^{(16)}\).

1.9. Management:

1.9.1. General management:

1.9.1.1. Genetic counseling:

A skill of communicating complex medical information to families is an important part of counseling, explaining the mode of inheritance, the risk of transmission of the disease, and its nature\(^{(67)}\). The biggest challenge of genetic counseling is helping families to cope with the emotional, psychological, medical, and economic consequences of the disease\(^{(68)}\).

1.9.1.2. Child activity:

As infants begin to become mobile, all items around must be safe. Toddlers fall a lot and they should be observed for any pain or discomfort, which may indicate bleeding in a joint or a muscle\(^{(69)}\). A critical part of every child development is playing, but contact sports such as football are strongly discouraged, socialization and active participation should be encouraged. Early psychological intervention helps families to achieve a balance between over protection and permissiveness\(^{(69)}\).

1.9.1.3. Drugs:

The general principle is to avoid use of aspirin, non-steroidal anti-inflammatory drugs, and other agents that interfere with platelets aggregation. There are, however, exceptions to this rule\(^{(24)}\).

1.9.1.4. School environments:

The school years are especially stressful to parents and teachers. It is the parent’s responsibility to inform the school of the child diagnosis\(^{(70)}\). Shapiro and others studied the academic achievement in children with hemophilia and they concluded that there is an association between the number of bleeding episodes and academic achievement\(^{(70)}\).

1.9.1.5. Circumcision:

As a traditional procedure, is an important ritual for Muslims and Jewish. It is a social problem for all patients with bleeding disorders\(^{(71)}\). Kavin and others evaluate the psychosocial dimensions of circumcision on the opinion of the parents and children. They founded that 94% of parents want circumcision for their children and look at it as a mandatory procedure. Moreover, 82% of the parents and 60% of the patients have an inferiority complex if not performed. They concluded that circumcision is an important social problem that must be solved\(^{(71)}\).

1.9.1.6. Intramuscular vaccines:
These are of great risk to hemophiliacs in severe hemophilia all intramuscular vaccines should be given by a subcutaneous route, hemophiliacs should receive hepatitis B vaccine, an accelerated schedule, followed by a booster dose is recommended to obtain an early, more persistent immunity (72, 73).

1.9.2. Specific management:

1.9.2.1. Factor VIII replacement therapy:

Either can achieve this:

- Fresh frozen plasma, but large amount is needed and only 20% of factor level. Can be achieved as maximum and this is not sufficient always for hemostasis.

- Cryoprecipitate, when used can achieved normal factor level, but the dose cannot be adjusted (70).

Plasma derived factor VIII concentration (human), porcine factor VIII or recombinant factor VIII is preferred (1). The site and severity of hemorrhage determine the frequency and the dose of factor VIII to be infused. The dose is given according to the formula, dose of factor VIII = [desired rise in plasma F VIII (u/dl “%”) x body wt in kilograms x 0.5 (unit dl)] (1).

The desired level of factor VIII depend on the site and severity of hemorrhage, it should be corrected up to 100% for potentially serious hemorrhage such as CNS hemorrhage, and up to 15 – 20% of normal for minor bleeding (1). Continuous infusion of factor VIII by pump devices may be considered for severe hemorrhage (74).

1.9.2.1.1. Treatment of minor or moderate hemorrhage:

Superficial cuts and abrasion are managed with local measures, i.e., application of pressure (24). In non-persistant, uncomplicated hematuria patients should be instructed to drink large quantity of fluid, gross hematurea may require replacement therapy, and, in these patients, factor VIII level should be raised at least to 50% of normal and should be continued until it resolved (24). For hemarthrosis and superficial intramuscular hematomas, the desired factor level is 30 – 50% of normal every twelve hours for 1– 2 days (24). In gastrointestinal hemorrhage, the desired factor VIII level is 50% every 12 hours for 7 – 10 days and in epistaxis and oral mucosal bleeding the desired level is 30 – 50 percent of normal every 12 hours until it resolved (24).

1.9.2.1.2. Treatment of major non-surgical hemorrhage:

Immediate administration of factor VIII, sufficient to raise factor VIII level to normal, should be started with the first signs of intracranial hemorrhage or following history of head trauma, even asymptomatic patients with history of head trauma should receive at least one close of factor VIII as a prophylactic measure and this should be given before diagnostic procedure (24).

1.9.2.1.3. Replacement of factor VIII for surgical procedure:

For major surgical procedures, factor VIII should be raised to normal, and maintained for 7 to 10 days or until healing (74).
1.9.2.1.4. Prophylaxis:

1.9.2.1.4.1. Primary prophylaxis:

Prophylaxis or the routine scheduled replacement of clotting factor concentrate, often given to children with severe hemophilia, usually three doses a week, 25 I.U/kg/dose, to maintain factor VIII activity above one percent (75). This was found to prevent spontaneous bleeding, decrease the number of bleeding episodes, almost eliminate joint bleeding, and decrease chronic joint disease. Controversies still exist as to whether all severe hemophiliacs would benefit from primary prophylaxis, and whether the benefits justify the risk of a venous access device and the cost. Although safe, effective factor concentrate are far too expensive for the health systems in many countries. About risk of inhibitors, Oxford hemophilia center stated that, there is no evidence that prophylaxis treatment is associated with an increase incidence of inhibitors and the high cost is the major obstacle to its implementation in developing countries (76, 77, 78).

1.9.2.1.4.2. Secondary prophylaxis:

The term secondary prophylaxis “periodic prophylaxis”, is used for Scheduled replacement of factor VIII when delayed after the development of frequent bleeding. This therapeutic alternative has been less expensive than the primary prophylaxis. Secondary prophylaxis was studied in Sweden, Netherlands, the UK, and the US. These studies have demonstrated, reduction in the frequency of bleeding episodes and subsequent low incidence of arthropathy, reduced hospitalization and missed school days, improved physical function and capacity of self care, reduce pain and enhance quality of life, however, secondary prophylaxis is associated with an increased risk of, and eventual development of arthropathy compared with primary prophylaxis. It is recommended alternative for severe hemophiliacs not receiving primary prophylaxis (79).

Secondary prophylaxis also recommended for patient with chronic synovitis and for bleeding into (Target) joint, daily administration of factor VIII, raising the level to 100% of normal for 6 to 8 weeks (24).

1.9.2.1.5. Home therapy:

Home therapy using available factor VIII was introduced in USA in 1977, and represents a major advance in the treatment of all forms of hemophilia (80). The prompt treatment of hemarthrosis and hematomas made possible by home therapy, result in a marked improvement in morbidity and mortality associated with hemophilia. In addition, the quality of life was dramatically improved (81).

1.9.2.2. DDAVP (1,8 – DESAMINO – D- Arginine vasopressin, Desmopressin).

Started in 1970 for the treatment of mild to moderate hemophilia, patients with severe hemophilia does not respond (82). Intra venous preparation (a dose of 0.3 microgram/Kg- peak 30-60 minutes) and intra nasal spray (150 mg in each nostril) are
available. DDAVP increases factor VIII two to three folds above base line in most mild to moderate hemophilia through unknown mechanism, the problems of DDAVP is that with repeated administration result in diminished response to the agent (tachyphlaxis), hyponatremia may occur\(^{(83,24)}\).

### 1.9.2.3. Antifibrinolytic agents:

Antifibrinolytic agent e.g., epsilon aminocaproic acid (EACA) and tranexamic acid, have been used to enhance hemostasis in patients with hemophilia (A)\(^{(84,89)}\). Fibrinolytic inhibitors may be given as adjunctive therapy for bleeding from mucous membranes particularly valuable for dental procedures, antifibrinolytic therapy are contraindicated in the presence of hematuria\(^{(24)}\).

### 1.9.2.4. Fibrin Glue:

Fibrin tissue adhesive has been used as adjunctive therapy to factor VIII in hemophilic patients\(^{(86)}\). It contains fibrinogen, thrombin and factor XIII and calcium; it is especially useful for hemostasis in patients undergoing dental surgery, with pre-extraction bolus of factor VIII followed by application of fibrin glue to the teeth sockets. It is also used following circumcision\(^{(24)}\).

### 1.9.2.5. Pain control:

Ibuprofen was considered as safe as beneficial anti-inflammatory agent in the treatment of hemophilic arthropathy with benefit of relieving pain and early morning stiffness, recent studies showed safety of salicylates\(^{(87,88)}\).

### 1.9.2.6. Refractory epistaxis:

Refractory epistaxis, defined as children with recurrent epistaxis despite appropriate intravenous therapy and DDVP. An antihistamine “loratidine” which decrease vascular permeability as well as induce vasoconstriction, was used to decrease the episodes of bleeding\(^{(46)}\).

### 1.9.3. Management strategies:

Internationally, there is a growing consensus for primary prophylaxis for severe hemophilia as opposed to on “demand therapy” (administration of the factor after episodes of bleeding) in order to preclude end stage, crippling arthropathy. With respect to the treatment hemophilic patients received, 80% of all hemophiliacs worldwide are not receiving regular therapy, an estimated 19% are receiving “on demand” therapy, and only 1% are receiving primary prophylaxis. The selected prophylactic dose of 25 units per kilogram body weight was effective in preventing bleeding episodes and maintaining factor VIII plasma level above 2% in severe hemophiliacs\(^{(46)}\).

In Sweden, they infuse only once a week prophylactically in the first two years of life\(^{(46)}\). In South Africa, a study carried out in Western Cape showed that 73% of hemophiliacs receive on demand therapy, 20% for periodic prophylaxis (secondary prophylaxis), and 7% as a continuous prophylaxis\(^{(89)}\). In New Zealand, children with severe hemophilia are predominately treated with recombinant products on regular prophylaxis\(^{(90)}\). In United States, approximately half of children with severe hemophilia A are on prophylaxis regimen\(^{(91)}\). In Australia, the main treatment was on
demand therapy for acute bleeds; prophylactic therapy was used in only 7% of severe hemophiliacs\(^{(92)}\). In Tunisia, cryoprecipitate is the principal type of factor VIII concentrate used for treating hemophilia (A)\(^{(93)}\).

### 1.9.4. Clinical trials:

**Danazol:** Is an attenuated androgen, showed by controlled clinical trials in adult that it raises factor VIII concentration to five folds\(^{(94)}\).

**Methylprednisilone:** Intra-articular methylprednisilone (IAMP) was been evaluated as effective medical treatment for chronic hemophilic synovitis of the knee, even with radiographic signs of arthropathy\(^{(95)}\).

**D-penicillamine:** Preliminary studies suggested that D-penicillamine is beneficial in the treatment of chronic synovitis/ arthritis induced by hemarthrosis\(^{(96)}\).

**Transplantation of spleen cells:** It has been reported that beside liver, factor VIII is produced in the spleen and other organs, transplantation of splenic whole organ or spleen cell may, therefore, be used to treat patients with hemophilia (A). Clinical trials indicate that transplantation of splenic cells may be promising method for management of patients with hemophilia (A)\(^{(97)}\).

### 1.9.5. Gene therapy:

Hemophilia A considered as a best disease for gene therapy, because a single defective gene causes it, and only small increase in the missing factor provides good result\(^{(98)}\). Although gene therapy could potentially correct the defect in hemophilic individual, not in their genetic line, and they still pass hemophilia to their descendants. Treatment that could correct the defect in all cells is germ line therapy, which would have to be done at the embryo stage of conception. Many ethical considerations will need to be addressed before germ line therapy is attempted. For the present, gene therapy should be seen as a potential improvement option and not as a cure for hemophilia\(^{(98,99)}\). The most obvious benefit of gene therapy is that, hemophiliacs would no longer have frequent infusion of factor concentrate, and rehabilitation of muscles and joints could be undertaken without fear of causing bleeding\(^{(98)}\).

The experiment evaluated gene therapy in six patients with severe hemophilia. After four months, the amount of clotting substance in the blood was increased in four out of the six patients. However, ten months later the clotting substance was no longer in the patients’ blood. It is not clear if the implanted cells died or the added gene had stopped working\(^{(99)}\).

Yarovoi and colleagues engineered platelets to express F VIII, which was released from alpha granules and led to homeostasis at the site of injury\(^{(100)}\).

### 1.10. Management related complications
1.10.1. Viral hepatitis

1.10.1.1 Hepatitis B viral infection:

Hepatitis B virus (HBV) can cause acute and chronic liver disease in children. Age at the time of acquisition of primary HBV infection is a major determinant of chronicity, chronic infection with HBV related inversely to the age at the time infection occurs. The average time to onset of clinical liver disease following infection may range from 10-40 years. Many (HBV) carrier children, therefore, may not be brought to medical Attention for counseling and anticipating guidance in timely fashion\(^{(101)}\).

1.10.1.1.1. Epidemiology of HBV infection in children

HBV has been detected in all body fluids and secretions except for stool. Blood and serum contain the highest concentrations of virus. Transmission usually occurs parentally, through the exchange of blood or other body secretions or fluids.

Only the infectious property of blood, semen, vaginal secretions, and saliva has been demonstrated clearly. HBV is not transmitted by the fecal-oral route.
Modes of HBV transmission to children can be categorized broadly into perinatal or vertical transmission from mother to child at childbirth horizontal transmission through contact with and infected person’s blood, saliva, skin wounds, or abrasions. Sexual intimacy and paranteral transmission through exposure to blood products or other infective fluid the latter is now of historic interest only\(^{102-105}\).

### 1.10.1.1.2 Geographic variability:

The prevalence of HBV infection and the modes of transmission vary considerably in different geographic parts of the world. Countries are classified as low endemicity (less than 2% of the general population positive for HBsAg), intermediate endemicity (2-8% positive for HBsAg), and high endemicity (greater than 8% positive for HBsAg)\(^{101}\). In North America and Europe a carrier rate between 0.1% and 0.3 %\(^{105}\). In Southeast Asia, China, Taiwan, Sub-Saharan Africa and some countries of Eastern Europe, sizable pools of HBsAg carriers were traditionally present, accounting for 15% to 20% of the general population\(^{101}\).

### 1.10.1.1.4. Virology
The structure of HBV is now well known. The complete virus (HBV particle) is a 42-nm spherical particle. This particle has an outer coat consisting of the surface antigen (HBsAg) that cover an inner coat made of the core antigen (HBcAg). The two envelopes contain the viral genome, a double-stranded DNA made up of 3200 bases with single-stranded gap of 600 to 1200 nucleotides. The DNA of HBV has four open-reading frames these are the 5 gene, coding for an envelope protein carrying HBsAg, the C gene, coding for a nucleocapside protein bearing hepatitis B core antigen, the P gene, coding for DNA polymerase and the X gene coding for a protein with a transcriptional trans-activating function.\(^{105}\)

1.10.1.1.5. Serologic markers

Serologic and tissue markers are identical, since all the antigens detectable in serum may be demonstrated in tissue by immunofluorescent or enzymatic techniques\(^{105}\).

The presence of anti HBc antibodies for the IgM class is indicative of recent infection. The antigen was described it presence corresponds to active viral replication. Seroconversion from e-antigen (HBeAg) to anti e antibody (HBeAb) indicates the end of the viral replication and of the period of infectivity. All these serologic markers are now detectable with commercial RIA or ELISA kits\(^{105}\).

The DNA itself is used both as serologic and tissue marker of infection. HBV DNA in serum is the most reliable marker of active viral replication and infectivity\(^{105}\). HBsAg is first detectable about 4 weeks before the clinical onset. HBsAg usually persists 2 to 4 month and anti HBsAg appears and indicates recovery\(^{105}\).
In chronic carriers HBsAg persists, an e antigen may be replaced by e-antibody, two types of chronic carriers have been described. The first is characterized by evidence of active viral replication. HBeAg and viral DNA are detectable in serum. In the second, there is absence of viral replication, anti-HBe is present, and no viral DNA is detectable\(^{(105)}\).

1.10.1.1.6. Clinical feature and serologic course:

The clinical course of acute HBV infection typically can be divided into three distinct phases, the incubation (prodromal) phase, the symptomatic (icteric) phase, and the convalescence (recovery) phase, with typical serologic profile. There exist non-hepatic clinical conditions that are associated with HBV infection and seem to be immunologically mediated, secondary to circulating immune complexes composed of HBsAg and anti HBsAg such as Membranous nephropathy, vasculitic syndromes and papular acrodermatitis of childhood\(^{(101,106)}\).

1.10.1.1.7. Treatment of HBV infection:

The goal of an effective treatment is interruption of disease evolution as evidenced with serologic, biochemical and histological remission\(^{(101)}\).

1.10.1.1.7.1. Interferon therapy;
Interferon -α- 2b (IFN) is a recombinant interferon with antiviral anti-tumor, and immunomodulatory properties. IFN has been approved in the treatment of chronic HBV in children\(^{(101)}\).

1.10.1.1.7.2. Newer therapies:

Lamivudine and famciclovir. Lamivudine is an oral nucleoside analogue, which is a reverse transcriptase inhibitor with fewer side effects as compared to interferon. Lamivudine has been studied in a wide variety of patients with HBV and it had durable response\(^{(107,108,109)}\).

1.10.1.1.8. Prevention of HBV:

1.10.1.1.8.1. Institution of proper hygienic measures:

General infection controls procedures directed against biological hazards (universal precaution, hand washing, sterilization and disinfection of non-disposable medical equipment) and increased educational effort. HBV has been reduced by careful screening and selection of blood donors\(^{(101)}\).

1.10.1.1.8.2. Hepatitis B vaccine:
Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) are available for prevention of HBV infection. Two recombinant DNA vaccines are available in United States\textsuperscript{(105)}. A universal immunization of all infants with HB vaccine is recommended in both pre-exposure, post exposure situations, and provides long-term protection\textsuperscript{(105)}.

1.10.1.2. Hepatitis C viral infection:

Surveys for hepatitis C infection indicate that this infection is clearly related to transfusion practice and geographic endemicity and that chronic hepatitis mirrors the frequency in the general population\textsuperscript{(110)}. In general population fulminant hepatitis is unusual, but as many as 65\% will develop chronic hepatitis and cirrhosis. Chronic hepatitis is subtle with only 25\% of patients having AST/ALT as high as twice normal\textsuperscript{(111)}.

Persistent elevation of AST/ALT, positive PCR for viral RNA are indication for treatment with interferon plus ribavirin\textsuperscript{(111)}.

Sakran studied the prevalence of hepatitis (C) among children at high risk, including hemophiliacs, 50\% of hemophiliacs were positive, most of them above 13 year\textsuperscript{(112)}.

1.10.2. HIV infection:

1.10.2.1. Epidemiology of HIV infection:

The world health organization has estimated that 2 million children had been infected with human immunodeficiency virus (HIV) by the year 2000.

The prevalence of HIV infection in Asia and Europe varies considerably because of varied cultural practices in the area\textsuperscript{(113)}. In Africa, more than 3 millions cumulative HIV infections had been reported in the pediatric population through January 1996, with more than 400,000 new HIV infections annually in children, 67\% of whom are from sub Saharan Africa\textsuperscript{(113)}. In 1984, the centers for disease control amounted that, between the years 1979 and 1942, 90\% of patients with hemophilia who were treated with clotting factor concentrates had been infection with the (HIV)\textsuperscript{(114)}.

1.10.2.2. Mode of transmission:

HIV may be transmitted by sexual contact with an infected partner, by paranteral drugs use with a contaminated needle, by exposure to infected blood or blood products, and by perinatal exposure from an infected mother to an infant, which is the main route by which childhood infection is acquired\textsuperscript{(24)}.

1.10.2.2.1. Transmission through infected blood products:
The risk of HIV after receiving 1 unit of infected blood approximates 90 percent\(^\text{(115)}\). Transfusion of blood products derived from multiple units of pooled blood can also transmit HIV and accounted for the initially high prevalence of HIV infection among patient with hemophilia. Currently, the risk of acquiring HIV through receipt of a unit of blood that tests negative for antibodies a HIV-1 is approximately in 493,000\(^\text{(116)}\). Blood transfusion contributes to 10% - 15% for HIV transmission in Africa\(^\text{(117)}\).

\textbf{1.10.2.3. Virology:}

HIV is a retrovirus that exhibits a variety of structural and nonstructural proteins that determine the interaction of the virus with the host’s immune system and cellular components\(^\text{(113)}\). HIV-1 has three structural genes necessary for replication: GAG, POL and GNV\(^\text{(118)}\). These viral genes encode proteins, which required for binding to the host cells, intracellular synthesis of protein by reverse transcriptase, and viral assembly and release\(^\text{(119)}\).

The HIV virus attaches to the host cell by the association of a surface glycol-protein to the CD4 molecule; therefore, it primarily infects CD4+ lymphocytes and macrophages\(^\text{(113)}\). Once the virus core enters the cell cytoplasm of the host, viral reverse transcriptase copies viral RNA to DNA of the host. The viral DNA is transported to the nucleus and incorporated into the DNA of that cell. If activated, viral expression can result in new viral RNA and proteins\(^\text{(113)}\). HIV infection results in aberrant immune regulation and immunodeficiency.

The defects in immune response include, decrease lymphocytes proliferation to soluble antigens, decrease helper response in immunoglobulin synthesis, decreased interferon – y production, and decreased T-cell mediated cytotoxicity of the infected cells and progressive loss of CD4 posture (CD+) T lymphocytes\(^\text{120-123}\).

\textbf{1.10.2.4. Clinical features:}

The presentation of the disease include recurrent bacterial infections, unrelenting fever, unrelenting diarrhea, unrelenting thrush, recurrent pneumonia, chronic parotitis, generalized lymphadenopathy, delay in development with failure to thrive, and significant pruritic dermatoses and Muco-cutaneous eruption\(^\text{113}\).

\textbf{1.10.2.5. Serological markers:}

The laboratory markers of the acute retroviral syndrome are non-specific during the acute illness the HIV viremia can be detected by molecular methods such as reverse transcriptase polymerase chain reaction (RT-PCR)\(^\text{124}\).

The primary diagnostic screening tool is detection of antibodies via the enzyme- Linked immunoassay (ELISA), positive results are not specific for HIV-1 infection, immunoblotting HIV-1 antigens, should verify positive results\(^\text{124}\).

By ELISA and immunoblot techniques, the median time from initial infection to first detection of the antibodies has been estimated to be 2-4 months, white 95 percent of HIV of cases are expected to seroconvert within 5.8 months\(^\text{124}\).

The presence of the P24 antigen or HIV RNA in serum or plasma may precede seroconversion by several weeks with initial rise of P24 antigen correlates with the burst of viremia\(^\text{125}\).

\textbf{1.10.2.6. Treatment:}
The preferred regimen is combination therapy with two nucleoside reverse transcriptase inhibitors (Zidovudine (AZT), Lamivudine (Thymidine analogues)) plus one protease inhibitors (Ritonavir) and (Nelfinavir)\(^{(113)}\).

### 1.10.3. Factor VIII inhibitors:

Other than the transmission of viral diseases by factor VIII infusions, the main complication of hemophilia A is the development of specific inhibitor antibodies that neutralized factor VIII\(^{(116)}\). This complication occurs in approximately 30% of patients with severe hemophilia A; these inhibitors sharply reduce the haemostatic effects of F VIII concentrate, resulting in an increase morbidity and resource utilization with a significantly increased dosage compared to patients without inhibitors\(^{(127)}\).

#### 1.10.3.1. Nature of factor VIII inhibitors:

Factor VIII inhibitors antibodies most often of the IgG class and frequently restricted to the IgG4 subclass. Antibodies against the A2 and C domains of factor VIII are most common. These antibodies interfere with the interaction of factor VIII with its cofactors and activators\(^{(128)}\).

#### 1.10.3.2. Risk factors for the development of inhibitors:

- Disease severity: 80% hemophilia A patients with inhibitors have < 1% factor VIII activity.
- Exposure to factor VIII concentrates: The majority of high titer inhibitors develop after > 90 days of exposure to factor VIII.
- Genetic factors:
  - Family history of inhibitors development.
  - Negative correlation with HLA CWS antigen.
  - Molecular defects: The inversion and crossing-over defect in intron 22, gene deletions, and nonsense point mutations resulting in patients without factor VIII antigen.
- Methods of purification of factor VIII concentrates. At least one outbreak of inhibitors appeared to be related to treatment with specific plasma – derived factor VIII product of intermediate purity\(^{(129)}\).

#### 1.10.3.3. Diagnosis of factor VIII inhibitors:
The presence of inhibitors can be suspected on clinical grounds, as, for example, when a patient does not respond to conventional doses of factor VIII (24).

Factor VIII inhibitors are time and temperature dependent. Screening for inhibitors by correction method, the prolong APTT of the patient plasma does not correct by normal plasma after incubation at 37°C for 1 to 2 hours (130). Confirmation is by Bethesda Assay, in which the patient’s plasma is diluted to a point that, when mixed with an equal volume of normal pooled human plasma and incubated for 2 hours will decrease the factor activity in the mixture by 50 percent (130). A modification of the Bethesda Assay is the Nijmegen assay in which the PH of the sample over the 2 hours period of incubation is controlled (131).

1.10.3.4. Management of patients with inhibitors:

There are several approaches to the treatment of factor VIII inhibitors depending on whether the patient with an inhibitors is “high” or “low” responder and whether the bleeding episode requiring treatment is considered minor or major (132).

1.10.3.4.1. High – responders’ patients:

By definition, high responder patients are those patients whose inhibitor titer is more than 10 Bethesda units (Bu) at base line, or whose inhibitor titer rise to great than 10 Bu after administration of factor VIII. High responders’ patients constitute 60 percent of patients with factor VIII inhibitors (24).

High responders with initial titer is < 10 Bu with major bleeding episodes should be treated with either human or porcine factor VIII in a dose sufficient to neutralize the inhibitor and to attain adequate factor VIII level for hemostasis (24).

High responders’ patients whose initial inhibitor is less than 10Bu and who experience a minor bleeding episode, the agent of choice would be factor VIII inhibitor-bypassing agents ((Recombinant factor VIIa, activated or inactivated prothrombin complex concentrates)). Factor VIII should be avoided in most instances in view of an anamnestic response of the inhibitor to factor VIII (24).

High responders’ patients whose initial inhibitor titer is greater than 10 Bu with major or minor bleeding episode, recombinant factor VIIa is considered to be the treatment of choice, activated or inactivated prothrombin complex may be used (24).

1.10.3.4.2. Low – responders’ patients:

Low-responders patients are defined as those whose inhibitor titer is less than 10 Bu even after challenge with factor VIII. For major bleeding episode, high doses of human factor VIII or porcine factor VIII may be used for minor bleeds, recombinant factor VIIa; prothrombin complex concentrates are recommended (24).

1.10.3.4.3. Factor VIII inhibitor bypassing agents:

Prothrombin complex concentrates:

Prothrombin complex concentrates contain variable amount of activated factors, including factor VIIa, IXa, and Xa it is postulated that they bypass the inhibitor by enhancing the tissue factor VIIa pathway of coagulation (24).

Recombinant factor VIIa:
Is the most effective factor VIII inhibitor-bypassing agents, it acts by activating factor X on the surface of activated platelets in the absence of tissue factor. Factor Xa can then associate with factor Va and converts prothrombin to thrombin, recombinant factor VIIa has a potential to down regulate fibrinolysis via activation of thrombin activatable fibrinolysis inhibitor (TAFI) in vitro studies \(^{(133,134,135)}\).

1.10.3.4.4. Immune-suppression:

This is a new approach for treatment of factor VIII inhibitor, by removal of the antibody by plasmapharesis, adsorption of the antibody or an affinity column during plasma exchange and administration of intravenous gamma globulins \(^{(136)}\). A combination of cyclophosphamide, daily administration of factor VIII; and intravenous gamma globulin showed promising results \(^{(137)}\).

1.10.3.4.5. Immune tolerance:

The most promising approach although costly. The basis of this approach is to administer daily doses of factor VIII until the inhibitor titer is undetectable \(^{(138)}\). There are different protocols for tolerizing therapy. Factor VIII inhibitor bypassing agents are used for acute bleeds that occur during immune tolerance induction (ITI). ITI showed efficacy rate ranging from 63% to 83% in most series \(^{(139)}\).

1.11. Outcome and prognosis:

After the advent of factor VIII concentrates in the 1960s, there was a significant reduction in the morbidity and mortality from bleeding in hemophilia, at least until the (AIDS) crises that had began in the late 1970s until 1985\(^{(140)}\). The most majority of severely affected patients infected with HIV before the era of viral inactivation technique. Chronic liver disease in hemophilic patients resulting from transfusion – related hepatitis B and C, may be accelerated by HIV infection and by the associated hepatotoxicity of antiviral drug therapy \(^{(141)}\). Fortunately, patients treated after 1985 can expect to have virtually normal life spans. Overall, the mortality rate for patients with hemophilia is twice that of the healthy male population, for severe hemophilia the rate is 4-6 times higher. If hepatitis, AIDS, and cirrhosis were excluded thee overall mortality rate of patients with severe hemophilia is 1.2 times that of the healthy male population. The life expectancy of patient with inhibitors is only slightly higher than the life expectancy of people with non-inhibitors group. Fewer patients with inhibitors have seroconversion for HIV \(^{(146)}\).

1.12. Similar studies:

In the Unites States, a study carried out in 1993, the infection rates of hepatitis B was 7% and 9.5% per annum in two different periods, despite screening of individual blood donation for HBsAg \(^{(142)}\). While in another study in the state of Georgia, no child below ten was positive to neither hepatitis nor HIV \(^{(143)}\). In India seroprevalence of HIV among hemophiliacs was 3.8%, with lowest age 8yrs, and 6% for hepatitis B, hepatitis C was 23.9%. While in another study, the prevalence of inhibitors was 8.2% \(^{(144,145)}\). In Turkey the incidence of hepatitis B among hemophiliacs children was 26.8%, HBc 24.4%, the incidence of inhibitors was comparable to the international \(^{(146)}\). In Senegal, Dakar city, severe hemophiliacs account for 4%, moderate 40% and mild was 56% of hemophiliacs. The inhibitor
prevalence was 12%, hepatitis B was 7.4%, and HIV was 4% \(^{(147,148)}\). In Tunisia, the prevalence of inhibitor in one study was 27\% \(^{(93)}\).

### 1.13. Justifications and objectives:

#### 1.13.1. Justifications:

- Hemophilia is the commonest hereditary coagulation disorder, which has a significant morbidity and impact on the patients, their families and health services.
- Children with hemophilia (A) are at risk group for blood – borne infections.
1.13.2. Objectives:

1. To determine the clinical picture of hemophilia (A) in children.
2. To study the complications of hemophilia (A) & management-related complications.
3. To evaluate the existing practice of management and comparing it to the international trends.

Chapter Two

Material and Methods

2.1. Study Design:

This is a descriptive cross-sectional hospital based study.

2.2. Study Area:

- Khartoum Teaching Hospital, Central Blood Bank, Hemophilia Clinic
- Pediatric wards in Khartoum State Hospitals.
2.3. **Study Period:**

The study was conducted during the period from December 1st 2003 to 20th June 2004.

2.4. **Study Population:**

2.4.1. **Patients:**

Confirmed hemophilia (A) cases (Factor VIII level < 40 percent).

2.4.2. **Inclusion criteria:**

All children age 0 up to 16 year who were diagnosed as having hemophilia (A) by factor (VIII) assay were included in this study.

2.4.3. **Sampling and sample size:**

- The data was collected during 6 months period, six days a week “Full coverage”, the sample obtained was 71 patients.

The sample size was 49 patients according to the formula.

\[
   n = \frac{z^2 \times (p^2)}{d^2}
\]

- \( n \) = Sample size
- \( z \) = Statistical certainty (1.96 at 95% level of confidence)
- \( p \) = Prevalence (0.01 – 0.02%)
- \( q \) = Probability of failure (1-p)
- \( d \) = Desired margin of error (0.05)

Two to minimize the error multiplied the sample size.

2.5. **Ethical consideration:**

- Verbal consent was obtained from, the doctors in charge of hemophilia (A) patients, child and/or his parents or guardians.

- Verbal consent from, the head of the Sudanese Association for Blood Transfusion Services, the head of the Diagnostic and Research Laboratory in Khartoum Teaching Hospital.

2.6. **Research team:**

The research team was composed of:

- Author.

- Lab technician.
2.7. **Input of the author:**

1. Fill the questionnaires.
2. Perform full physical examination of the patients.
3. Collect the blood samples.

2.8. **Study techniques and tools:**

2.8.1. **Questionnaires:**

Complete detailed questionnaire was completed for all subjects.

This provided an account of personal, social, medical history, age at presentation, age at diagnosis, number of blood transfusion or blood derived products, number of factor VIII administered and orthopedics care.

Clinical examination was conducted; pallor, jaundice, signs of bleeding, signs of joints and central nervous system complications, signs of chronic liver disease, and signs of opportunistic infection as well as anthropometric measurement, weight using bathroom scale and height using tape were recorded.

2.8.2. **Blood sampling:**

Sterile disposable syringes labeled for each case were used to collect 6 mls venous blood. 2.5 ml were poured in a citrated tube (3.8%), and taken immediately to the laboratory for processing and analysis.

The remaining 3.5 ml, were left in the syringes to clot, then transferred to the laboratory where it was centrifuged and the serum separated. The serum was stored frozen until further analysis.

2.8.3. **Principles of the tests:**

2.8.3.1. **Hepatitis (B):**

Hepatitis kits were used in this study, from AniLabsystems Ltd, Finland. The principle of the Ani Labsystem’ HBsAg EIA plus (third generation EIA) is based on a direct, non-competitive solid phase enzyme immunoassay with horseradish peroxidase as a marker enzyme. The assay proceed according to the following reactions.

1. When present in the patient serum, HBsAg will combine with the mouse, monoclonal anti-HBs attached to polystyrene surface of the microstrips, and
simultaneously bind to with the horseradish peroxidase conjugated sheep poly-
and mouse monoclonal anti-HBs.

2. Wells are washed and a colorless enzyme substrate (hydrogen peroxide) and
chromogen (tetramethylbenzidine) are added. The enzyme action on
substrate/chromogen produces a colored end product.

The enzyme-substrate/chromogen reaction is terminated with acid (H₂SO₄). The
color intensity is directly related to the concentration of hepatitis B surface
antigen in the patient sample. Reactive results are tested in duplicate, repeatedly
reactive samples are confirmed by neutralization and immune blotting.

2.8.3.2. (HIV):

The principle of AniLab system’ HIV kit is based on an indirect solid phase
enzyme immunoassay with horseradish peroxidase as a marker enzyme. The assay
proceeds according to the following reactions.

1. When present in a patient, serum HIV antibodies combine with HIV peptides
attached to polystyrene surface of the micro strip wells.

2. Residual patient sample is removed by washing and horseradish peroxidase
conjugated anti-human IgG (sheep) is added.

3. Wells are washed and a colorless enzyme substrate (H₂O₂) and chromogen
(tetra methyl lebenthadine) is added.

4. Enzyme-chromogen/substrate reaction is terminated with acid (H₂SO₄). The
color intensity is directly related to the concentration of HIV antibodies in a
patient sample. Positive reactions were confirmed by immunoblot.

2.8.3.3. Factor VIII inhibitor screening test:

Three plastic tubes were prepared, 0.5 ml of normal plasma in a first tube, 0.5
ml of the patient's plasma in a second tube, and a mixture of 0.25 ml of normal and
0.25 ml of patient's plasma in a third tube.

The tubes were then incubated for 120 min at 37ºC and placed in water bath.
A mixture of 50 : 50 of the content of tubes 1 and 2 was put in a 4th tube, which was
used for check of the immediate Inhibitor, APTT was performed in duplicate on all four tubes and the result was interpreted according to a table.

2.9. **Statistical analysis:**

The data was been analyzed by computer using statistical package for social studies (SPSS) applying the appropriate tests of significance, Chi-Square test $P=0.05$ (Cut-off values on the degree of confidence 95%).

2.10. **The budget:**

The study is partially funded by the National Association for Blood Transfusion Services.

2.11. **Difficulties:**

- Samples transport.
- Investigations were expensive.

### Chapter three

#### Results

The overall numbers of cases enrolled in this study were 71 of hemophilia “A” patients.

One case was positive for HBsAg (1.4%), no case was reactive for HIV (0.0%), and factor VIII inhibitors were present in ten patients (14.1%) and an established arthropathy in 32 patients (45.1%).

3.1. **Factor VIII level among the study group:**

The majority of the study group, 39 patients (54.9%) were moderate hemophiliacs (factor VIII level between 1-5% of normal, mean of 3.57 $\pm$ 1.32 SD), 30 patients (42.3%) were mild hemophiliacs (factor VIII level >5-%<40% of normal, mean of 11.8 $\pm$5.44 SD), and two patients (2.8%) were severe hemophiliacs (factor VIII level <1% of normal) as shown in (Figure 1).

3.2. **Demographic profile of children under the study:**

3.2.1. **Gender distributions:**

The majority of hemophiliacs were males, 70 pts (98.6%), were females contribute for 1.4 %, (Only one patients) as shown in (Figure 2).
3.2.2. Age distributions:-

The distribution of the study group according to their age groups were only studied. The majority of hemophiliacs under study were between five and ten yrs, 31 (43.7%), no hemophilic was less than one year (0.0%) as shown in (Table 1).

3.2.3. Regional distribution:-

27 patients (38.0 %) were from the centre, 21 patients (29.6 %) from Northern descendant. 17 patients (23.9%) were from the west, Eastern and Southern descendants were 2.8% each as shown in (Table 2).

3.2.4. Occupation of the guardians:-

Most of hemophilic guardians were laborers 49 (69.9%), 18 (25.4%) were employees, 3 (4.2%) were professional, and one (1.4%) was unemployed as shown in (Table 3).

3.2.5. School level:-

The majority of the study population were in the basic school 35 patients (49.3%), 26 patients (26.6 %) were preschool children, 8 patients (11.3%) were in the secondary school where as only two patients (2.8 %) left the school because of their illness as shown in (Figure 3).

3.2.6. The impact of hemophilia on Residence:-

19 families (26.8%) moved from their Origins to the capital because of the disease, 52 families (73.2%) did not change their homes of origin as shown in (Figure 4).
3.2.7. Family history of bleeding disorders:

Family history of bleeding disorder was found in 46 patients (64.8%), family history was negative in 25 patients (35.2%) as shown in (Figure 5).

3.3. Clinical profile:

3.3.1 Age at initial presentation versus age at diagnosis:

40 patients (56.3%) presented during infancy Vs 21 patients (29.6%) diagnosed in the same period. 26 patients (36.6%) presented between 1-<5 years compared to 37 pts (52.1%) diagnosed in the same period. 5 patients (7%) presented from 5-10 yrs corresponded to 13 patients (18.3%) diagnosed in the same period. No patient neither was presented nor diagnosed after the age of ten years as shown in (Figure 6).

3.3.2. Presenting complaints among the study population:

The most common presenting symptoms was joints& muscles bleedings 35 patients (49.3%) followed by bleeding from mucous membranes 24 patients (33.8%), while 7 patients bled after circumcision (9.9%). Four patients (5.6%) bled from the umbilical stump and one patient presented with bleeding following deciduous teeth shedding (1.4%), (Figure 7).

3.3.3. Mucous membranes bleeding:

61 out of 71 patients (83.1%) had attacks of oral& nasal bleeding, 15 patients reported attacks of hematuria (21.1%) and attacks of melena in 10 patients (14.1%) as shown in (Table 4).

3.3.4. Frequency of bleeding Vs factor VIII level:

Three patients [75% out of those who bled twice or more per week] were moderate hemophiliacs (factor VIII level of 1-5%), 9 patient
[100% of the weekly bleeders] were moderate hemophiliacs, those who bled monthly, 1 patient has factor level of 1-5% and 4 patients with mild hemophilia (factor level of >5-%<40%). Bleeding episodes less than ten times per year was reported in only one patient with severe hemophilia (factor VIII level of <1%), 17 patients with moderate type and 25 patients of the mild type. The number of bleeding episodes were significantly related to the severity of factor VIII deficiency (P=0.02) (Figure 8).

3.3.5. Clinical signs among the study group:-

The majority of patients show signs of joints bleeding 45 patients (63.3%), 32 patients out of them had signs of established arthropathy (71.1%). 20 patients (28.1%) had signs of mucous membranes bleeding, 13 patients (18.3%) had muscle hematomas. Pallor was detected in 15 patients (21.1%) while two patients were jaundiced (2.8%), liver was enlarged in one patient (1.4%). Two patients had an abnormal neurological findings on examination. There was no patient with lymphadenopathy or signs of opportunistic infections (0.0%) (Figure 9).

3.3.6. Joints with hemarthrosis:-

The commonest joint affected was the knee in 37 patients (52.2%), ankles in 10 patients (14.1%), elbows in 6 pts (8.4%), wrists affected in 3 patients (4.2%) and metacarpals in only one patient (1.4%) (Figure 10).

3.3.7. Hepatitis B vaccination:-

Only four patients (5.6%) were immunized against hepatitis B, the remainders 67 pts (94.4%) were not immunized (Figure 11).

3.4. Management& management-related complications:-

3.4.1 Treatment strategies:-

93 %( 66 pts) were on demand therapy, 5 patients (7 %) were on secondary prophylaxis, no patient was on primary prophylaxis (Table 5).

3.4.2. Treatment options:-

The majority of patients received both dried factor VIII concentrates and plasma derivatives 49 patients (69.1%), 18 patients (35.3%) were on dried factor VIII alone and 4 patients (5.6%) received plasma derivatives alone. No patient received DDAVP or other medications (0.0%)(Table 6).
3.4.3. Factor VIII exposure & administration of plasma derivatives:–

45 patients received plasma derivatives < ten times and eight patients received plasma derivatives > ten times.

20 patients were exposed to factor VIII <10 times. 21 patients of patients were exposed around 10-<50 times, 21 patients were exposed about 50-90 times and five patients (7.5% out of 67 patients) were exposed >90 times in their lives (Figure 12).

3.4.4. Orthopedic care:–

51 patients (72.9%) were not seen by orthopedics surgeons, the remaining 20 patients all of them were advised courses of physiotherapy, 10 out of these 20 patients (14.1%) were under gone various orthopedics’ procedures, 13 patients were received analgesia mostly in the form of paracetamol (Table 7).

3.4.5. Hepatitis B screening:–

Only one patient (1.4%) was reactive for HbsAg while 70 patients (98.6%) were negative for HbsAg (Table 8).

3.4.6. HIV screening:–

HIV reactivity was not detected among the study group (71 patients).

3.4.7. Factor VIII inhibitors screening:–

Inhibitors were present in 10 patients (14.1%) and absent in 61 patients (84.4%) (Figure 13).
3.4.8. Established arthropathy:-

3.4.8.1 Factor VIII level in patients with arthropathy:-
Arthropathy developed in one patient, half those with the severe type, 21 patients (53.8%) out of those with moderate disease and in 10 patients (31.1%) out of those with mild type. Development of arthropathy is not significantly related to Factor VIII level among the study group (P=0.23) (Figure 14).

3.4.8.2. Age of patients with arthropathy:-
Arthropathy developed in 2 patients under five years, 13 patients in the age group 5-<10 yrs and 17 patients respectively (48.8%) out of those with arthropathy) among those above ten years. There is a significant risk of developing arthropathy with increasing age (P=0.03) (Figure 15).

3.4.8.3. First clinical presentation of patients with arthropathy:-
Arthropathy developed in 19 patients (54.3%) out of 35 patients who initially presented with joint and muscles bleeding and in eight patients (33.3% out of 24 patients) who presented with mucous membranes bleeding. Arthropathy also had developed in four patients (100%) who presented with umbilical stump bleeding, only one patient (14.1%) out of 71 patients bled after circumcision. A significant relationship between initial presentations with muscles and joints
hemorrhage, umbilical stump bleeding and later development of arthropathy (P=0.01) (Figure 16).

3.4.8.4. Type of treatment:-

Arthropathy developed in 28 patients (42.4%) out of 66 patients who were on demand therapy, four patients (80 %) out of five patients who were on secondary prophylaxis. A non-significant relationship between arthropathy and different regimen advocated in the study (P=0.12) (Table 9).

3.4.9. Factor VIII inhibitors: _

3.4.9.1. Factor VIII level among patients with inhibitor:-

As the figure shows no inhibitors were detected in severe or mild hemophiliacs, it present in 10 patients with moderate hemophilia (25% out of 39 patients moderate hemophiliacs). The presence of factor VIII inhibitors is significantly related to the severity of deficiency (P=0.01) (Figure 17).

3.4.9.2 Age of patients with inhibitors:-

No child under five developed inhibitors to factor VIII, in 5-<10 yrs group, inhibitors were detected in five patients (16.1%) out of 31 patients and in five patients (17.9%) out of 28 patients among those above ten years. A non-significant relationship between age and the development of inhibitors (P=0.30) (Figure 18).

3.4.9.3. Factor VIII exposure among patients with inhibitors:-

Four patients (40%) of those who developed inhibitors were exposed to factor VIII more than 90 times in their lives. Inhibitors were not detected in those who were exposed less than ten times, detected in four patients (80 %)out of those exposed >90 times, three patients (13 %) out of those expose 10-<50 times and in three patients (14.3 %) out of
those exposed 50-90 times in their lives. There is significant relationship between the development of factor VIII inhibitors and frequency of exposure to factor VIII ($P=0.04$) (Figure 19).
**Table (1)**

*Age distribution:*-

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-&lt;1</td>
<td>00</td>
<td>00.0</td>
</tr>
<tr>
<td>1-&lt;5</td>
<td>12</td>
<td>16.9</td>
</tr>
<tr>
<td>5-&lt;10</td>
<td>31</td>
<td>43.7</td>
</tr>
<tr>
<td>10-16</td>
<td>28</td>
<td>39.4</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table (2):

Regional distribution

<table>
<thead>
<tr>
<th>Descendant</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>21</td>
<td>29.6</td>
</tr>
<tr>
<td>Central</td>
<td>27</td>
<td>38.1</td>
</tr>
<tr>
<td>Westerns</td>
<td>17</td>
<td>23.9</td>
</tr>
<tr>
<td>Eastern</td>
<td>02</td>
<td>02.8</td>
</tr>
<tr>
<td>Southern</td>
<td>02</td>
<td>02.8</td>
</tr>
<tr>
<td>Immigrant</td>
<td>02</td>
<td>02.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
**Table (3)**

*Occupations of the guardians:*

<table>
<thead>
<tr>
<th>Occupations</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laborers</td>
<td>49</td>
<td>69.0</td>
</tr>
<tr>
<td>Employees</td>
<td>18</td>
<td>25.4</td>
</tr>
<tr>
<td>Professionals</td>
<td>03</td>
<td>04.2</td>
</tr>
<tr>
<td>Others</td>
<td>01</td>
<td>01.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table (4):

Mucous membranes bleeding:

<table>
<thead>
<tr>
<th>Sites of bleeding</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td><strong>Mouth &amp; nose bleeding</strong></td>
<td>61</td>
</tr>
<tr>
<td>Hematuria</td>
<td>15</td>
</tr>
<tr>
<td>Melena</td>
<td>10</td>
</tr>
</tbody>
</table>
### Table (5):

**Treatment strategies:-**

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>On demand</td>
<td>66</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>05</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>71</td>
</tr>
</tbody>
</table>
Table (6):

Treatment options:

<table>
<thead>
<tr>
<th>Type of factor VIII concentrate</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Dried factor VIII concentrate</td>
<td>18</td>
</tr>
<tr>
<td>Plasma derivatives</td>
<td>04</td>
</tr>
<tr>
<td>Combination of factor VIII &amp;</td>
<td></td>
</tr>
<tr>
<td>plasma derivatives</td>
<td>49</td>
</tr>
<tr>
<td>DDPT</td>
<td>00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
</tr>
</tbody>
</table>
### Table (7): Orthopedic care:-

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Analgesia</td>
<td>13</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>20</td>
</tr>
<tr>
<td>Orthopedic procedure</td>
<td>10</td>
</tr>
<tr>
<td>Did not receive management</td>
<td>51</td>
</tr>
</tbody>
</table>
### Hepatitis B screening:

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Negative</td>
<td>70</td>
<td>98.6</td>
</tr>
<tr>
<td>Positive</td>
<td>01</td>
<td>01.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table (9):

Treatment strategies among hemophiliacs with arthropathy:

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>With</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>arthropathy</td>
<td>arthropathy</td>
<td></td>
</tr>
<tr>
<td>On demand</td>
<td>28(24.4%)</td>
<td>38(57.6%)</td>
<td>66(100%)</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>4(80%)</td>
<td>1(20%)</td>
<td>5(100%)</td>
</tr>
<tr>
<td>Total</td>
<td>32(45.1%)</td>
<td>39(54.9%)</td>
<td>71(100%)</td>
</tr>
</tbody>
</table>

\[ P=0.12 \]
Figure (1): Factor VIII level

- Mild: 54.9%
- Moderate: 42.3%
- Severe: 2.8%
Figure (2): Gender distribution
Figure(3): School level

- Preschool (26.6%)
- Basic (49.3%)
- Secondary (11.3%)
- Off school (2.8%)
Figure (4): Impact of the disease on residence

- Not affected
- Change residence

26.8%

73.2%
Figure (5): Family history of bleeding disorders

Positive family history

Negative family history

% 35

% 65
**Figure 6:** Age at presentation Vs age at diagnosis

- **Age at presentation:**
  - 0% (16 yrs)
  - 10% (10 yrs)
  - 20% (1 yr)
  - 30% (5 yrs)
  - 40% (10 yrs)
  - 50% (16 yrs)
  - 60% (56.3%)

- **Age at diagnosis:**
  - 0% (16 yrs)
  - 7% (10 yrs)
  - 10% (1 yr)
  - 20% (5 yrs)
  - 30% (10 yrs)
  - 40% (16 yrs)
  - 50% (56.3%)
  - 60% (56.3%)
Figure (7): First clinical presentation

- Joints & muscles: 35
- Mucous membranes: 24
- Surgical circumcision: 7
- Umbilical stump: 4
- Deciduous teeth shedding: 1
**Figure (8):** Frequency of bleeding related to factor VIII level

- **P=0.02**

- **Legend:**
  - Blue: mild (factor level >5-<40%)
  - Maroon: moderate (factor level 1-5%)
  - Yellow: severe (factor level <1%)

- **Axes:**
  - Y-axis: Percentage
  - X-axis: Frequency of bleeding
    - <10 times/yr
    - Monthly
    - Weekly
    - Twice or more/week
Clinical signs

- Target joint bleed: 0%
- Muscle hematoma: 0%
- Mucous membranes: 14.4%
- Pallor: 21.1%
- Hemarthrosis: 18.3%
- Abnormal C.N.S: 18.3%
- Lymphadenopathy: 2.8%
- Hepatomegaly: 0%
- Opportunistic infection: 0%

Figure (9): Clinical signs
Figure (10): Hemoarthrotic joints

- Knees: (52.1%)
- Ankles: (14.2%)
- Elbow: (8.4%)
- Wrist: (4.2%)
- Metacarpals: (1.4%)
Figure (11): Hepatitis B vaccination

- Vaccinated: 94.40%
- Not vaccinated: 5.60%
Figure (12): Factor VIII & plasma product exposure
Figure (13): Factor VIII inhibitors

- Absent: 86%
- Present: 14%
Figure (14): Arthropathy related to factor VIII level
Figure (15): Arthropathy related to age group

$P = 0.03$
Figure (16): Clinical presentations in patients with arthropathy

P = 0.01
Figure (17): Factor VIII inhibitors related to factor VIII level

$P = 0.01$
Figure (18): Factor VIII inhibitors related to the age

- <1yr
- 1-<5yrs
- 5-<10yrs
- 10-16yrs

P = 0.30
Figure 19: Factor VIII inhibitors related to factor VIII exposure

P = 0.04
Chapter four

Discussion

The study was conducted to identify clinical picture of hemophilia “A” in Khartoum State and to detect the complications of the disease and its management.

4.1. Children with hemophilia “A”:-

Regarding the classification of hemophilia “A,” the majority was found to be moderate hemophiliacs 39 patients (54.9%) contrary to what was reported by Agaliotis, et al where the severe type makes up the bulk of hemophilia (16). This however is comparable to the report of Thiam, et al in Dakar (147).

Although a disease of male one patient (1.4%) was a female (morphologically normal), which may be due to imbalance X-inactivation, as described by Mori, et al (30).

The majority, 40 patients (56.3%), the disease was manifested in the first year of life and 58 patients (81.7%) were diagnosed before their fifth birthday, akin to what had been reported by Gitschier, et al (26).

Family history of bleeding disorders was found in 46 patients (64.8%), which similar to the report of Tuddenham, et al (27).
A round one third of hemophiliac families move to Khartoum due to lack of hemophilia services outside the capital which it’s impact on the economy and settlement of these families.

4.2. Clinical features:-

Despite the presentation during infancy of the majority, half them diagnosed during the same period reflecting delay in diagnosis due to lack of awareness to wards the disease by the families or their treating doctors with the consequent increase probability of complications.

Muscles and joints hemorrhages contributed for 49.3% of the initial presentation among hemophiliacs, alike what was shown by Brinkhous, et al (34).

Mucous membranes bleeding was a presenting feature in 33.8%, which was reported as common by Caron, et al (48). Hematuria registered as a common experience in 21.1% of patients, and as a first initial presentation in only one patient (1.4%), virtually a rare presentation of hemostatic disorders, as described by Harold, et al (24). 14.1% reported attacks of Melena, a frequent symptom in hemophiliacs as expressed by Seligsohn, et al (49).

Bleeding after deciduous teeth shedding was found in only one patient (1.4%) which is not constant with the report of Harold, et al (24).
Circumcisional bleeding was a presenting feature in seven pts (9.9%) similar to what was reported by Bachner, et al \(^{(50)}\). In severe hemophilia, circumcisional bleeding was the classical feature in Talmud writing, Corrigan, et al \(^{(1)}\).

Bleeding from the umbilical stump was reported in four patients (5.6%), a feature of fibrinogen rather than factor VIII deficiency as reported by King, et al \(^{(51)}\).

4.3. Complications:-

Established arthropathy and bleeding into a target joint was found in 45.1%. Arthropathy was insignificantly correlated to the level of factor VIII (P=0.23), but significantly related to the increasing age (P=0.03). A significant link was observed between presentation with joints and muscles bleeding and later development of arthropathy (P=0.01) as reported by Mocho, et al \(^{(53)}\).

The knee joint accounted for 52.1% of the hemoarthrotic joints, followed by the ankles 14.1% as illustrated by, Nalon, et al and Bretter, et al \(^{(34,35)}\).

4.4. Managements-related complications:-

4.4.1 Hepatitis B & HIV:-
HIV reactivity was not found among the study population, while prevalence of hepatitis B was found to be 1.4% which up to the US studies, Hill, et al (143). It is far below the reports from India, Ghosh, et al and that from Senegal, Diop, et al (144,148). The low prevalence of HIV and hepatitis B may be due to screening of individual blood donation.

4.4.2. Factor VIII inhibitors:-

4.4.2.1 Prevalence:-

The prevalence of factor VIII inhibitors was found to be 14.1%, resembling the reported prevalence in India, Ghosh et al and Senegal, Thiam et al, unalike report from Tunisia, Houissa, et al (145,147,93).

4.4.2.2 Risks factors:-

Factor VIII inhibitors were found to be significantly related to the severity of factor VIII deficiency (P=0.01) as stated by Rizza, et al (129).

The frequency of factor VIII exposure was shown to be significantly related to the development of inhibitors (P=0.04) as reported by the previous author.

The development of factor VIII inhibitors was insignificantly related to age (P=0.3) which was comparable to Briet, et al report (62).

4.5. Management strategies:-
Concerning treatment of hemophilia, “A” 93% were on demand therapy 7% on secondary prophylaxis. Primary prophylaxis was not advocated among the study population, which is similar to the practice in Australian hemophiliacs as reported by Ekert, et al (92).

The principal type of factor VIII concentrate utilized was dried factor VIII concentrate, interchanged with plasma products in 69%. In contrast to administration of recombinant factor VIII concentrates only, as advocated by the International Federation of Hemophilia. However, a more advanced regimen compared to some countries in the region as reported by Kouides, et al and Houissa, et al Tunisia (46,93).

Although hepatitis B is a serious blood born complications, yet preventable only 5.6% of hemophilia were vaccinated.

Although the prevalence of arthropathy was 45% affecting 35 patients yet 72.5% did not receive orthopedic care.

Despite high frequency of hemarthrosis and pain, analgesia was given to only 18% mostly in the form of paracetamol. Use of non-steroidal anti-inflammatory drugs are debatable as described by Harold et al (24). It must be used cautiously according to Inwood and Steven et al (87,88).
Orthopedic management together with encouragement of secondary prophylaxis for target joints bleeding decrease the incidence of crippling arthropathy as reported by Valentino, et al \(^{(79)}\).

**Conclusion**

- Moderate hemophilia (factor VIII level 1-5% of normal) was the principal type, contributed for 54.9% followed by the mild type (factor VIII level >5 % and < 40% of normal) contributed for 42.3% and 2.4% with severe type (factor VIII level <1% of normal). Family history of bleeding disorders was found in 65.3%.

- The commonest presenting complaint was muscles and joints bleeding in 49.3% followed by mucous membranes bleeding in 33.8 %. 56.3% presented during infancy, half them were diagnosed in the same period.

- Arthropathy developed in 45%, increasing age (P=0.03) and initial presentation with joints and muscles hemorrhages (P=0.01) were
found to be risk factors, the knee joint was commonly affected accounting for 52 % out of those with arthropathy.

- The prevalence of factor VIII inhibitors was found to be 14%. The severity of the disease (P=0.01) and frequent exposures to factor VIII concentrates (P=0.04) were found to be risk factors.

- The prevalence of hepatitis B was found to be 1.4 % affecting only one patient.

- No hemophiliac was reactive to HIV.

- The principal factor concentrate administered was dried factor VIII concentrate interchanged with plasma products 69% for acute bleeding (on demand therapy).
Recommendations

- Hepatitis B vaccine should be included in the EPI program or at least for those at risk such as hemophiliacs.
- A comprehensive centre for treatment of hemophilia had to be constructed, with different specialties of medicine including pediatrician, hematologist, orthopedic surgeon, psychologist, and social worker, in Khartoum city as well as the peripheries.
• A unified protocol for hemophilia care has to be designed.

• Advocations of primary and secondary prophylaxis minimize the development of crippling complications.

• Dried factor VIII has to be encouraged instead of blood products.

References


