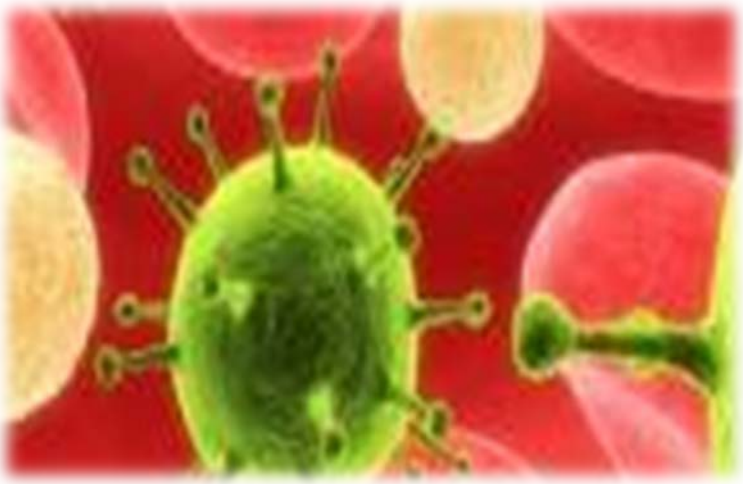
Haemophilia care in Arabic countries compared to western European countries

(Yemen and Germany as examples**)**

Asllan Tahiraj



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“There is no disease that God has sent down except that He also has sent down its treatment.”

Prophet Muhammad

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1 Abbreviations

AAV	Adeno Associated Virus
AIDS	Acquired Immunodeficiency Syndrome
APTT	Activated Partial Thromboplastin Time
CJD	Creuzfeldt Jacobs Disease
CNS	Central Nervous System
CT	Computed Tomography
DDAVP	1-Desamino-8-D-Arginine Vasopressin
DNA	Deoxyribonucleic Acid
EHC	European Haemophilia Consortium
ESCHQoL	European Study in Clinical, Health Economic and Quality of Life
EU	European Union
FFP	Fresh Frozen Plasma
GDP	Gross Domestic Product
GNI	Gross National Income
GIT	Gastro-intestinal Tract
HC-Av	High Capacity Adenovirus
HIV	Human Immunodeficiency Virus
HTC	Haemophilia Treatment Centres
ICB	Intracranial Bleeding
IU	International Units
MCH	Mother and Child Health
MRI	Magnetic Resonance Imaging
MOPH	Ministry of Public Health
NGO	Non-governmental Organisation
PHC	Primary Health Care
PT	Prothrombin Time
PWHA	Person with Haemophilia A
TCT	Thrombin Clotting Time
UAE	United Arab Emirates
VWD	von Willebrand Disease
VWF	von Willebrand Factor
WFH	World Foundation of Haemophilia
WHO	World Health Organisation

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3 Summary

A significant proportion of the world's population is affected by hereditary defects in one or more of the clotting factors. Haemophilia A is a sex-linked genetic disorder resulting in deficiency of plasma factor VIII coagulant activity. Haemophilia B (Christmas disease) is due to deficiency of clotting factor IX [7, 8]. The clinical manifestations of haemophilia A and haemophilia B are indistinguishable, and occur in mild, moderate, and severe forms. The severe form of haemophilia is characterized mainly by frequent haemarthroses leading to chronic crippling haemarthropathy when not treated very early or prophylactically. Highly purified concentrates, prepared from human plasma or manufactured by recombinant technology, are available for treatment and are considered safe and effective [1, 2].

In developed countries, early treatment of bleeding episodes and home therapy quickly evolved as the primary management option. Presence of specialized interdisciplinary centres with 24 hours service, training and education of patients are the main advantages of the comprehensive treatment concept in developed countries. This is not the case in most developing countries where the government does not have the resources to buy the necessary quantities of coagulation factors in the face of more urgent health priorities and hardly any patients can afford to pay for their own treatment even for on-demand home therapy. Other problems are insufficient supply with clotting factor concentrates, lack of access to these concentrates and absence of specialized care centres [6].

Haemophilia care in Arabic region shows variations from country to country depending on socio economic status and varies from good organized care to absence of it at all. Only 13 of 21 Arabic countries have reported at least a Hemophilia Center and an organized care provided to haemophiliacs. Factor use per capita is low compared to western countries, and none of Arabic countries reached minimal level of 1 IU per capita. High income countries, such as Saudi Arabia, have reported a larger amount of factor concentrates, compared to those with lower income.

Haemophilia care in western European countries is a well organized process providing a qualified management to all haemophiliacs, through the Haemophilia treatment centers (HTCs) which exist in all the EU Member States. Choice and levels of treatment, availability of comprehensive care and access to prophylaxis vary widely from one Member State to another [31 ,72].

Yemen represents those Arabic countries where only a minimal care is provided to haemophilic patients. Facing other common and serious health problems, the health authorities pay only a small attention to haemophiliacs. In this country with a population of over 22 millions, and an estimated number of about 1460 haemophilia cases, there is no specialized center for treatment of haemophilia.

In Germany, people with haemophilia are entitled to a choice of all treatments ranging from an optimal level of factor replacement therapy on demand as well as on

a prophylactic basis for those who need it, to comprehensive care at a Haemophilia Treatment Centre [81]. Haemophilia care in Germany is provided through 12 specialized Haemophilia Treatment Centers (HTC). Apart from treatment and care at the HTCs, specialized physicians in practices and at haematology units in general hospitals provide care. Home treatment is available for children as well as for adult people suffering from severe haemophilia[72].

In this short analysis, 20 Yemeni haemophilic patients were compared to 40 German patients. We analyzed demographic data, clinical manifestations, treatment options, complications and costs. The majority of Yemeni haemophiliacs, about 60 % of them, were children and the peak age was only 29 years. Alarming evidence is the fact that the Yemeni haematologists have not reported any patient older than 30 years.

In Yemen, despite the sufficient number of specialized haematologists, only two general hospitals located in the capital city provide some care to haemophilic patients. This care includes no prophylaxis program but only treatment on demand. It is offered only to severe affected cases and is based still on old medications such as Cryoprecipitate, FFP and DDAVP. About 65 % of the total cases participating in our study were treated with factor concentrates, which, even in cases with life threatening manifestations was not given in adequate amounts. During a period of 6 months, severe affected Yemeni haemophiliacs received an average of 1.157 IU of factor concentrates, or 90 times less than a German one. Access to factor concentrates was very difficult even for severe affected Yemeni haemophiliacs.

The awareness and education about the nature of disease among Yemeni haemophiliacs and their relatives is low, especially in rural areas, where most of Yemeni population lives. Couples who have haemophilic boys want to have still other children; circumcision, done routinely for all boys, is performed at home by a nurse, usually within the first 4 weeks of life, resulting in life threatening bleeding for haemophiliacs.

Absence of the health insurance system is another big challenge, as the patient should pay for every kind of health care and the costs of treatment are high compared to the income. The cost of care among Yemeni haemophilic patients during last 6 months varied from EUR 200 to EUR 2000, with an average of EUR 865 per patient. This amount of money exceeds the average of annual income among Yemeni population.

Under such conditions, without a health insurance, haemophilic patients face a big challenge on dealing with complications of the disease like transmitted infections or musculoskeletal complications. Facing those problems, the chances to survive are low and no haemophilic patient reaches the fourth decade of life. In a country as Yemen, where neither government nor the patient are able to pay for an adequate management of haemophilia,until now there is no initiative for creation of donators found in order to support people affected by this disease.

As a conclusion, we consider that the major problems facing haemophilia care in Yemen include: absence of a specialized center for treatment of haemophilia, inadequate supply with factor concentrates and lack of awareness and education about the nature of the disease.

We consider that the following recommendations will be useful for improvement of haemophilia care in Yemen:

- Initiation of a first step for a Haemophilia Center in Sana'a, as a result of coordination between Yemeni authorities and WFH representative for Arabic Region
- Stimulation of a humanitarian financial support for Yemeni haemophiliacs, from rich Arabic neighbor countries (Saudi Arabia, Emirates, Qatar, Kuwait)
- Formulation of educational guidelines for haemophiliacs about the nature of the disease
- Organization of a national network and creation of a registry for haemophiliacs
- Home therapy (living far away from capital city, Yemeni haemophiliacs have to cross hundreds of miles to seek for some care)
- A twinning program between haemophilia centers in Germany and clinics dealing with haemophilia in Yemen.

Zusammenfassung

Erbliche Defekte in einem oder mehreren der Gerinnungsfaktoren gehören zu den seltenen Erkrankungen, sogenannten „Orphan diseases“. Hämophilie A ist eine geschlechtsgekoppelte genetische Erkrankung gekennzeichnet durch einen Mangel an Faktor VIII Gerinnungsaktivität. Bei Hämophilie B (Christmas disease) liegt der Defekt im Gerinnungsfaktor IX. Die klinische Symptome der Hämophilie A und Hämophilie B sind nicht unterscheidbar, und umfassen leichte, mittelschwere und schwere Formen. Die schwere Form der Hämophilie zeichnet sich durch häufige Gelenkblutungen aus, die zu schweren Gelenkdeformitäten und Verkrüppelung führen, wenn sie nicht rechtzeitig behandelt werden. Hochgereinigte Konzentrate, die aus humanem Plasma oder durch rekombinante Technologie hergestellt werden, sind für die Behandlung verfügbar und gelten als sicher und effektiv[1, 2].

In den entwickelten Ländern, ist eine Primärphrophylaxe mit Faktor VIII bei Kindern die Therapie der Wahl mit einer kontinuierlichen Faktor VIII Gabe durch „Home Therapy“, also Schulung der Eltern und Behandlung zu Hause. Organisation der Therapie in spezialisierten interdisziplinären Zentren mit 24-Stunden-Service, Schulung und Ausbildung von Patienten aller Altersgruppen, und sofortige Behandlung von Blutungen sind die wichtigsten Vorteile dieses umfassenden Behandlungskonzepts. Dies ist nicht der Fall in den meisten Entwicklungsländern, in denen die Regierung keine Finanzmittel bereitstellen kann, um die erforderlichen Mengen an Gerinnungsfaktoren zu kaufen. Die Patienten können es sich nicht leisten, die teure Faktor VIII-Behandlung zu bezahlen, auch nicht eine on-demand Therapie akuter Blutungen zu Hause. Grundsätzliche Probleme sind unzureichende Versorgung mit Gerinnungsfaktor-Konzentraten, fehlender Zugang zu ärztlicher Versorgung und das Fehlen spezialisierter Pflegeeinrichtungen[6].

Hämophilie Behandlung im arabischen Gebiet zeigt Variationen von Land zu Land je nach sozio-ökonomischem Status und variiert von gut organisierter Pflege bis völliger Abwesenheit einer Behandlungsmöglichkeit. Nur 13 von 21 arabischen Ländern haben überhaupt mindestens ein Hämophiliezentrum und eine organisierte Versorgung von Hämophilie-Patienten gemeldet. Faktor VIII Verbrauch pro Kopf ist im Vergleich zu westlichen Ländern gering, und kein einziges der arabischen Länder erreicht ein minimales Niveau von 1 IU Faktor VIII Verbrauch pro Kopf. Länder mit hohem Einkommen, wie Saudi-Arabien, haben einen größeren Verbrauch von Faktor VIII Konzentrat, im Vergleich zu arabischen Ländern mit niedrigerem Pro-Kopf-Einkommen ausgewiesen[31 ,72].

Jemen represäntiert die arabische Länder, in denen nur eine minimale Versorgung für hämophile Patienten erreichbar ist. Im Vergleich zu anderen überwiegenden , ernsthaften Erkrankungen, beachten die Gesundheitsbehörden hämophilie Patienten nur wenig. In diesem Land mit einer Bevölkerung von über 22 Millionen und einer geschätzten Anzahl von ca. 1460 Hämophilie Fällen, gibt es kein einziges spezialisiertes Zentrum für die Behandlung von Hämophilie-Patienten.

Hämophilie Behandlung in den westeuropäischen Ländern ist dagegen hervorragend organisiert und bietet qualifizierte Versorgung für alle Hämophilie-Patienten durch spezielle Hämophilie-Behandlungszentren an, die in allen EU-Mitgliedstaaten bestehen. Auswahl und Ebenen der Behandlung, die Verfügbarkeit einer umfassenden Versorgung, Faktor VIII Verbrauch und Zugang zu Prophylaxe variieren jedoch auch hier stark von einem Mitgliedstaat zum anderen .

In Deutschland können Patienten mit Hämophilie das Faktor VIII Konzentrat frei wählen, und erhalten eine umfassende Betreuung und Anleitung in 12 Hämophilie Behandlungs Zentren. Zusätzlich unterstützen spezialisierte Ärzte in Praxen und Krankenhäusern die Behandlung der Hämophilie Patienten. Prophylaxe ist für alle Kinder mit schwerer Hämophilie vorgesehen, sowie für erwachsene Patienten mit schwerer Hämophilie bei Bedarf[72].

In der vorliegenden Arbeit wurden 20 jemenitische Hämophilie Patienten mit 40 deutschen Hämophilie Patienten verglichen. Demographische Daten, klinische Erscheinungsformen, Behandlungsmöglichkeiten, Komplikationen und Kosten wurden in beiden Patientengruppen analysiert. Etwa 60% der jemenitischen Hämophilie Patienten waren Kinder. Der älteste Hämophilie Patient in dieser Gruppe was 29 Jahre alt. Laut Bericht jemenitischer Hämatologen wurde in der Abteilung kein Hämophilie Patient mit einem Alter über 30 Jahren gesehen.

Im Jemen bieten trotz einer ausreichenden Anzahl von spezialisierten Hämatologen nur zwei allgemeine Krankenhäuser in der Hauptstadt eine Minimalversorgung für Hämophilie Patienten an. Diese Versorgung umfasst kein Prophylaxe-Programm für Kinder mit Faktor VIII, sondern nur die Behandlung akuter Blutungen in schweren Fällen überwiegend mit veralteten Präparaten wie Kryopräzipitat, FFP und DDAVP. In über 65% der Gesamtzahl der Fälle, die in unserer Studie teilgenommen haben, wurden Faktor-Konzentrate gegeben, allerdings auch in Fällen mit lebensbedrohlichen Manifestationen nicht in ausreichender Menge. Während eines Beobachtungszeitraums von sechs Monaten erhielten die jemenitischen Patienten mit schwerer Hämophilie durchschnittlich 1.157 IE Faktor-Konzentrat (pro Patient), das heißt 90-mal weniger als ein deutscher Patient mit schwerer Hämophilie. Der Zugang zu Faktor VIII Konzentrat war auch für jemenitische Patienten mit schwerer Hämophilie und lebensbedrohlichen Blutungen sehr schwierig.

Die Sensibilisierung und Aufklärung über das Wesen der Krankheit unter jemenitischen Hämophilie Patienten und ihren Angehörigen ist niedrig, vor allem in ländlichen Gebieten, in denen der größte Teil der jemenitischen Bevölkerung lebt. Ehepaare mit hämophilen Jungen wollen noch andere Kinder haben. Die Beschneidung, die routinemäßig bei allen Jungen erfolgt, wird meistens zu Hause von einer Krankenschwester durchgeführt. Dies geschieht in der Regel innerhalb der ersten vier Lebenswochen und kann zu einer lebensbedrohlichen Blutung führen.
Das Fehlen jeglicher Krankenversicherung ist eine weitere große Herausforderung, da der Patient für jede Art von Gesundheitsversorgung die Kosten der Behandlung selbst übernehmen muss. Die Kosten für die Behandlung bei jemenitischen Hämophilie Patienten im Beobachtungszeitraum von sechs Monaten variierte von

EUR 200 bis EUR 2000, mit durchschnittlichen Kosten von EUR 865 pro Patient. Dieser Betrag übersteigt das durchschnittliche Jahreseinkommen der jemenitischen Bevölkerung.

Die Überlebenschancen jemenitischer Hämophilie Patienten sind gering und kein Hämophilier erreicht das vierte Lebensjahrzehnt. In einem Land wie Jemen, wo weder Regierung noch der Patient in der Lage sind für eine angemessene Behandlung der Hämophilie zu zahlen, gibt es bis jetzt keine Initiative zur Bereitstellung von Spendengeldern um Menschen, die von dieser Krankheit betroffen sind, zu helfen.

Die großen Probleme der Hämophilie Versorgung im Jemen lassen sich wie folgt zusammenfassen: unzureichende Versorgung mit und Zugang zu Faktor Konzentraten, Abwesenheit von spezialisierten Zentren für die Behandlung von Hämophilie Patienten und unzureichende Aufklärung über die Art der Krankheit in der Bevölkerung, insbesondere in Zusammenhang mit der frühzeitigen Beschneidung der männllichen Kinder.

Folgende Empfehlungen zur Verbesserung der Hämophilie Behandlung in Jemen lassen sich daraus ableiten:

• Gündung eines Hämophilie-Zentrums in der Hauptstadt Sana'a, durch eine Kooperation der jemenitischen Behörden mit WHF Vertretern für die arabische Region

• Beginn einer humanitären finanziellen Unterstützung für jemenitische Hämophilie Patienten, mit Hilfe reicher arabischer Nachbarländer (Saudi-Arabien, Emirate, Qatar, Kuwait)

• Aufklärung von Hämophilie Patienten und ihrer Familien über die Art der Krankheit und ihre Folgen

• Organisation eines nationalen Netzes und die Schaffung eines Registers für Hämophilie Patienten

• Home-Therapie (weit weg von der Hauptstadt, müssen jemenitische Hämophilie Patienten Hunderte von Meilen durchqueren, um eine Behaldlung zu bekommen)

• Gründung eines Twinning-Programms zwischen Hämophilie-Zentren in Deutschland und hämatologischen Kliniken in Jemen.

4 Introduction

A significant proportion of the world's population is affected by hereditary defects in one or more of the clotting factors. These defects lead to abnormal and sometimes life-threatening bleeding episodes.

Haemophilia is a group of X-linked bleeding disorders due to deficiency of clotting factors VIII (Haemophilia A) and IX (Haemophilia B). The clinical manifestations of haemophilia A and haemophilia B are indistinguishable, and occur in mild, moderate, and severe forms. They are the only blood clotting disorders inherited in a sex-linked pattern. The severe forms of haemophilia are characterized mainly by frequent haemarthroses leading to chronic crippling haemarthropathy when not treated very early or prophylactically. Highly purified concentrates, prepared from human plasma and manufactured by recombinant technology, are available for treatment and are considered to be safe and effective. The main complication of treatment is the development of antibody inhibitors against either factor VIII or factor IX, which are more common in patients with haemophilia A than in patients with haemophilia B[1, 2].

Haemophilia is the most severe bleeding disorder, after von Willebrand's disease which is the most common congenital bleeding disorder overall. In 2009, the World Federation of Haemophilia (WFH) has identified 153,251 people with haemophilia throughout the world[3]. This estimation included 91 % of world population.

The WFH estimates that the majority of people with haemophilia in the world do not receive adequate care. Seventy-five per cent of the global haemophiliacs lives in developing countries, where probably only one in five cases is diagnosed, and there is little or no care available[4].

Prior to the 1960s, when no adequate treatment was available, individuals with haemophilia suffered a similar fate worldwide. Severe joint disabilities appeared in early teens, and most patients died before the age of 20. At this time Haemophilia was treated primarily with fresh blood transfusions. Discovery of cryoprecipitate and subsequent development of clotting factor concentrates dramatically increased clinical management options. As concentrates could be easily stored, administered at home and carried with patients during travel, patients began to adopt a practice of home therapy[5].

Haemophilia as a disease and its management has a large impact on the community, including social integration and economics. Inability to be an active part of society and high cost of the medical care make this disease an important problem for all haemophilic patients.

In developed countries, early treatment of bleeding episodes and home therapy quickly evolved as the primary management option. Presence of specialized interdisciplinary centres, training and education of patients are the main advantages of the comprehensive treatment concept in developed countries.

This is not the case in most developing countries where the government does not have the resources to buy the necessary quantities of coagulation factors in the face of more urgent health priorities and hardly any patients can afford to pay for their own treatment even for on-demand home therapy. Other problems are insufficient supply with clotting factor concentrates, lack of access to these concentrates and absence of specialized care centres [6].

In this short analysis we have taken two examples from two different parts of the world, Yemen and Germany. There is a big gap between these two countries regarding education, socio-economic status, health care and also haemophilia care, and we can assume that these two countries represent two extremities regarding health services provided to the community.

Taking in consideration that Germany has an advanced health care system with many facilities, potential human and financial resources, we want to find out the recent ways and strategies used for management of Haemophilia. On the other hand we have chosen Yemen, for two reasons: ***first***, it is one of the developing countries facing many challenges in different fields of life, among which is the health care; and ***second***, I studied there having the chance to know and touch the reality of this country. This Arabic country, rich in natural resources such as oil and gas, is suffering since many years from political crisis and instability, leading civil wars, poverty, absence of proper health care and education.

The primary objective of this study is to define useful recommendations and advices for clinics and hospitals that concern with this disease in Yemen. For that reason we will describe the management of haemophilia in Yemen and identify the major challenges and problems regarding the haemophilia care in this country. After that, will be described the management of haemophilia in western European countries, particularly in Germany.

5 Theoretical part

5.1 Haemophilia

5.1.1 Definition

Haemophilia A is a sex-linked genetic disorder resulting in deficiency of plasma factor VIII coagulant activity. Haemophilia B (Christmas disease) is due to deficiency of clotting factor IX[7, 8].

5.1.2 Epidemiology

The incidence of haemophilia A is 1 in 10,000 live births, or 1 in 5,000 male births. Haemophilia B is less common with an incidence of 1 in 30,000 live male births. The prevalence rates are 105 and 28 per million male population for Haemophilia A and Haemophilia B respectively[4]. In 2009, 153,251 people with haemophilia throughout the world have been documented in a survey which included 105 countries and about 91 % of world's population. About 43% of total documented haemophiliacs severe affected cases [3, 9].

5.1.3 Genetics

The factor VIII and factor IX genes are located on the X chromosome. Many different defects in the gene have been identified, ranging from single-base changes to deletions and inversions. Major disruption of the gene, e.g. a large deletion, results in severe haemophilia whereas a single base change will only cause a partial loss of function, with moderate or mild disease [10]. As the factors' gene is on the X chromosome, haemophilia is a sex-linked disorder. Thus all daughters of haemophiliacs are obligate carriers and sisters have a 50% chance of being a carrier. If a carrier has a son, he has a 50% chance of having haemophilia, and a daughter has a 50% chance of being a carrier. Carriers generally have adequate levels (> 60%) of clotting FVIII or FIX to control bleeding. However, clotting factor levels vary from one carrier to another due to lyonization, in which the expression of one of the two X chromosomes is randomly suppressed [11, 12]. A reduced factor VIII or IX level in a carrier will result in a mild bleeding disorder; thus all known or suspected carriers of haemophilia should have their factor VIII or factor IX level measured[10, 12].

5.1.4 Diagnosis

5.1.4.1 Clinical features

Haemophilia results in prolonged oozing after injuries, tooth extractions, or surgery, and delayed or recurrent bleeding prior to complete wound healing. The age of diagnosis and frequency of bleeding episodes are related to the factor VIII clotting activity[7, 8].

It occurs in mild, moderate, and severe forms. Although patients with mild haemophilia usually bleed only after trauma or surgery, those with severe haemophilia A or B bleed spontaneously or after trivial trauma, particularly into joints and muscles[13].Soft tissue haematomas and haemarthroses leading to severe, crippling haemarthropathy are characteristic of the disease[14]. Subacute haemarthroses is generally associated with previous synovitis or arthropathy, while

acute haemarthroses commonly occurs in a previously healthy joint. Acute bleeding is usually felt by the patient as a burning sensation in the joint. Haemarthroses develops within a few hours; the joint becomes inflamed, tense, warm, and the skin becomes bright red. The affected joint is held in an antalgic flexion position, with painful and limited mobility[15, 16].

Muscle haematomas are also characteristic of haemophilia. These occur most commonly in the calf and psoas muscles but they can arise in almost any muscle. The untreated child almost always has subcutaneous hematomas; some have been referred for evaluation of possible non-accidental trauma[7, 8].

Haematuria is less common than joint or muscle bleeding in individuals with haemophilia, but the most severely affected patients, have one or two episodes per decade. These may be painless and resolve spontaneously, but, if bleeding is heavy, it can produce clot colic. Clots may obstruct renal tubules or the ureter, causing temporary hydronephrosis[16].

Possibly the most frequently encountered emergent haemorrhagic event in haemophilia management is central nervous system (CNS) bleeding. Most of these events, which involve bleeding inside the skull or spinal canal, are caused by trauma. However, since patients with haemophilia can experience bleeding even weeks after a minor head injury, a history of head trauma may be hard to determine, particularly in children[17, 18].

Intestinal tract bleeding usually presents as obstruction due to intramural haemorrhage, but haematemesis and melaena also occasionally occur and should be routinely investigated, as they may be due to peptic ulcer or malignancy[16].

There is a wide spectrum of esophageal and gastrointestinal (GI) bleeding. A review of 41 episodes of gastrointestinal bleeding in one institution over 10 years implicated duodenal ulcer (22%) and gastritis (14%) as the most common source. In 22%, no source was identified. Mallory-Weiss Syndrome has also been cited as a cause for upper GI bleeding in haemophilia patients[20].

Surgery and open trauma invariably lead to dangerous haemorrhage in the untreated individual with haemophilia. There may be persistence of haemorrhage often after an initial short lived period of haemostasis. The incidence of bleeding in different sites is given in the tables 1 and 2[14].

Table 1: Incidence of different sites of bleeding in percentages

Site of bleeding	**Incidence in percentage**
Haemarthroses	70%-80%
Muscle/soft tissue	10%-20%
Other major bleeds	5%-10%
Central nervous system (CNS) bleeds	< 5%

Table 2: Incidence of bleeding in different joints

Joint	Incidence of bleeding in %
Knee	45%
Elbow	30%
Ankle	15%
Shoulder	3%
Wrist	3%
Hip	2%
Other	2%

5.1.4.2 Laboratory findings

Evaluation of an individual with a suspected bleeding disorder includes: platelet count and platelet function analysis (PFA closure times) or bleeding time, activated partial thromboplastin time (APTT), and prothrombin time (PT). Thrombin time and/or plasma concentration of fibrinogen can be useful for rare disorders[7, 8].

Screening tests show a long activated partial thromboplastin time (APTT), normal prothrombin time (PT), thrombin clotting time (TCT) and bleeding time, and a normal platelet count. Specific assays show factors VIII and IX clotting activity below 0.05 U/mL, with all other factors normal[21].

The normal level of factors VIII and IX is 50-150% and is measured by a clotting assay[7, 8]. In haemophilia the propensity to bleeding is related to the plasma factor VIII level. The classification of severity of haemophilia is set out in the Table 3[22]:

Table 3: Classification of severity of haemophilia

Severity	Clotting factor level % activity (IU/ml)	Bleeding episodes
Severe	1% (< 0.01)	Spontaneous bleeding, predominantly in joints and muscles
Moderate	1%-5% (0.01-0.05)	Occasional spontaneous bleeding. Severe bleeding with trauma, surgery
Mild	5%-40% (0.05-0.40)	Severe bleeding with major trauma

5.1.5 Treatment

The major precept of haemophilia care consists of adequate replacement of the deficient coagulation factor protein so as to prevent or reverse acute bleeding episodes. This is most effectively and efficiently accomplished by the administration of clotting factor concentrates, which contain an abundance of the specific deficient coagulation factor [23].

5.1.5.1 Clotting factor concentrates

Modern management of haemophilia began in the 1960's when the first FVIII plasma concentrates became available. This first generation of FVIII enabled a much more effective treatment than simple plasma. The life expectancy and quality of life saw unprecedented improvement[24].The effect of replacement therapy has significantly improved the morbidity and mortality of people with haemophilia[25].

The introduction of coagulation factor replacement therapy over the past half century has greatly contributed to the improvement in care of people with haemophilia [26]. Following the sequencing of the FVIII gene in 1984, the various mutations were identified (meaning that the severity of haemophilia and probability of the occurrence of inhibitors could be predicted) and the first recombinant concentrates were developed. The first generation of these rFVIII was licensed in 1993. Production of rFVIII using genetic engineering in theory eliminates the risk of infection by a human virus[13, 24]. Hamster cells are transfected with human clotting factor genes by recombinant DNA technology. Factor VIII produced by recombinant DNA techniques is available, safe, and effective[16].

5.1.5.2 DDAVP

Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) is a synthetic analogue of antidiuretic hormone (ADH). The compound boosts the plasma levels of FVIII and vWF after administration [22]. It can be used to treat mild haemophilia. This synthetic analogue of vasopressin retains the antidiuretic action of the natural hormone and also stimulates the release of tissue plasminogen activator. In practice, these effects can be used to elevate the plasma factor VIII level two- to fourfold above the baseline, presumably by its release from storage site(s). DDAVP is contraindicated in elderly patients and those with vascular disease, because arterial thrombosis is a theoretical risk and has been reported following DDAVP in these circumstances[27].

5.1.5.3 Gene therapy

Haemophilia continues to represent a leading candidate condition for the successful application of gene therapy[28].The ultimate goal of gene therapy is the replacement of a defective gene sequence with a corrected version to eliminate disease for the lifetime of the patient[29]. Although new paths to treatment are available, the path to a cure still has barriers that must be overcome. Whether some of these approaches might be applicable to human patients with inhibitory antibodies is not yet known, and additional preclinical studies are still needed [30].

5.1.5.4 Comprehensive Care Concept

Comprehensive haemophilia care has been defined as the continuing supervision of all medical and psychosocial factors affecting the person with haemophilia [31]. Comprehensive care is vital for patients with haemophilia to prevent early death and free patients from the complications that inhibit living normal lives. Experience has shown that once introduced in a country, there is a progressive restoration of normal healthy lives to the haemophilia community[5].

Services offered by haemophilia treatment centres (HTCs) adopting the comprehensive care model include establishing prophylaxis and other treatment protocols, development of psychosocial, education and research programme, maintenance of a patient registry, genetic and reference diagnostic services, orchestration and management of a wide variety of multidisciplinary interventions. Most centres practising this model of care are based in developed countries and can meet costs for plentiful treatment products through government or insurance-company funding. Not all the programmes are dependent on the level of product supply, however, many have been supported in countries with emerging economies as part of national healthcare systems, particularly in relation to blood management[31].

As the management of haemophilia is complex, it is essential that those with the disorder should have ready 24 hours access to a range of services provided by a multidisciplinary team of specialists [32]. Haemophilia is a relatively rare but complex disorder in terms of diagnosis and management. Optimal management of these patients, especially those with severe forms of the disease, requires more than the treatment and prevention of acute bleeding. Keys to improvement of health and quality of life include[33]:

•Prevention of bleeding
•Long-term management of joint and muscle damage and other sequelae of bleeding
•Management of complications from treatment including inhibitor development and viral infection(s) transmitted through blood products requiring long-term management.

These management goals are best met by a team of healthcare professionals providing comprehensive care. Haemophilia patients should ideally be managed in a comprehensive care centre staffed by the following core team members [31]:

• Haematologist(s);
• Nurse coordinator;
• Physiotherapist; and
• Social worker.

These staff members should have expertise and experience in treating bleeding disorders. The core team members should have access to the following support resources[22]:
• A coagulation laboratory capable of clotting factor assays and inhibitor detection;

• Appropriate clotting factor concentrates, either plasma derived or recombinant;
• If clotting factor concentrates are not available, a blood bank with expertise in preparing fresh frozen plasma (FFP) and cryoprecipitate.

Specialists should be available as consultants, as needed, and should include, among others, the followings[33].
• Orthopedic surgeon;
• Physiatrist/rheumatologist;
• Occupational therapist;
• Dentist;
• Geneticist;
• Hepatologist;
• Infectious disease specialist; and
• Immunologist.
In centres where there are many patients with chronic musculoskeletal problems from frequent bleeding, an orthopaedic surgeon should be a core team member.

5.1.6 Prophylaxis
Prophylaxis is defined as treatment by intravenous injection of factor concentrates in anticipation of and in order to prevent bleeding[34].It is recommended as preventive therapy for young boys with severe haemophilia in countries where safe factor concentrates are available[35].Prophylaxis can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A[36].To prevent hemophilic arthropathy, prophylactic treatment of children with severe haemophilia should be started before joint damage has occurred[37].

Many studies demonstrate the advantage of continuous FVIII prophylaxis over on-demand treatment in haemophilia A patients. Continuous prophylaxis reduces the number of bleeding episodes significantly. However, it cannot prevent bleeds completely and requires an almost 4-fold higher consumption of FVIII[38].

Prophylactic factor replacement therapy prevents the occurrence of joint bleeds and reduces the overall risk of disability associated with joint bleeds in haemophilia patients [39]. While primary prophylaxis(i.e. regular continuous long-term infusion of factor concentrates started before the age of two years and/or after no more than one joint bleed) is nowadays considered the gold standard for preserving joint function in patients with severe haemophilia, the benefits of secondary prophylaxis (i.e. all the long term regular treatments not fulfilling the criteria of primary prophylaxis) are still controversial[40].

5.1.7 Complications of Haemophilia

5.1.7.1 Complications of therapy

5.1.7.1.1 Immunological reactions

The immune response to factor VIII and factor IX, and the development of inhibitory antibodies is a complex multi-factorial process involving a variety of immune regulatory genes and cells, several of which have the potential to determine risk[41]. The development of inhibitors has been characterized as the most serious remaining complication of clotting factor treatment in persons with severe hemophilia. The characteristics of the mutation responsible for the disease is the strongest predictor of the risk of inhibitor development so far identified, but other genetic and environmental factors clearly are also involved[42].

Recent evidence suggests that alongside the strong genetic contribution to inhibitor formation, there are a number of non-genetic factors which promote formation of inhibitors [43]. Based on studies from around the world, it is estimated that the incidence of antibody development in persons with severe or moderately severe hemophilia A is between 20% and 33%. Among persons with haemophilia B, inhibitors are much less frequent, affecting only 1-6%[44].

Factors that appear to affect inhibitor development include the severity of haemophilia, age, genetics, and, possibly, the type of replacement therapy administered. Recent studies raise the concern that recombinant factor therapies may be associated with more rapid development and higher levels of inhibitors in previously untreated patients [33].

Management of patients with inhibitors involves control of acute bleeding episodes and, over the long term, induction of immune tolerance for the coagulation replacement therapy. Many with low or moderate levels of inhibitors may be treated simply by administering higher doses of dotting factor. Other therapies appropriate for those with high levels of inhibitors include porcine factor VIII and factor VIII bypassing agents, such as recombinant factor VIIa. Long-term immune tolerance has been achieved through the high-dose Bonn regimen and immunosuppressive regimens such as the Malmö method. Although management of inhibitor patients has improved, it still represents a major challenge [45].

Once replacement therapy is ineffective, acute management of bleeding requires agents that bypass factor VIII activity. Long-term management consists of eradicating the inhibitor through immune tolerance. Despite success in the treatment of acute bleeding and inhibitor eradication, there remains an inability to predict or prevent inhibitor formation. Ideally, prediction and ultimately prevention will come with an improved understanding of how patient specific and treatment-related factors work together to influence anti–factor VIII antibody production[46].

5.1.7.2 Infectious Complications

5.1.7.2.1 Hepatitis

Almost all multitransfused haemophilia patients treated before 1985 were infected with one or more agents of viral hepatitis. Although many infected patients did not suffer acute symptoms, at least 50 percent developed chronic persistent or chronic active hepatitis that led to cirrhosis[47]. The antigen-positive adult patients frequently have a superimposed infection with the delta agent, leading to severe active hepatitis and cirrhosis and an increased risk of hepatocellular carcinoma. Therapy with recombinant interferon alpha and ribavirin can reduce viral load and improve survival of affected patients[48]. A considerable number of these patients were also infected with human immunodeficiency virus (HIV)[49].

5.1.7.2.2 Human Immunodeficiency Virus (HIV)

Many individuals who received blood products from 1979 to 1985 contracted HIV. Approximately half of these individuals died of AIDS prior to the advent of effective HIV therapy[8]. Most HIV infection in the haemophilic population occurred before the virus was discovered and therefore before individual donor testing was introduced [50, 51].

Following the identification in 1984 of HIV as the causative agent of AIDS, investigators discovered that heat treatment (60°C for more than two hours) of concentrated clotting factors inactivated HIV. This, with the development of serologic methods to screen blood for HIV and the self-deferral of high-risk blood donors, minimized further risk of infection in persons with haemophilia[52].

5.1.7.2.3 Prions

Prions are infectious particles consisting of proteinaceous material devoid of a nucleic acid genome. Creutzfeldt-Jakob disease (CJD) is a member of a group of diseases known as Transmissible Spongiform Encephalopathies (TSEs) or prion diseases[53]. These are rare, fatal disorders that result in the progressive destruction of the nervous system. The potential for transmission of CJD through contaminated blood and blood products is of particular concern for the bleeding disorders community. Some studies support the idea that transmission of CJD by blood transfusions or blood products is very rare if it exists. However, because of the short incubation times seen in the studies and the very small number of cases, no one can definitely say that transmission is nonexistent[54].

5.1.7.3 Musculoskeletal complications

5.1.7.3.1 Muscle Haematomas

Haemorrhages in muscle or soft tissue are particularly dangerous when they occur in closed compartments, such as the volar aspect of the wrist and forearm, the deep palmar compartments of the hand, or the anterior or posterior tibial compartments. Such nerve compression due to a closed space hemorrhage, known as *"compartment syndrome,"* can compromise limb function [55].

5.1.7.3.2 Chronic haemophilic arthropathy

The most common complication of haemophilia is crippling joint disease. The degeneration of a normal joint after recurrent bleeds is a result of a number of mechanisms which finally interact to produce severe distortion[56]. This can develop any time from the second decade of life, sometimes earlier, depending on the severity of bleeding and its treatment. With advancing cartilage loss, a progressive arthritis condition develops along with secondary soft tissue contractures, muscle atrophy, and angular deformities. The goal of treatment is to improve joint function and relieve pain. Supervised physiotherapy is a very important part of management at this stage. Factor replacement is necessary if recurrent bleeding occurs during physiotherapy. Pain should be controlled with appropriate analgesics. If these conservative measures fail to provide satisfactory relief of pain and improved function, surgical intervention may be considered[14].

Between the second and fourth decades, many haemophiliac patients develop severe articular destruction. At this stage possible treatments include joint debridement, arthrodesis and arthroplasty[57].

Total joint replacement has been successfully performed in people with haemophilia for over 30 years. By far the greatest numbers have been total knee replacements. The benefits of pain relief and improved function provided by total joint replacement make this procedure the most successful orthopedic operation for managing chronic hemophilic arthropathy[58].

5.1.7.3.3 Chronic synovitis

The origin of haemophilic synovitis is clearly related to chronic accumulation of blood within a joint [59]. With repeated bleeding in a joint, the synovium becomes chronically inflamed and eventually hypertrophies, causing the joint to appear grossly swollen. This swelling is usually not tense, nor is it particularly painful. Diagnosis made by performing a detailed physical examination of the joint. The presence of synovial hypertrophy may be confirmed by ultrasonography and MRI. Plain radiographs and particularly MRI will assist in defining the extent of articular changes. The goal of treatment is to control the synovitis and maintain good joint function[14].

It has long been recognized that the emergence of chronic haemophilic haemarthroses is incited by a hypertrophic and highly vascular synovium and that removal of this synovium is the key to prevention of further joint damage. Removal of the synovium can be accomplished through surgical and non-surgical procedures[60].

5.1.7.3.4 Pseudotumour formation

Pseudotumors are blood cysts that occur in soft tissues or bone. They are rare but dangerous complications of haemophilia. Most pseudotumors are not associated with pain unless rapid growth or nerve compression occurs. They usually contain either serosanguineous fluid or a viscous brownish material surrounded by a fibrous membrane. Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) is useful for diagnosis. Needle biopsies of pseudotumors should be avoided because

of the risk of infection and haemorrhage. Surgical management is the most effective treatment for pseudotumor, although more conservative therapies cannot be overlooked in selected cases [61, 62].
While pseudotumors in patients with haemophilia are in themselves not haemophilic emergencies, an acute rupture of a large pseudotumour in the pelvis or thigh may lead to acute hypotension from blood loss. When such an event occurs, an immediate correction of the FVIII or FIX level is indicated, while keeping in mind that the presence of chronic clots with fibrinolysis in the pseudotumour may also predispose to further haemorrhage[55].

5.1.7.3.5 Fracture

Fractures are not uncommon in the person with haemophilia and occur most commonly around the knee and hip. The person with haemophilia is at risk for fracturing around joints that have significant loss of motion and in bones that are osteoporotic. Fractures managed with closed reduction and casts require clotting factor replacement therapy for 3-4 days, until swelling subsides[16].

5.2 Haemophilia in Arabic countries

5.2.1 Health care in Arabic region

Health care in Arabic countries is among the lowest levels worldwide. Although there are variations from country to country, in general the indicators of health care are low compared with western developed world. Many of these countries have now clear strategies towards an improved health care, but the expenditure on health is still low [63, 64].

The health care financing in Arabic countries is provided mainly from government revenues. The budgetary provision for the Ministries of Health has continued to increase (for example in Saudi Arabia from 2.8% of the national budget in 1970 to 5% in 2009). The remaining health services financing is derived from private sources (e.g. personal out-of pocket payments) and from occupational health insurance premiums mainly subscribed to by large private company employees[64]. Tables 4 and 5 shows the health expenditure and health indicators in Arabic countries.

Table 4: Health expenditure among Arabic countries[1]

Nr.	Country	GNI per capita in $	Total expenditure on health per capita $	Total expenditure on health as % of GDP
1.	Jordan	5,720	499	9.3
2.	Lebanon	11,750	1,054	8.1
3.	Sudan	1,920	161	7.3
4.	Djibouti	2,320	162	7.0
5.	Tunisia	7,460	524	6.2
6.	Algeria	7,890	544	5.8
7.	Yemen	2,220	142	5.6
8.	Morocco	4,190	251	5.5
9.	Saudi Arabia	24,500	1,150	5.0
10.	Egypt	5,470	282	5.0
11.	Bahrain	33,430	1,557	4.5
12.	Libia	16,270	709	3.9
13.	Iraq	n.a	167	3.9
14.	Kuwait	53,480	1,498	3.3
15.	Oman	22,170	787	3.0
16.	Syria	4,490	138	2.9
17.	Emirates	45,660	1,756	2.8
18.	Somalia	n.a	18	2.6
19.	Mauritania	1,990	47	2.5
20.	Qatar	n.a	2,090	2.5

[1] Source: World Health Organization, Countries profiles, 2009

Table 5: Health status indicators in Arabic countries[2]

Nr.	Country	Life expectancy at birth m/f	Healthy life expectancy at birth m/f	Probability of dying under 5 years per 1000 population
1.	Emirates	77/79	64/64	7
2.	Qatar	78/79	67/64	9
3.	Bahrain	73/76	64/64	12
4.	Oman	72/77	63/65	12
5.	Lebanon	71/77	59/62	12
6.	Kuwait	78/79	67/67	13
7.	Syria	71/76	60/63	16
8.	Libia	70/75	62/65	19
9.	Tunisia	73/77	61/64	21
10.	Saudi Arabia	69/75	60/63	21
11.	Egypt	69/73	58/60	21
12.	Jordan	69/74	60/62	25
13.	Algeria	71/74	60/62	32
14.	Morocco	71/75	59/61	38
15.	Iraq	62/70	49/51	44
16.	Yemen	63/66	48/51	66
17.	Djibouti	58/62	43/43	94
18.	Sudan	59/59	47/50	108
19.	Mauritania	57/60	43/46	117
20.	Somalia	54/56	36/38	145

5.2.2 Haemophilia care in Arabic world

Haemophilia care in Arabic world shows variations from country to country. It varies from a good available care with presence of specialized haemophilia centers (e.g. Egypt, Jordan) to absence of care at all (e.g. Yemen, Somalia).

In the Global Survey of WFH in 2009, 9702 cases of haemophilia were reported from 13 Arabic countries [3, 9]. Of 22 countries of the Arab League, only 13 have at least one haemophilic center. Countries such Egypt, Algeria, Tunisia, Jordan and Syria have good organized programs and more than one haemophilia center. Other countries provide a relatively weak care compared to their financial resources; for example Saudi Arabia, with a population of about 24 million, and 326 reported cases of haemophilia has only one specialized care center for haemophiliacs[3].

Factor use also varies from country to country, according to economical level. High income countries consume large quantities; for example Saudi Arabia reported the highest use of factor concentrates in the region, about 191 736 IU per person with haemophilia A (PWHA)[25].

[2]Source: World Health Organization, Countries profiles, 2009

In other countries such as Yemen, Somalia, Djibouti, Mauritania, there is no specialized center and only little or no care for haemophiliacs is available. The major problems with regard to haemophilia care in those countries are[6]:

- Lack of facilities for a proper laboratory diagnosis;
- Inadequate supply of safe factor concentrates.

The majority of population in such Arabic countries lives in rural area, under poor health care and where educational status is at the lowest levels with high illiteracy rate. Awareness and knowledge about the nature of the disease among patients and their families is low. Factor concentrates are available only in central hospitals, usually in the capital cities. Many haemophiliacs in villages have no access to factor concentrates and probably die from life threatening manifestations of the disease such as intracranial bleeding, before they reach the central clinics for a specialized treatment.

Table 6: Some indicators of haemophilia care among some Arabic countries[3]

Nr.	Country	Population in thousands	Estimated cases of haemophilia[4]	Reported cases of haemophilia	Number of Haemophilia centers
1	Egypt	80,471	5,320	5,307	10
2	Algeria	34,178	2,260	1,291	10
3	Iraq	28.506	1,888	841	1
4	Sudan	41,087	2,500	618	1
5	Saudi Arabia	29,207	1,941	326	1
6	Syria	22,198	1,290	300	2
7	Tunisia	10.215	665	250	4
8	Jordan	6,342	412	248	3
9	Lebanon	4.055	266	165	1
10	Palestine	4,013	266	131	6
11	Qatar	833	56	112	2
12	Oman	3,418	226	93	2
13	Bahrain	739	50	20	1

[3]Source: World Federation of Haemophilia, Global survey report, 2009

[4] These values were estimated according to prevalence rates used by WFH: Hemophilia A and B: 133 per million male population

5.3 Haemophilia in Yemen

5.3.1 Introduction to Yemen

5.3.1.1 Geography and demography

Figure 1: Political Map of Republic of Yemen[5]

Republic of Yemen is located in Southwest Asia at the southern tip of the Arabian Peninsula between Oman and Saudi Arabia. It is situated at the entrance to the Bab-el-Mandeb Strait, which links the Red Sea to the Indian Ocean (via the Gulf of Aden) and is one of the most active and strategic shipping lanes in the world. Yemen has an area of 555,000 square kilometers, including the islands of Perim at the southern end of the Red Sea and Socotra at the entrance to the Gulf of Aden. Yemen's land boundaries total 1,746 kilometers. Yemen borders Saudi Arabia to the north and Oman to the northeast[65].

According to the latest census in 2008, the Republic of Yemen had a population of 22.879.805 persons[66]. Yemen's population has more than doubled since 1975 and has grown approximately 35 percent since the 1994 census, making Yemen the second most populous country on the Arabian Peninsula[64].

Population pyramid is with a wide base and about half of the population is under 15 years old adding to the burden on the health sector for their special diseases management and protective programs. Population growth rate, at 3.02 percent per year is among the highest in the world, family planning activities are minimal, and the use of modern contraceptives is particularly low at 13 percent[64].The situation is compounded by the wide regional disparities and the significant differences between urban and rural conditions.

The main demographic indicators are given in Table 7 and Figure 2.

[5] World Fact Book, Middle East, Yemen Profile, 2010

Table 7: Demographic indicators on Yemen[6]

The indicator	Values	Year of estimation
Total population in thousands	22,198	2008
Males population in thousands	11,826	2008
Females population in thousands	10,372	2008
% Urban population out of total population	29	2008
Crude birth rate per 1000 population	39.7	2006
Crude death rate per 1000 population	9.0	2006
% Population growth rate	3.0	2007
% Population below 15 years	45.0	2007
% Population 65 years and over	3.5	2007
Total fertility rate (R) per woman	6.1	2006

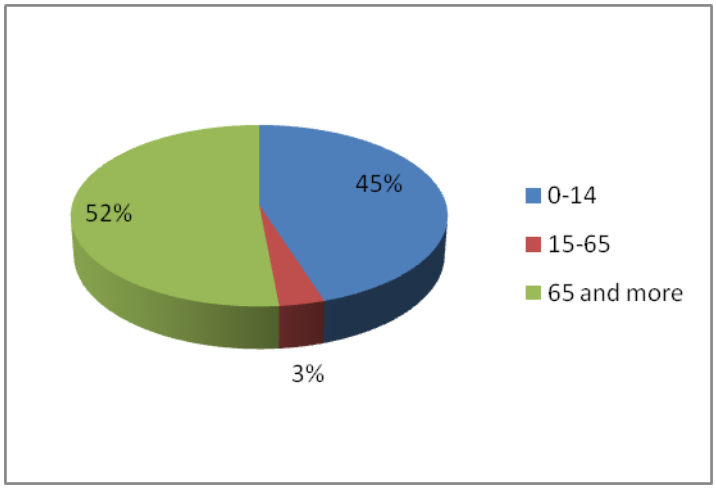

Figure 2: Composition of Yemeni population by age groups[7]

[6] Yemeni Ministry of Public Health and Population, Annual Report, 2009
[7] WHO, Eastern Mediterranean Regional Office, Yemen profile, September 2009

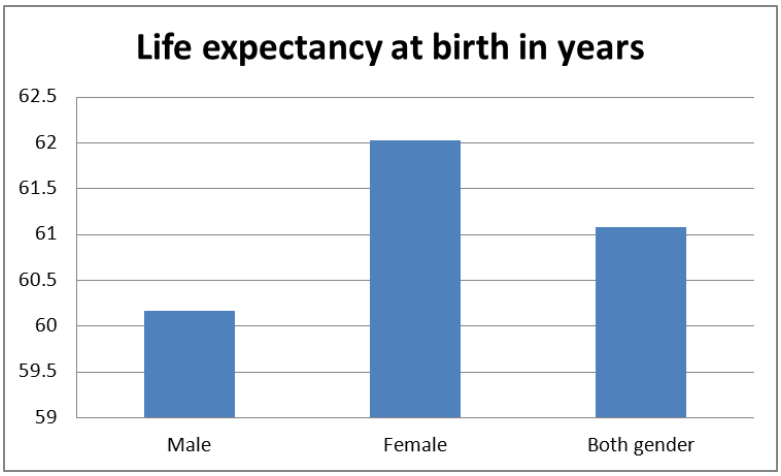

Figure 3: Life expectancy at birth[8]

Yemen's population is predominantly Arab, but it also includes Afro-Arabs and South Asians. Arabic is the official language. English is also used in official and business circles. In the Mahra area (the extreme east), several non-Arabic languages (including Mehri) are spoken. Virtually all citizens of Yemen are Muslims, either belonging to the Zaydi order of Shi'a Islam or to the Shafa'i order of Sunni Islam. There are also Jews, Christians and Hindus.

5.3.1.2 Socio-economic status

Yemen is one of the poorest countries in the Arab world and its economic fortunes depend mostly on oil. Most people are employed in agriculture and herding, services, construction, industry, and commerce account for less than one-fourth of the labor force. Unemployment rate is 15% and population below poverty line 34,8%. GDP is $26.6 billion, GDP - real growth rate is 3.9%, GNI - per capita is $1060 and labor force is 5.98 million[67].

5.3.1.3 Education

Education indicators have improved during the last two decades but are still very low. The adult literacy rate is only 53 percent, and the gross enrollment ratio for basic education is 73 percent. Quality is widely acknowledged to be poor. The gender gap is among the widest in the world, with only 56 percent of primary school-aged girls in school, and much less freedom of female social and economic opportunity[64].

Some education indicators are given in Table 8.

[8] WHO, EMRO, Yemen profile, September 2009

Table 8: Education indicators among Yemeni population[9]

Indicators	Values in %
Adult literacy rate 15+ years, total	*53*
Adult literacy rate 15+ years, males	73
Adult literacy rate 15+ years, females	31
Gross primary school enrolment ratio - total	65
Gross primary school enrolment ratio - male	73
Gross primary school enrolment ratio - female	56
Gross secondary school enrolment ratio - total	50
Gross secondary school enrolment ratio - males	69
Gross secondary school enrolment ratio - females	31

5.3.1.3 Health care system

The Yemen Health Care system represents about 95% of the total health care and services provided to the citizen with government finance to its prevention, medical and rehabilitation activities. Its structure is based on the health centers and units at the first touchline[66].

5.3.1.3.1 Public health care

The health care system in Yemen consists of a large public sector with a sizable private sector**.** Public health care is organized in three levels: Primary Health Care (PHC) supported by secondary and tertiary referral care. PHC focuses on preventive health programs (immunization, Mother and Child Health (MCH) and family planning, health education, etc.) and provides first level curative care. It starts at the village level where PHC units are run by paramedical staff; the units are backed up by PHC centers, most of which are managed by one physician and have laboratory and X-ray facilities. Patients who cannot be properly managed at the PHC level are referred to rural, district or governorate hospitals (secondary care) for further diagnostic and curative treatment[66]. Some of these hospitals also provide support for national or regional immunization and disease control programs. Finally, tertiary hospitals provide specialized care and serve as teaching hospitals for the medical faculties of the country's universities[64].

Tables 9, 10, 11 and 12 show some health indicators in Yemen.

[9] WHO, EMRO, Yemen profile, September 2009

Table 9: Health expenditure indicators of Yemen[10]

Indicator	Value	Year
GDP per capita US$ exchange rate	1,060	2008
Total expenditure on health (per capita) US$ exchange rate	41	2006
Government expenditure on health (per capita) US$ exchange rate	21	2006
Total expenditure on health of % of GDP	4.5	2006
General government expenditure on health as % of total health expenditure	50.1	2006
Out-of-pocket expenditure as % of total health expenditure	47.5	2006
General government expenditure on health as % of total government expenditure	5.5	2006
Ministry of health budget as % of government budget	4.0	2006

Table 10: Public Health facilities in Yemen[11]

Facilities	No
Referral Hospitals	2
General Hospitals	53
District Hospital	182
Health Center	793
Health Units	2774
Total Number of Health Facilities	3852
Referral Hospitals Beds	1207
General Hospitals Beds	8924
District Hospitals Beds	4669
Total Numbers of Beds	15184

[10]Source: WHO, Countries profiles, Yemen, 2008

[11]Source: Yemeni Ministry of Public Health and Population, 2009

Table 11: Public Health Manpower[12]

Categories	**No**
Physicians	6338
Dentist	535
Pharmacist	2336
Nurses	12227
Medical Assistants	2455
Morshed/ Morshedah[13]	2801
Technical Assistants	5729
Others	11182
Total	46331

Table 12: Health facilities per 10000 of population

Items	**No**
Hospitals	0.1
Beds	7
Physician	3
Dentist	0.2
Pharmacist	1
Nurses	7.3
Paramedical	10.2
Health Centers &Units	2

[12] Source: Yemeni Ministry of Public Health and Population, 2009
[13] Health Advisor

5.3.1.3.2 Private Health Care System (Modern, for-profit)

The role of the private sector increasingly grows. It concentrated in the capital city and main cities of the governorates. The size of this sector indicates the availability of 1336 doctors' clinic, 615 foreign doctors and 309 foreign technicians[66].There is evidence of an expanding role for the private for –profit health sector in the delivery of health services. Although the exact number and scope of their activities are not yet known, it is likely that the coordination of investment and activities between the public and the private sectors will become an important issue in the coming years[64]. Table 13 gives some information about private health facilities in Yemen.

Table 13: Private Health facilities[14]

Facilities	**No**
Hospitals	167
Polyclinic	321
Health centers	420
Physicians clinic	1336
Spec. clinics	838
Dental clinic	654
Dental Lab	155
Laboratory	1189
Radiology Clinic	224
PHC	1355
Midwifery	69
Pharmacy	2681
Drug Stores	2123

These services are provided by the Non-governmental Organizations (NGO) local or international, religious or social. There are two local NGOs having wide health activities all over the country the first is the Yemen's Charity Society, which was launched and licensed in 1990. It had multiple agreements with the Ministry of Health, Social Fund for Development, international organizations, World Bank, and international NGOs for financing the health projects[64]. Their health facilities

[14] Source: Yemeni Ministry of Public Health and Population, 2009

cover13 out of 20 governorates and they have 11,500 employees serving population of 786,959. They have 5 hospitals (2 are specialized), 11 health centers, 3 dispensaries, and 1 health unit. All these facilities are equipped with the latest technology. They also have outreach activities and school health provision. The second is the Society of Family Care, which provides all the reproductive health services and mainly works in Sana'a[66].

5.3.1.3.3 Traditional

Traditional medicine still plays an important role in Yemen. In many rural areas, it is the only medical assistance available to people, but it also competes with modern public and private health care which is either more expensive or regarded with suspicion. Medical practices are rooted in the Greco-Arabic tradition and have physical as well a spiritual dimension. Some of the more common procedures are cupping to draw off blood, cautery, bone setting and minor surgical techniques. In addition, local plant and animal products, some minerals and changes in dietary habits are used to treat ailments. Local birth attendants assist with deliveries and provide post-natal care. There are many aspects of traditional health care which are beneficial to individuals and the community, and which could complement modern medical practice. Traditional cures are often effective although they fail with most of the endemic diseases.

5.3.1.3.4 Public /private interactions

There is a private sector department at the MOPH with its policy and system but in reality it is only in papers and needs to be activated. There is a little interaction between the MOPH and the local NGO-s especially the Islah Social Charity Society, which implement some health projects with the MOPH. The interaction was based on competition with wide lack of coordination to improve the coverage and accessibility of health care services. The services were of low standards and there was poor management[68].

5.3.1.3.5 Health Insurance

Currently the MOPH&P provide health insurance coverage only for the government employee. The private companies and organizations cover also their employees. The rest of population has no health insurance. The health insurance policies in Yemen are offered by private or nonprofit seeking organizations. At present, there are very few insurance companies in Yemen that offer insurance policies to both public and private organizations[66].

5.3.2 Epidemiology of Haemophilia in Yemen

There are no official data about the prevalence of haemophilia in Yemen as there is no organized care strategy for this disease. The cases are not reported and even the major hospitals or the Ministry of Health have no registry or statistics regarding haemophilia patients. However, referred to the standard incidence used by WHO and WFH, Yemeni haematologists estimate that about 1460 people in Yemen are affected by haemophilia[69].

Something that could be considered as specific for Yemen and Arabic countries in general, is the fact of consanguinity and marriage between the members of same large family[15]. This factor may probably increase the prevalence of this disease in this Arabic country. A haemophilia study was made among a large family in a province of Yemen. The pedigree was composed of 76 members, including 33 females and 43 males. 27.2 % of the females were obligative carriers, each having at least one hemophilic son. 39.5 % of males were hemophilic, and among them 64.7 % died of hemophilia at age ranging from 20 days to 26 years, while the rest still live[70].

During my visit to the Branch of Blood Diseases at Thawra General Hospital in capital city, Sana'a, I found that during second half of year 2009, were treated 135 cases of haemophilia. The age of patients varied between 11 months and 29 years. Most of cases were considered as severe according to the clotting factor assay.

5.3.3 Ways of management, facilities, centres and clinics

Republic of Yemen is the only country of Arabic peninsula without a specialized centre for haemophilia. Taking in consideration that Yemen is a poor developing country spending about 5,6 % of its GDP on the health care, the Ministry of Health concern is focused on the major health problems of the country, such as Infectious diseases[16] and Malignancies. As a result only a small or no attention is paid to rare diseases such as haemophilia.

There are only two hospitals in the capital city, which offer treatment for Yemeni haemophiliacs. Thawra General Hospital and Republican Hospital are the two largest government hospitals in the country. In either of them, there is a branch of Haematology, at the Internal Medicine Department, dealing with haemophilia cases.

Many cases are diagnosed accidentally during routine investigations done before surgical interventions or after circumcision. Usually, the new cases are diagnosed by haematologists or internists at their private clinics and then they are referred to the centres mentioned above. After the confirmation of the diagnosis, the patients are either admitted as stationary or treated as day ambulatory cases with factor concentrates. No unified protocol is used by haematologist, and each of them follows certain recommendations and protocols following the international literature and guidelines. Patients with complications are treated in other departments according to their conditions [71].

Until year 2000 there was no factor concentrates available, and the cases were either treated with FFP or DDAVP or referred outside the country for a better treatment. After an absence for two years (2007-2009), factor concentrates are again available in adequate amount. They are supposed to be offered free of charge by Ministry of Health, which supply only the two hospitals mentioned above[69, 70].

[15]Marriage between cousins in Arabic countries is a common old tradition

[16]About 15000 people die annually from Malaria, which is endemic in many areas of Yemen

As no specialized centre is available, there is no comprehensive care and no educational program about the nature of the disease and its prophylaxis. Absence of genetic counseling and in-existence of facilities for early and prenatal diagnosis, are among the factors that help in the increase of number of haemophiliac individuals in Yemeni community[70].

Another challenge for haemophiliacs in Yemen is the large distance they have to cross, from their hometowns and villages until they reach the capital city. Most of the population lives in rural areas where no facilities are available. With a difficult mountainous terrain and a bad infrastructure, many of them have to travel more than 10 hours with their own cars, until they arrive in Sana'a. Under such conditions some of hemophiliacs with severe forms of the disease and life threatening complications have little chances to survive.

Another treatment option is referring of cases outside the country. Some patients, who are capable to pay the high costs of such choice, choose other Arabic countries like Egypt or Jordan or even western countries, seeking for a better care. However, the poor majority of haemophiliacs do not have such a chance[69].

5.3.4 Costs and financial resources

Haemophilia is a complex health problem rather than only a deficiency of a single clotting factor. The impact and consequences of this disease affect significantly the socio-economic status of the community. For a proper care of a haemophilic patient, thousands of dollars are needed every year.

In a country such Yemen, neither government nor the patient are able to pay for a proper management. The Yemeni Ministry of Health is supposed to provide factor concentrates free of charge for every haemophilic patient according to the need, but nothing more. In the absence of health insurance system, the patient should pay for every kind of intervention and management of subsequent complications. Even the services provided by government hospitals are not free.

In Yemen, as in many other countries, the health services are under a severe financial strain which cannot be resolved with the present budgetary allocations. The actually available funds for health care provision are insufficient and the burden of obtaining adequate quality care is left to the individual patient, often at high cost [71].

In 1994, a cost sharing strategy has been introduced. Its objective was to secure sufficient funds through revenues from fees and charges for services in order to improve maintenance of facilities and supply of drugs, as well as the motivation and performance of health personnel. Cost sharing in Yemen depends on two types of charges. The first is fee for service, or user fees, for curative services. In Yemen, it is expected that user fees will contribute approximately 10-15% to overall running costs in government facilities. The second type of charge will be for essential drugs. The government will import low cost, good quality, generic essential drugs, and recover

100% of the costs for these basic essential drugs through client payments into a revolving drug fund[64, 66].

When patients do go to health facilities the cost is high, with on average $96.57 for an admission and $18.70 for an outpatient consultation. The average total cost for a hospital admission in government facilities is slightly lower than in private hospitals. This finding – contrary to common thought that private hospitals are much more expensive – is due to fact that cost linked to patients, required to buy drugs outside in private pharmacies. Outpatient consultancies in government facilities is cheaper ($13.06) than in private health facilities ($24.33), but is considered by most respondents of poorer quality[64].

Under such conditions, without a health insurance, haemophilic patients face a big challenge on dealing with complications of the disease like transmitted infections or musculoskeletal complications.

5.4 Haemophilia in western European countries

5.4.1 Health care in western European countries

Health care in western European countries ranks among the highest levels worldwide. Such good care is a result of combination of adequate financial resources, presence of specialized centers and well trained medical staff. As shown on table 14, some European countries spent more than 10% of their GDP on health care, and this to high compared to Arabic countries[63].

Table 14: Health expenditure among some western European countries[17]

Nr.	Country	GNI per capita in $	Total expenditure on health per capita $	Total expenditure on health as % of GDP
1.	Luxemburg	52,770	6,526	7.8
2.	UK	36,240	3,399	9.3
3.	Italy	30,800	3,027	9.5
4.	Finland	35,940	3,357	9.7
5.	Spain	30,830	3,150	9.7
6.	Norway	59,250	5,395	9.7
7.	Sweden	37,780	3,690	9.9
8.	Netherland	40,620	4,389	10.8
9.	Germany	35,950	4,129	11.3
10.	Switzerland	39,210	5,072	11.3
11.	France	33,280	3,943	11.7
12.	Belgium	35,380	4,237	11.8

Life expectancy shows high levels, varying from country to country, between 77 - 80 years for men, and 82-85 for women as shown in table 15. Another important health indicator, probability of dying under 5 years, is very low compared to Arabic region. This indicator is up to 12 times higher in some Arabic countries, as an example, it is 60 in Yemen, but only 4 in Germany[63].

Table 15 shows some health care indicators in some western European countries.

[17]Source: Organization for Economic Cooperation and Development (OECD); World Health Organization, Countries profiles, 2009

Table 15: Some Health indicators among European countries[18]

Country	Life expectancy in years at birth m/f	Healthy life expectancy at birth m/f	Probability of dying under 5 years per 1000 population
Luxemburg	78/83	69/74	2
Finland	77/83	69/74	3
Italy	79/84	71/75	4
Sweden	78/85	72/75	4
Spain	78/84	70/75	4
Norway	79/83	70/74	4
Germany	78/83	70/74	4
France	78/85	69/75	4
Switzerland	80/84	71/75	4
Netherland	78/83	70/73	5
Belgium	77/83	69/73	5
UK	78/82	69/72	5

5.4.2 Haemophilia care

In year 2007 were reported 27,874 cases of Haemophilia A and 5,271 cases of Haemophilia B in European Union (EU) countries were reported[72].

Haemophilia care in western European countries is a well organized process providing a qualified management to all hemophiliacs, through the Haemophilia treatment centers (HTCs) which exist in all the EU Member States. Choice and levels of treatment, availability of comprehensive care and access to prophylaxis vary widely from one Member State to another [31].

In 2009, a questionnaire was circulated to 19 national haemophilia patient organizations in Europe affiliated to the European Haemophilia Consortium (EHC) and the World Federation of Hemophilia (WFH) to seek information about the organization of haemophilia care and treatment available at a national level. The responses received highlighted differences in the level of care despite the recent promulgation of consensus guidelines designed to standardize the care of haemophilia throughout the continent of Europe[73]. Table 16 shows the way of organization for haemophilia care in European countries.

[18]Source: World Health Organization, Countries profiles, 2008

Table 16: Central organization for haemophilia care[19]

Country	Has a general organization for haemophilia care
Romania	Yes
Bosnia-Herzegovina	No
Bulgaria	No
Lithuania	Yes
Latvia	Yes
Portugal	No
Russia	Yes
Switzerland	No
Poland	Yes
Slovakia	Yes
Belgium	Yes
France	Yes
Hungary	Yes
United Kingdom	Yes
Ireland	Yes
Germany	No
Sweden	No
Czech Republic	Yes
Netherlands	Yes

There is a wide range in factor VIII consumption with usage ranging from 0.38 IU per capita in Romania to 8.7 IU per capita in Sweden (median: 3.6 IU per capita). Despite the specific inclusion of coagulation factor concentrate in the WHO list of essential medications, cryoprecipitate is still used in some eastern European countries[73].

The most significant advantage of haemophilia care in most of these countries is presence of the prophylactic treatment. Clinical studies show that the cost for treating haemophilia patients prophylactically is significantly higher than the cost of on-demand treatment; however, reducing the number of joint bleeds reduces other medical treatment costs and prevents disability in this population. Indeed, while analyses were not able to demonstrate significant differences with these other medical treatment costs, it is observed a trend that suggested hospital costs were lower for haemophilia patients treated prophylactically [39].

Table 17 shows that access to treatment for haemophilia patients in different European countries is different.

[19]O'Mahony B, Haemophilia care in Europe: a survey of 19 countries, 2011

Table 17: Access to treatment for haemophilia patients in some European countries[20]

Country	Plasma	Cryoprecipitate	Plasma derived Factor Concentrates	Recombinant Factor Concentrates
Belgium	Never	Never	Rarely	Always
Bosnia-Herzegovina	Rarely	Rarely	Always	Rarely
Bulgaria	Never	Never	Always	Rarely
Czech Republic	Never	Never	Always	Rarely
France	Never	Never	Always	Always
Germany	Never	Never	Always	Always
Hungary	Never	Never	Always	Always
Ireland	Never	Never	Never	Always
Latvia	Never	Never	Always	Never
Lithuania	Rarely	Rarely	Always	Rarely
Netherlands	Rarely	Never	Always	Always
Poland	Never	Never	Always	Never
Portugal	Never	Never	Always	Always
Romania	Always	Rarely	Rarely	Rarely
Russia	Rarely	Rarely	Always	Rarely
Slovakia	Never	Never	Always	Rarely
Sweden	Never	Never	Rarely	Always
Switzerland	Never	Never	Rarely	Always
United Kingdom	Never	Never	Rarely	Always

The expected annual cost (in the year 2000 prices) for a 30-year-old patient with average individual and treatment characteristics for on-demand EUR 51 832 and for prophylaxis EUR 146 118, was obtained from panel-data analysis of an 11-year retrospective panel of 156 patients with severe haemophilia in Norway and Sweden. Costs included haemophilia-related treatment costs within the health-care sector (factor concentrate, doctors' visits, diagnostic procedures, hospitalization, invasive procedures, etc.) and cost for haemophilia-related resource use in other sectors [74].

Some haemophilia care indicators among some western European countries are given in the Table 18.

[20] O'Mahony B, Haemophilia care in Europe: a survey of 19 countries, 2011

Table 18: Indicators of haemophilia care among some western European countries[21]

Country	Reported cases of haemophilia	Haemophilia centers	Reported use of factor concentrates VIII and IX	Reported factor use per PWH
Germany	4,320	32	770,000,000	178,240
France	5,153	40	456,372,550	88,564
UK	6,460	87	458,919,047	71,040
Italy	3,270	52	350,000,000	107,033
Sweden	1,020	3	95,422,000	93,550
Netherlands	1,397	13	n.a	n.a
Belgium	936	7	n.a	n.a
Spain	1,985	38	230,080,500	115,909
Norway	397	1	20,000,000	n.a
Finland	322	8	n.a	n.a
Denmark	475	2	n.a	n.a
Switzerland	672	11	35,000,000	52,083

[21]Source: World Federation of Haemophilia, Annual Global Report, 2009

5.5 Haemophilia in Germany

5.5.1 Introduction to Germany

5.5.1.1 Geography and demography

Figure 4: Map of Federal Republic of Germany[22]

The Federal Republic of Germany is a country in Central Europe, stretching from Alps to the North Sea, with a territory of 357,021 km^2, consisting of 349,223 km^2 of land and 7,798 km^2 of water[75]. Germany has the second largest population in Europe and the seventh largest area, sharing borders with nine European countries: Denmark, Poland, Czech Republic, Austria, Switzerland, France, Belgium, Luxembourg and Holland.

According to the official statistics, Germany has about 82,218,000 inhabitants which correspond to a population density of 230 persons per square kilometer[76].

Table 19: German Population and its gender distribution[23]

Specification	2005	2006	2007
Total	**82,438.0**	**82,314.9**	**82,217.8**
Male	40,340.0	40,301.2	40,274.3
Female	42,098.0	42,013.7	41,945.5

[22] Source: CIA Fact Book, Germany profile, 2011
[23] Source: German Federal Statistical Office, 2010

Table 20: Live births and deaths among German population[24]

Specifications	2007	2008	2009
Live births	684,862	682,514	665,126
Per 1 000 inhabitants	8.3	8.3	8.1
Deaths	827,155	844,439	854,544
Per 1 000 inhabitants	10.1	10.3	10.4

5.5.1.2 Economy

Germany has the largest national economy in Europe, and the fifth largest GDP in the World[75]. Exports account more than one-third of national input. Germany is the second largest exporter in the World[77].

GDP is $ 3,330 billion, GNI - per capita is $ 42,450 and labor force is 43.51 million. The service sector contributes around 70% of the total GDP, industry 29,1% and agriculture 0,9%. Most of country's products are in engineering, especially in automobiles, machinery, metals, and chemicals[77].

5.5.1.3 Health care system

Federal Republic of Germany has a modern and efficient health care system that ensures its citizens the provision of high-quality care. The roots of the German health system date back to 1883, when nationwide health insurance became compulsory. Today's system is based on social health insurance and characterized by three co-existing schemes. In 2003, about 87% of the population were covered by statutory health insurance; based on income, membership was mandatory for about 77% and voluntary for 10%. An additional 10% of the population took out private health insurance; 2% were covered by governmental schemes and 0.2% were not covered by any third-party-payer scheme[78, 79].

Nearly 2,200 hospitals and more than 300,000 doctors care for upwards of 72 million members of the statutory and 8.5 million members of the private health insurance. At the same time, an increasing number of people are finding work in the health care system, their current number standing at about 4.3 million. Since 1999, this workforce has increased by approx. 200,000 in spite of the difficult economic situation[80].

Annual health care expenditure amounts to 11,3 % of the gross domestic product. Being the largest European market, Germany is a highly attractive location for the pharmaceutical industry, medical technology and biotechnology. The German health care system is markedly less regulated than most of its counterparts throughout Europe, so that innovative products make it to market very quickly. In 2005 alone,

[24] Source: German Federal Statistical Office, 2010

we saw more than 3,000 new patents in the medical sector. Germany is second only to the USA among world market leaders in the field of medical technology[78, 80].

5.5.2 Haemophilia Care in Germany

According to last Global Survey of World Federation of Haemophilia (WFH) there are about 4320 people affected by haemophilia in Germany[3].

In Germany, people with haemophilia are entitled to a choice of all treatments ranging from an optimal level of factor replacement therapy on demand as well as on a prophylactic basis for those who need it, to comprehensive care at a Haemophilia Treatment Centre. All these measures are cost effective as they help secure a high quality of life through lowering the risk of disability, thus reducing direct costs for management of damaged joints and extensive care for a disabled person, as well as indirect costs through loss of workforce[81].

Haemophilia care in Germany is provided through 12 specialized Haemophilia Treatment Centers. Apart from treatment and care at the HTCs, specialized physicians in practices and at haematology units in general hospitals provide care. Home treatment is available for children as well as for a number of people suffering from severe haemophilia[72].

Germany stand out for using a huge amount of FVIII IUs per PWHA (person with hemophilia A), about 114 333 IU per PWHA [25]. About half of the factor concentrates used in Germany are recombinant clotting factors and the other half are human plasma-derived concentrates, with the average number of units of factor VIII concentrate used per capita being 5.9 IU. About 90% of children and 40% of adult people with haemophilia in Germany receive prophylactic treatment[81].

6 The empirical study

6.1 Study design

The empirical study is divided in two parts. The first part is based on data and chart abstraction analysis collected through interviews of haemophilic patients from Haematology Department at Thawra General Hospital in Sana'a, Yemen. Thawra General Hospital is the largest referral hospital in the country with a capacity of 900 beds[66]. Demographic data, diagnosis, treatment modality, complications of haemophilia and cost of treatment, were collected and discussed in a retrospective analytical study. In the second part, were analyzed the data obtained from European Study in Clinical, Health Economic and Quality of Life (ESCHQoL) regarding the haemophilic patients in Germany. European Study in Clinical, Health Economic and Quality of Life outcomes in Haemophilia treatment is a study funded by European Commission and applied to 1400 haemophiliacs in 21 European countries between 2004 and 2006.

6.2 Methods

The theoretical part is based on:

- Literature research including original grey and peer reviewed articles regarding epidemiology, diagnosis and management of haemophilia.
- Interviews of Yemeni haematologists and WFH representatives for Arabic region regarding the haemophilia care in Yemen and other Arabic countries.
- Web based research.

The empirical part is based on data collection and descriptive data analysis.

6.3 Patients

This study was focused on Yemeni and German patients affected with Haemophilia A or Haemophilia B. Only cases with severe form of the disease took part.

6.4 Data sources and survey instruments

In addition to direct interviews of haemophilic patients, medical records and files provided by Hematology Department at Thawra General Hospital in Sana'a were used as data sources for this study. The ESCHQoL questionnaire survey was applied to all Yemeni patients who took part in this study. Data of German patients are obtained from ESCHQoL program with the permission of its authorities. The data and information obtained from questionnaire were analyzed through Microsoft EXCEL 2010 program. The questionnaire sample applied in this study is given in the appendix.

6.5 Data collection and interpretation

Data collection was a part of a study which took place between Munich and Sana'a during a period of time from 01.07.2009 to 01.12.2010. Two separate visits to Thawra General Hospital and other private clinics in Sana'a were focused on collection of all necessary data and information about situation of Yemeni haemophilic patients and care provided to them in the last 6 months. The Yemeni patients were collected according to their clinical presentation and laboratory findings. The German patients

were matched to Yemeni haemophiliacs, regarding their age and severity of disease. The data were interpreted on the light of recommendations and advices given from experienced haematologists at Thawra General Hospital and Republican Hospital in Sana'a. The Yemeni patients were collected according to their clinical presentation and laboratory findings. The German patients were matched to Yemeni haemophiliacs, regarding their age and severity of the disease.

6.6 Results

6.6.1 Yemen

6.6.1.1 Case collection

During my visit in the Haematology Department at Thawra Hospital in Sana'a we interviewed 20 severe cases of haemophilia. I collected them from a total number of 39 patients who were seeking for medical care in the Haematology Department. The rest of patients (19 patients) were mild or moderate haemophiliacs. The age of patients varied from 1 to 29 years and the majority of them were below 18 years with a mean age of 11, 6 years. Haemophilia A and Haemophilia B cases were distributed with a proportion of 80% to 20% of total cases, respectively. The general characteristics of patients are given in Table 21. A more detailed table is given in the appendix.

Table 21: General characteristics of Yemeni haemophiliacs

Total number of patients	20
Severe cases	20
Mild and moderate cases	0
Age	
Min-Maximal	1 year - 29 years
Mean	11.6 years
Median	9 years
Type of Haemophilia (severe cases)	
A	16 cases
B	4 cases

The majority of cases were children, 35% of them preschooler. About 40% of patients were pupils in the primary school and 20% attended or still attend the high school. One patient has completed the university studies. None of the adults was able to work at time of interview.

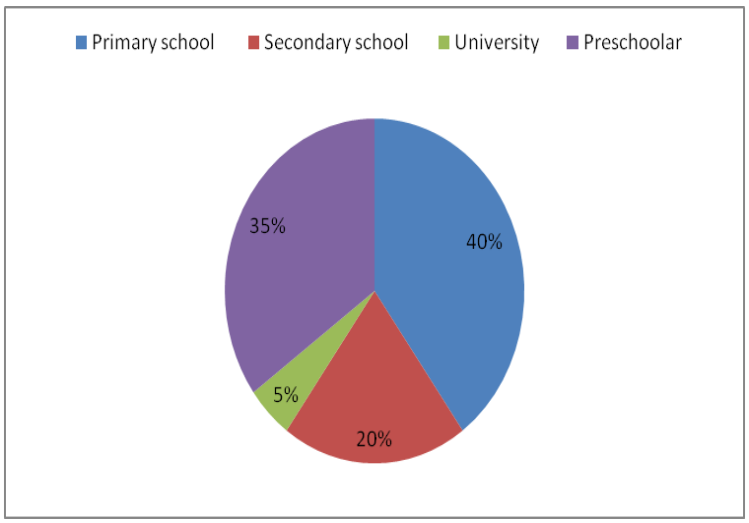

Figure 5: Educational level among Yemeni haemophilic patients

About 70 % of patients came from rural areas. No one of them had a health insurance.

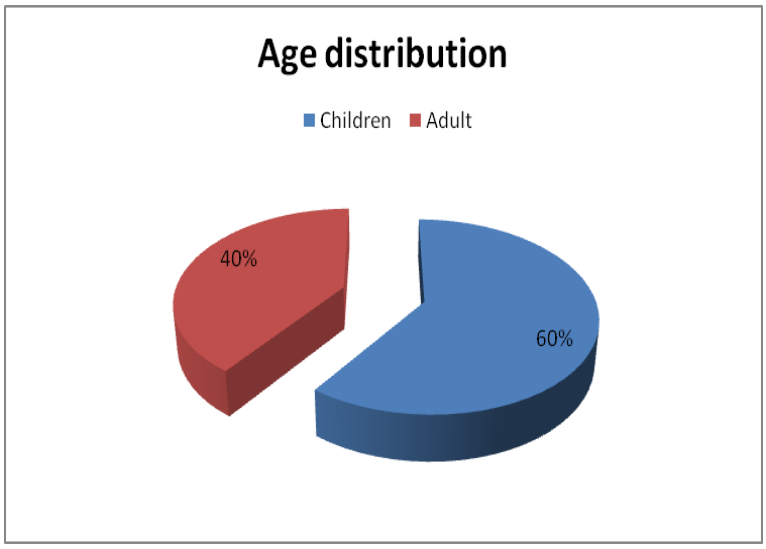

Figure 6: Age group distribution among Yemeni patients

6.6.1.2 Clinical manifestations

Age at first bleeding varied from 1week to 10 months. In 45% of cases the bleeding occurred during circumcision, a religious ritual among Muslims, done mostly within the first 2 weeks of life.

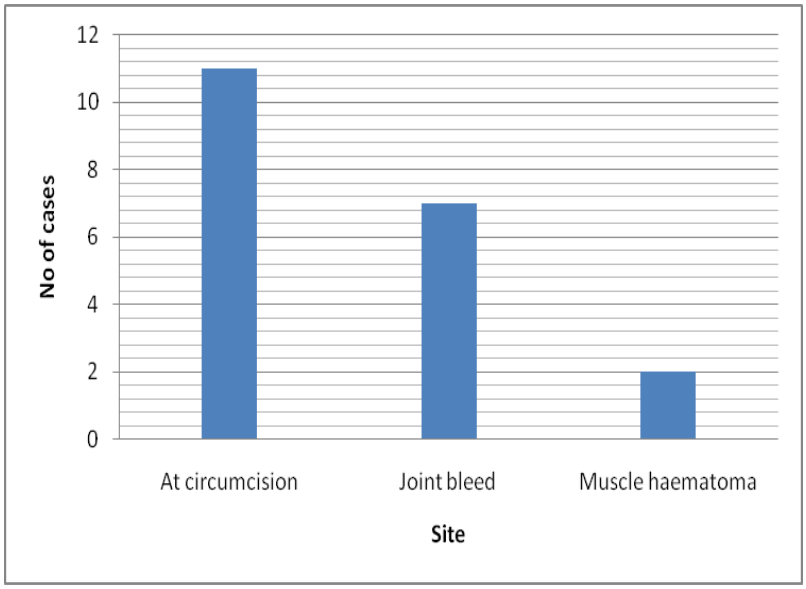

Figure 7: First bleeding site among Yemeni haemophiliacs

First joint bleeding occurred at ages between 6 and 10 months. The most affected joint was the knee followed by ankle and wrist joint. The frequency of joint affection is given in Figure 8.

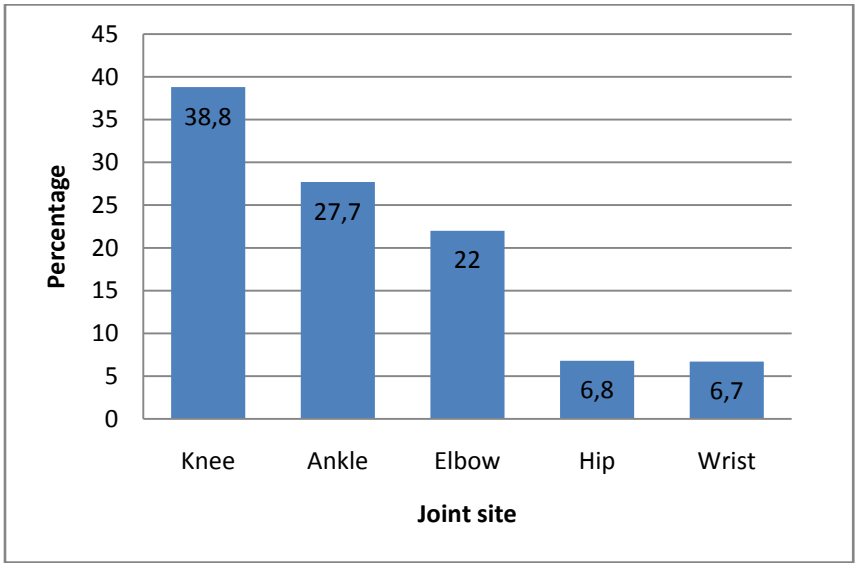

Figure 8: Frequency of joint bleeding among Yemeni haemophiliacs

Regarding other clinical manifestations rather than joint bleeding, 14 patients have had a muscle haematoma during the last 6 months. Two brothers had spontaneous intracranial bleeding, 5 cases had a gastrointestinal manifestation and 3 cases had a genitourinary bleeding in the last 6 months.

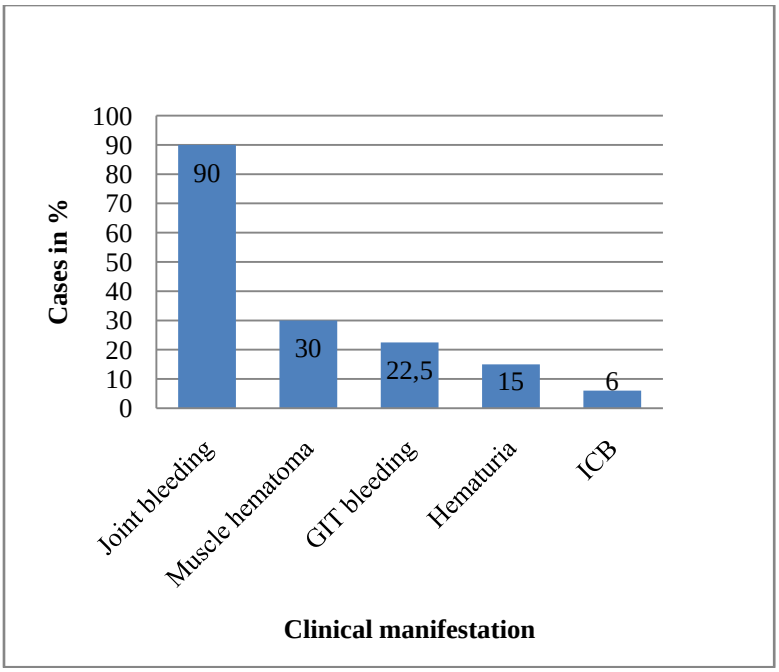

Figure 9: Clinical presentation during last 6 months

6.6.1.3 Concomitant diseases and complications

About 40% of cases were documented to be anaemic. Concerning chronic diseases, no case was known to be affected by hepatitis, malignancies, AIDS or other diseases. No case of pseudotumor formation or fracture was reported. As no laboratory facilities for detection and diagnosis of immunological reactions are available in Yemen, no one knows about the incidence of inhibitor formation among patients who receive factor concentrates as treatment.

6.6.1.4 Treatment modality

No case was treated prophylactically, as there is no such a strategy in Yemen. All patients were treated on demand at haematological clinic, and no one was on home treatment. First infusion age varied from 2 weeks to 10 months, with an average value of 3 months.

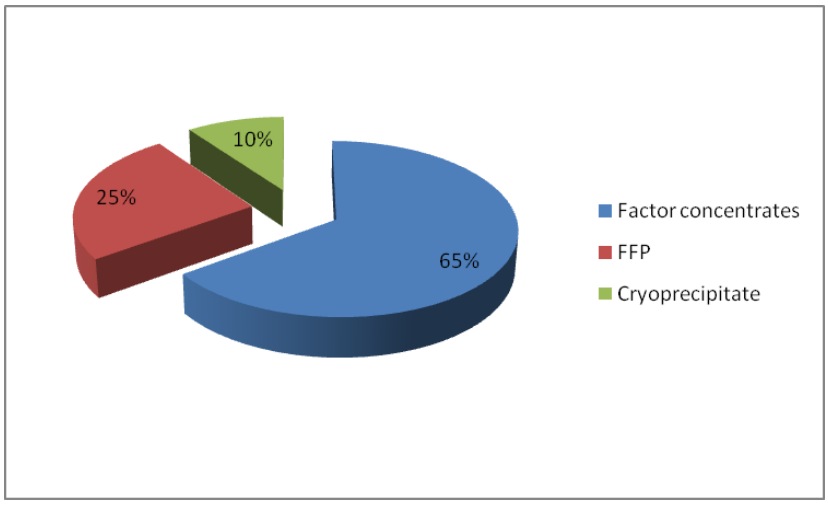

Figure 10: Treatment modality in last 6 months

During the last 6 month period, factor concentrates were given to only 65% of patients. In total, an amount of 15,050 units of factor concentrates were consumed. Other cases were treated with FFP or Cryoprecipitate. There was no use of recombinant factor concentrates, DDAVP or any other drug.

6.6.1.5 Cost of treatment

The cost of treatment was relative high, considering the economical level of Yemeni patients. During the last 6 months, the Yemeni haemophiliacs spent much more than their annual income. The costs varied from EUR 200 to EUR 2000, with an average of 865 Euro per patient, including costs of investigations, treatment and follow up, hospitalisation and travel for those coming from outside the capital city.

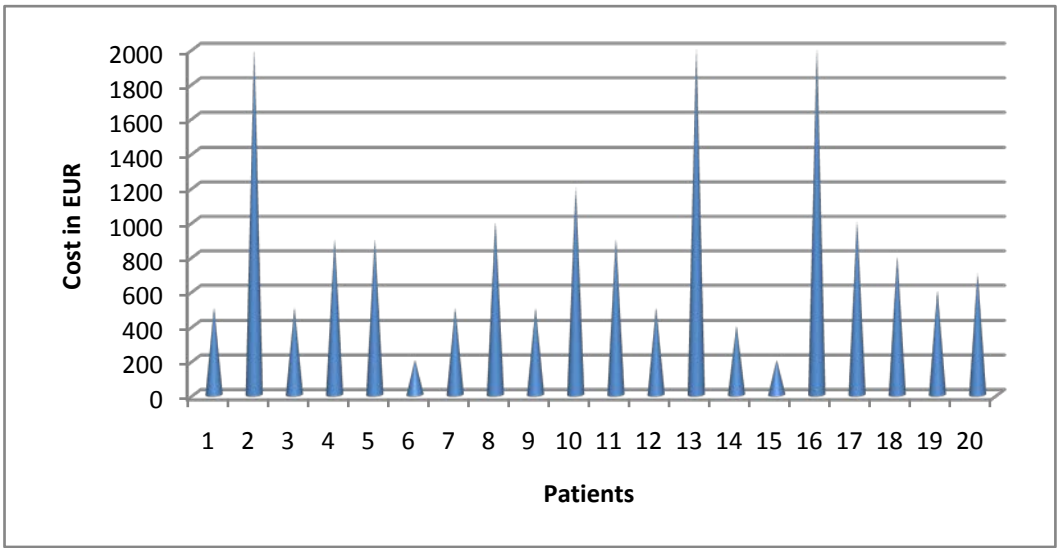

Figure 11: Cost of treatment in last 6 months

The MOPH is supposed to supply factor concentrates free of charge for all patients with severe form of disease. However, the majority of patients pay much money in order to have the needed treatment.

6.6.2 Germany

6.6.2.1 Case collection

Regarding German haemophiliacs, we analyzed the clinical data of 40 severe affected cases, obtained from ESCHQoL program. As the ESCHQoL program includes also haemophiliacs from other European countries including old patients up to 88 years, we have collected only those German severe affected cases of haemophilia who match the Yemeni haemophiliacs regarding their ages. The age of collected patients varied from 3 years to 29 years with a mean of 12.7 years. Haemophilia A and Hemophilia B cases were distributed with a proportion of 80% to 20% of total cases, respectively.

The general characteristics of patients are given in Table 22. A detailed table is given in the appendix.

Table 22: General characteristics of German haemophiliacs

Total number of patients	40
Severe cases	40
Mild and moderate cases	0
Age	
Min-Maximal	3years - 29 years
Mean	12.7 years
Median	10 years
Type of Haemophilia	
A	32 cases
B	8 cases

6.6.2.2 Clinical manifestations

Age at first bleeding varied from 0 to 39 months, with an average of 10 months. The first bleeding site was mainly a joint bleed. The number of bleedings in the last 6 months varied from 0 to 12 with an average of 2.5 bleeds. The most affected joint was knee followed by ankle, as shown in Figure 13.

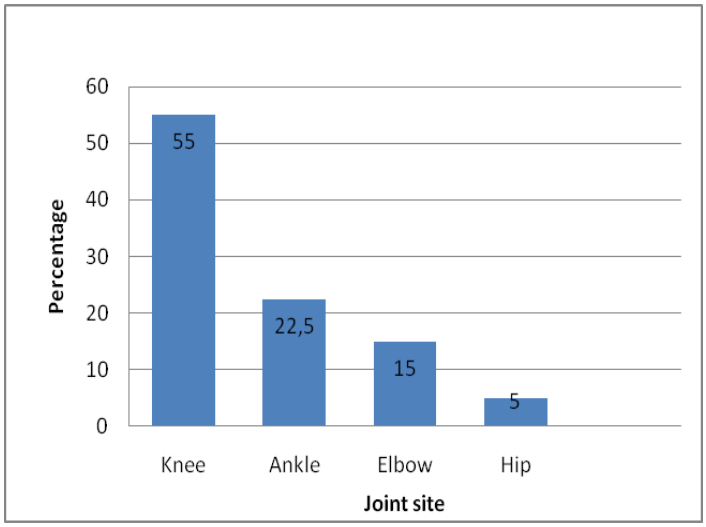

Figure 12: Frequency of joint bleeding in German patients

Regarding other clinical manifestations rather than joint bleeding, only one patient has had an intracranial bleeding (ICB) during the last 6 months. The clinical manifestations among German haemophiliacs during last 6 months are shown in Figure 14.

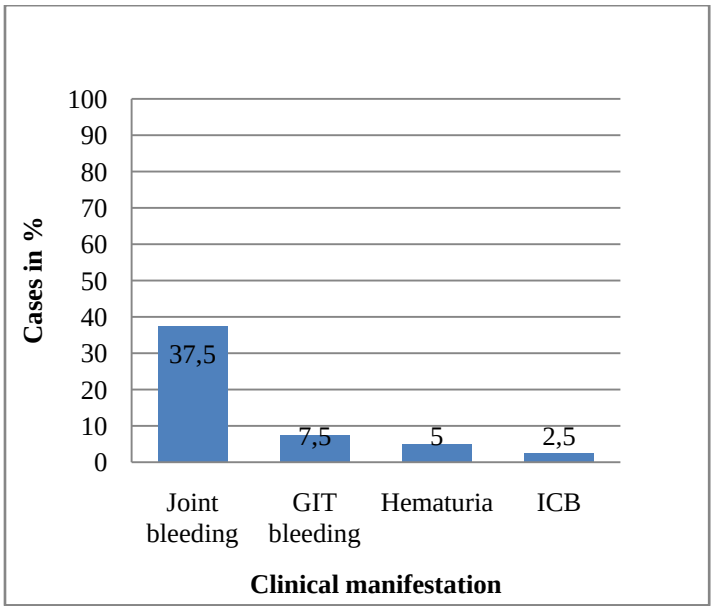

Figure 13: Clinical manifestations among German haemophiliacs

6.6.2.3 Concomitant diseases and complications

Concerning chronic diseases, one case was affected by hepatitis C virus (HCV), 2 cases with HIV, one case with joint atrophy and one case was complicated with anaemia.

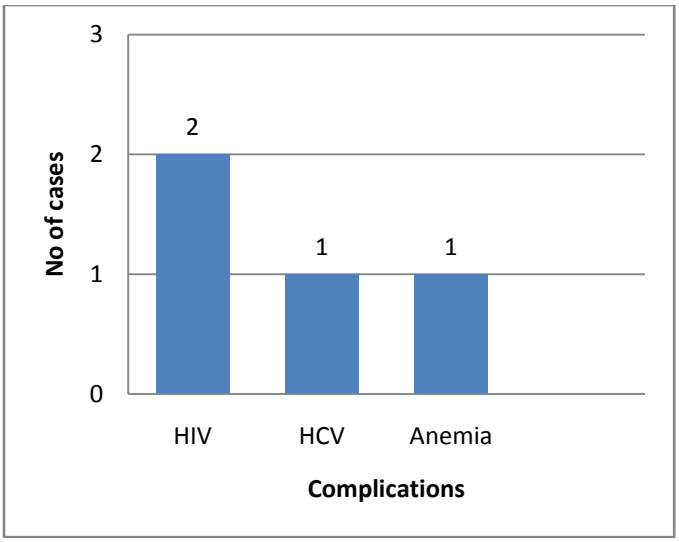

Figure 14: Complicated German cases

Five cases developed inhibitors during therapy with factor concentrates. They represented 12.5% of total cases.

6.6.2.4 Treatment modality

All cases were on prophylactic treatment, most of them with secondary prophylaxis, and almost all of them, except one case, receive home treatment.

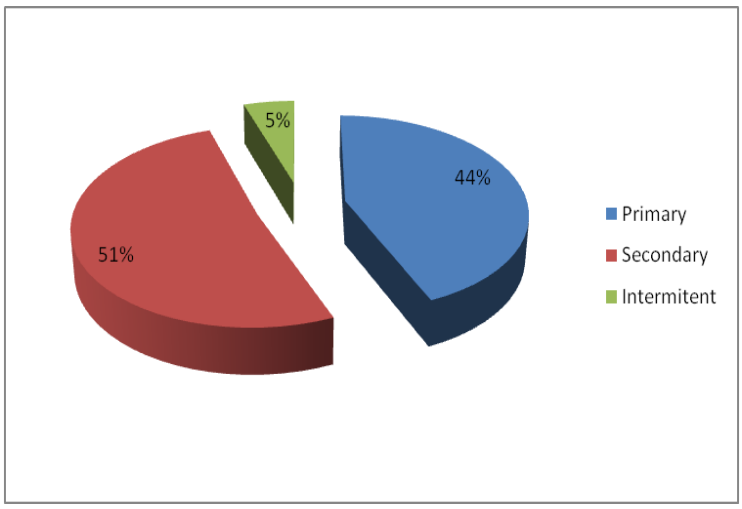

Figure 15: Type of prophylaxis provided to German haemophiliacs

During the last 6 months period, factor concentrates were given to all of 40 patients. In total, an amount of 4,009,770 IU of factor concentrates were consumed during the last 6 months with a mean of 100,244 IU per patient. The majority of cases, as shown in Figure 17, were treated by recombinant factor concentrates. No case was treated with FFP, Cryoprecipitate or DDAVP.

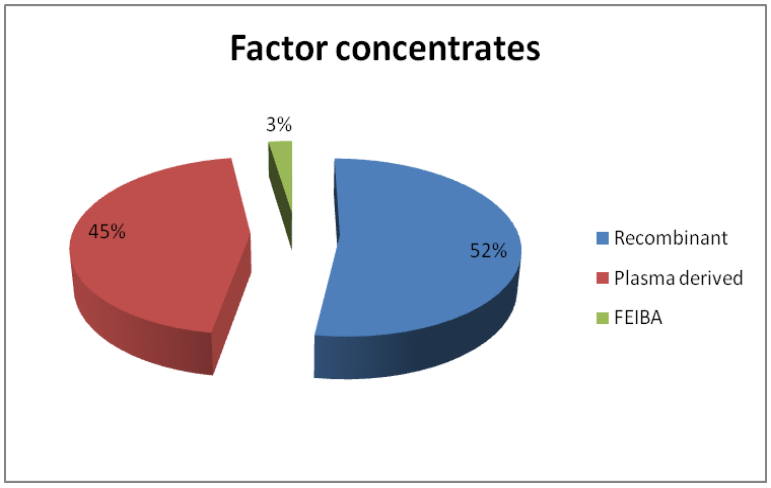

Figure 16: Type of factor concentrates used during last 6 months

6.6.2.5 Costs

Regarding German haemophiliacs, the cost of care was covered almost 100% from the health insurance.

6.7 Discussion

Haemophilia is a group of X-linked bleeding disorders affecting a considerable number of world populations. Highly purified concentrates are now available for treatment and are considered safe and effective. The main complication of treatment is the development of antibody inhibitors against either factor VIII or factor IX [1, 2].

The WFH estimates that 75% of people with haemophilia in the world do not receive adequate care [4].In developed countries, early treatment of bleeding episodes and home therapy quickly evolved as the primary management option. Presence of specialized centres, training and education of patients to achieve comprehensive haemophilia care are the main advantages of the comprehensive treatment concept in developed countries. This is not the case in most developing countries where the government does not have the resources to buy the necessary quantities of coagulation factors in the face of more urgent health priorities and hardly any patients can afford to pay for their own treatment even for on-demand home therapy. The main problems are insufficient supply with clotting factor concentrates, lack of access to these concentrates and absence of specialized care centres [6].

The Arabic region includes 22 member countries of Arab League. The Arab League is rich in natural resources, with enormous oil and natural gas resources in certain member states. Economic development in the Arab League is very disparate. Significant difference in wealth and economic conditions exist between the rich oil states like UAE, Qatar, Kuwait, on the one hand, and poor countries like Yemen, Mauritania and Djibouti on the other.

The health care provided to community, a part of which is the haemophilia care, also shows variations from country to country depending on economical level. In the Global Survey of WFH in 2009, 9702 cases of haemophilia were reported from 13 Arabic countries [3, 9]. Of 22 countries of the Arab League, only 13 have reported at least one haemophilic center. Countries such Egypt, Algeria, Tunisia, Jordan and Syria have good organized programs and more than one haemophilia center. Other countries provide a relatively weak care compared to their financial resources; for example Saudi Arabia, with a population of about 24 million, and 326 reported cases of haemophilia has only one specialized care center for haemophiliacs [3]. Factor use also varies from country to country, according to economical level. High income countries consume large quantities; for example Saudi Arabia reported the highest use of factor concentrates in the region, about 191 736 IU per PWHA [25].

Yemen is one of the poorest countries in the Arab world and its economic fortunes depend mostly on oil [67]. It is the only country of Arabic peninsula without a specialized centre for haemophilia. Taking in consideration that Yemen is a poor developing country spending about 5,6 % of its GDP on the health care, the Ministry of Health concern is focused on the major health problems of the country, such as infectious diseases and malignancies. As a result only a little or no attention is paid to rare diseases such as haemophilia. There are only two hospitals in the capital city, which offer treatment for Yemeni haemophiliacs. Thawra General Hospital and

Republican Hospital are the two largest government hospitals in the country. In either of them, there is a branch of Haematology, at the Internal Medicine Department, dealing with haemophilia cases [69].

As Yemen is a country with a large area, about 555,000 km^2, and most of population live in rural area, haemophiliacs have to cross hundreds of miles in order to seek for some care in the capital city, Sana'a. With a difficult mountainous terrain and a bad infrastructure, many of them have to travel more than 10 hours with their own cars, until they arrive in Sana'a. Under such conditions some of haemophiliacs with severe forms of the disease and life threatening complications have little chances to survive[71].

In contrast to Arabic region, haemophilia care in western European countries is a well organized process providing a qualified management to all haemophiliacs, through the Haemophilia treatment centers (HTCs) which exist in all EU Member States. Choice and levels of treatment, availability of comprehensive care and access to prophylaxis vary widely from one Member State to another [31].

In Germany, people with haemophilia are entitled to a choice of all treatments ranging from an optimal level of factor replacement therapy on demand as well as on a prophylactic basis for those who need it, to comprehensive care at a Haemophilia Treatment Centre [81]. Haemophilia care in Germany is provided through 12 specialized Haemophilia Treatment Centers. Apart from treatment and care at the HTCs, specialized physicians in practices and at haematology units in general hospitals provide care. Home treatment is available for children as well as for a number of people suffering from severe haemophilia[72].

Germany stand out for using a huge amount of FVIII IUs, about 114 333 IU per PWHA [25]. About half of the factor concentrates used in Germany are recombinant clotting factors and the other half are human plasma-derived concentrates, with the average number of units of factor VIII concentrate used per capita being 5.9 IU. About 90% of children and 40% of adult people with haemophilia in Germany receive prophylactic treatment [81].

Regarding results of the empirical study, the peak age among Yemeni haemophiliacs who participated in this study was 29 years. This fact should be attributed to two major reasons; first and most important is the fact that due to absence of care in the last few decades the patients couldn't survive and eventually died before they reach their 30's as a result of life threatening conditions and complications. The other reason is that the majority of patients with mild and moderate form of the disease do not seek for medical care, even if they have bleeding episodes. The Yemeni haematologists reported that they didn't find any patient older than 30 years[71].

In the majority of Yemeni haemophiliacs, the first bleed occurred during circumcision within first 2 weeks of life, which, in many cases if not mainly, is performed at home by a nurse. In such conditions, many newborns with very low levels of factor VIII or IX face continuous bleeding and probably die. Education and

awareness about the nature of this disease could play an important role in preventing such induced life threatening bleedings.

Currently no Yemeni patient is treated prophylactically as there is no such strategy in Yemen. The minimal care provided to severe cases is based still on FFP, Cryoprecipitate, DDAVP and even whole blood transfusions. The amount of factor concentrates used by only some severe cases with life threatening manifestations, such as ICB, is very low. According to our observation, the total amount of factor concentrates administered by 13 patients during the last 6 months was 15,050 IU, with an average of 1,157 IU per patient. Compared to Yemeni haemophiliacs, a German patient received 100,224 IU or about 90 times more factor concentrates, in addition to a good organized care with a prophylaxis program.

In Germany, the health care costs for haemophilic patients, including cost of factor replacement, were almost 100% covered by health insurance. As we mentioned in chapter 5, the majority of Yemeni population do not have a health insurance. As a result all patients, including those affected by haemophilia, should pay for every kind of care and medical procedure. The majority of haemophiliacs are not able to cover the high cost of factor concentrates, which is *supposed* to be covered by Ministry of Health. The cost of care among Yemeni haemophilic patients during last 6 months varied from EUR 200 EURO to EUR 2000, with an average of EUR 865 per patient. These amounts of money, which are modest in our vision, exceed the average of annual income among Yemeni population. It should be mentioned that access to factor concentrate even for severely affected Yemeni haemophiliacs is impossible[69].

As it is shown in this analysis, there is a huge difference regarding the haemophilia care provided in both regions, particularly between Yemen and Germany. The fact that other Arabic countries such as Saudi Arabia, Oman, UAE have huge financial resources and a good organized haemophilia care, is an evidence that Yemen is totally isolated and abandoned from its Arab neighbors regarding this problem.

In Yemen, as in other developing countries, the major problems with regard to haemophilia care are: absence of haemophilia centers; inadequate supply of safe factor concentrates, lack of awareness and education about the nature of the disease[6].

6.8 Recommendations

After the analysis of current situation of haemophiliacs in Yemen and care provided to them, we consider that application of the following recommendations will improve the haemophilia care in this country:

- Initiation of a first step for a Haemophilia Center in Sana'a, as a result of coordination between Yemeni authorities and WFH representative for Arabic Region
- Stimulation of a humanitarian financial support, from rich Arabic neighbor countries, to found an initial center for haemophiliacs in capital city Sana'a.
- Formulation of educational guidelines for haemophiliacs about the nature of the disease
- Organization of a national network and creation of a registry for haemophiliacs
- Home therapy (living far away from capital city, Yemeni haemophiliacs have to cross hundreds of miles to seek for some care)
- A twinning program between haemophilia centers in Germany and clinics dealing with haemophilia in Yemen.

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8. APPENDIX

8.1 Clinical data of German patients

Nr	Age in years	Type of Hemophilia	Age in months at first bleeding	No of bleedings in last 6 months	Prophylaxis	Home Treatment	Type of factor concentrates	Amount of factor used in the last 6 months in IU	Other medications
1	3	A	0	2	Yes	Yes	Recombinant	68,250	
2	3	A	13	5	Yes	yes	Recombinant	39,780	
3	4	A	12	2	Yes	no	Recombinant	49,000	
4	4	A	2	0	yes	Yes	Plasma derived	72,000	
5	4	A	3	4	Yes	Yes	Recombinant	126	
6	5	A	14	0	Yes	Yes	Recombinant	51,000	
7	5	A	8	0	Yes	Yes	Plasma derived	79,000	
8	5	A	12	1	Yes	Yes	Recombinant	72,000	
9	6	A	2	4	Yes	Yes	Recombinant	76,000	
10	6	A	17	2	Yes	Yes	Recombinant	78,000	
11	7	A	12	5	Yes	Yes	Plasma derived	94,000	
12	7	A	5	0	Yes	Yes	Recombinant	97,500	
13	8	A	13	1	Yes	Yes	Recombinant	78,000	
14	8	A	39	3	Yes	Yes	Plasma derived	63,000	
15	8	B	9	2	Yes	Yes	Recombinant	72,000	
16	8	B	11	1	Yes	Yes	Plasma derived	392,000	
17	9	B	0	1	Yes	Yes	Plasma derived	273,000	
18	9	A	3	1	Yes	Yes	Plasma derived	83,000	
19	9	B	0	3	Yes	Yes	Plasma derived	266,400	
20	10	B	9	2	Yes	Yes	Plasma derived	48,000	
21	10	A	1	5	Yes	Yes	FEIBA	180	
22	11	A	22	4	Yes	Yes	Plasma derived	144,000	
23	11	A	11	2	Yes	Yes	Plasma derived	72,000	
24	13	A	3	1	Yes	Yes	Plasma derived	52,000	
25	13	A	10	1	Yes	Yes	Recombinant	146,000	
26	14	B	10	11	Yes	Yes	Recombinant	88,000	

27	16	A	14	1	Yes	Yes	Plasma derived	153,000	
28	16	A	1	5	Yes	Yes	Recombinant	110,000	
29	17	A	10	3	Yes	Yes	Recombinant	68,000	
30	17	A	12	0	Yes	Yes	Recombinant	112,000	
31	20	A	14	1	Yes	Yes	Recombinant	78,000	
32	20	A	24	1	Yes	Yes	Plasma derived	190	
33	21	B	10	2	Yes	Yes	Plasma derived	72,000	
34	21	A	5	0	Yes	Yes	Plasma derived	98,000	
35	25	A	16	4	No	Yes	Recombinant	80,000	
36	25	A	6	12	Yes	Yes	Recombinant	156,000	
37	27	B	12	3	Yes	Yes	Plasma derived	30,000	
38	27	A	6	10	Yes	Yes	Recombinant	85,000	
39	29	A	6	2	Yes	Yes	Recombinant	190,000	
40	29	A	12	2	Yes	Yes	Recombinant	78,000	

8.2 Clinical data of Yemeni patients

Nr	Age in years	Type of Hemophilia	Age in months at first bleeding	No of bleedings in last 6 months	Prophylaxis	Home Treatment	Type of factor concentrates	Amount of factor used in the last 6 months in IU	Other medications
1	1	A	1	12	No	No	Plasma derived	1,200	
2	1	B	8	15	No	No	Plasma derived	1,400	
3	1.5	A	0.5	10	No	No		0	FFP
4	2	A	10	8	No	No	Plasma derived	500	
5	3	A	9	12	No	No	Plasma derived	1,250	
6	4	A	1	8	No	No		0	FFP
7	7	A	4	5	No	No		0	Cryoprecipitate
8	8	B	0.25	10	No	No	Plasma derived	750	
9	8	A	1	7	No	No		0	FFP
10	9	A	1	11	No	No	Plasma derived	1,000	
11	9	A	1	10	No	No	Plasma derived	900	
12	10	A	6	9	No	No		0	Cryoprecipitate
13	13	A	6	17	No	No	Plasma derived	1,800	
14	16	A	0.5	6	No	No		0	Cryoprecipitate
15	18	A	3	9	No	No		0	FFP
16	20	B	6	21	No	No	Plasma derived	2,500	
17	21	B	8	18	No	No	Plasma derived	1,500	
18	25	A	0.5	12	No	No	Plasma derived	1,000	
19	27	A	7	7	No	No	Plasma derived	750	
20	29	A	2	6	No	No	Plasma derived	500	

8.3 ESCHQoL Questionnaire sample

Page 1

Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

ESCHQOL Study

Medical Documentation Form

SECTION - 1
Demographics

Patient initials **(to fill in on the top of each section)** ☐☐ ☐☐

First 2 letter of the name — First 2 letter of the surname

Patient birthdate ☐☐ ☐☐ ☐☐☐☐

DD MM YY

Country of birth _____

Weight (Kg) ☐☐☐.☐ **Height (cm)** ☐☐☐

Smoker: **NO** ☐ **Ex-smoker** ☐ **YES** ☐ **If Yes no. of cigarettes per day** ☐☐

Haemophilia A ☐ B ☐

Factor VIII or IX level < 1% : **YES** ☐ **NO** ☐ **if No specify** ☐☐ **%**

Education

- Low/middle school degree ☐
- High/technichal school degree ☐
- University degree ☐
- Post-degree diploma/PhD ☐
- Pre-Scolar ☐
- Student / Pupil ☐

Employment

Student	☐				
Houseman/wife	☐				
Unemployed	☐				
Military/Civil service	☐				
Clerk	☐	full time ☐	part time ☐	no. hours/week	☐☐☐
Blue collar	☐	full time ☐	part time ☐	no. hours/week	☐☐☐
White collar	☐	full time ☐	part time ☐	no. hours/week	☐☐☐
Shop keeper	☐				
Professional	☐				
Executive/Manager	☐				
Enterpreneur	☐				
Retirement pensioner	☐				
Early pensioner for haemophilia	☐				
Early pensioner for other reasons	☐				

specify _____

Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 2
Bleeding history

A. Age at first bleeding episode requiring treatment: ☐☐☐ months

B. Age at first joint bleeding episode: ☐☐☐ months

C. Total number of bleeding events in the previous 6 months ☐☐

C.1. Out of these events, how many were joints bleeding events ☐☐

D. There are target joints? ☐ ***NO*** ☐ ***YES***
(Definition: 3 or more bleeds in the same joint in the previous 6 months)

IF YES: D.1. Number of target joints: ☐☐

D.2. Sites: ankle R ☐ L ☐

elbow R ☐ L ☐

knee R ☐

other, specify _____

E. Has an iliopsoas haematoma ever occurred ? ☐ ***NO*** ☐ ***YES***

If yes, did it occur in the past 6 months? ☐ *NO* ☐ *YES*

F. Has a gastrointestinal bleeding ever occurred ? ☐ ***NO*** ☐ ***YES***

If yes, did it occur in the past 6 months? ☐ *NO* ☐ *YES*

G. Has a cerebral bleeding ever occurred ? ☐ ***NO*** ☐ ***YES***

If yes, did it occur in the past 6 months? ☐ *NO* ☐ *YES*

H. Has a genitourinary bleeding ever occurred ? ☐ ***NO*** ☐ ***YES***

If yes, did it occur in the past 6 months? ☐ *NO* ☐ *YES*

I. Has a pseudotumor/haemorrhagic cyst ever occurred ? ☐ ***NO*** ☐ ***YES***

If yes, did it occur in the past 6 months? ☐ *NO* ☐ *YES*

J. Has an haematoma ever been complicated with infection or compartimental syndrome? ☐ ***NO*** ☐ ***YES***

If yes, did it occur in the past 6 months? ☐ *NO* ☐ *YES*

Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 3
Inhibitor history

Past or present history of inhibitor development Yes ☐ No ☐

IF NO : GO TO THE NEXT SECTION

IF YES :

A. Age at inhibitor development: ☐☐☐ months

B. Historical peak titre: ☐☐☐☐ BU/ml

C. Is the inhibitor still present?

☐ No

☐ Yes

IF YES : C.1. last titre: ☐☐☐☐ BU/ml

C.2. Usual treatment of bleedings events:

☐ HIGH DOSE FVIII

☐ RFVIIa

☐ APCC/FEIBA

☐ PCC

D. Has the patient undergone immunotolerance treatment?

No ☐ Yes ☐

If Yes, was it successful? ☐ Yes

☐ No

still on immune tolerance ☐

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Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 4
Concomitant diseases

(Definition: diseases that have required in the past 6 months regular visits or treatment)

A. Other known bleeding abnormalities ***N.A.** ☐ **YES** ☐ **NO** ☐

If Yes, specify: _____

B. Malignancy **YES** ☐ **NO** ☐

If Yes, specify: _____

C. Chronic viral infection: ***N.A.** ☐ **YES** ☐ **NO** ☐

If Yes: hepatitis B virus(HBs Ag+) ☐ hepatitis delta virus(delta Ag+) ☐ hepatitis C virus(PCR+) ☐

- no signs or symptoms of advanced liver disease ☐
- PT ratio > 2.0 ☐
- low serum albumin (< 3 g/dl) ☐
- portal hypertension (US scan) ☐
- cirrhosis ☐
- oesophageal varices ☐
- ascites ☐
- encephalopathy ☐

Treatment with IFN/Ribavirine/lamivudine: NO ☐ finished ☐ current ☐

D. HIV infection: **YES** ☐ **If Yes:** asymptomatic ☐ minor HIV-related signs ☐ full blown AIDS ☐ **NO** ☐

CD4 cell counts >500/cmm ☐ 200-500/cmm ☐ <200/cmm ☐

Treatment: NO ☐ with 1-2 drugs ☐ with 3 or more drugs ☐

E. Anemia: ***N.A.** ☐ **YES** ☐ **If Yes:** light (10-12 g/dl) ☐ moderate (8-10 g/dl) ☐ severe (6-8 g/dl) ☐ very severe (<6 g/dl) ☐ **NO** ☐

F. Dental disorders: ***N.A.** ☐ **YES** ☐ **If Yes:** caries ☐ parodontitis ☐ infections(abcess, osteitis) ☐ partial edentition ☐ total edentition ☐ **NO** ☐

G. Abuse of recreational drugs: ***N.A.** ☐ **YES** ☐ **If Yes:** alcohol ☐ opiate ☐ non-opiate ☐ **NO** ☐

H. Other diseases: ***N.A.** ☐ **YES** ☐ **NO** ☐

if Yes specify : _____

_____

****Not Available***

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Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 5
Surgery

A. Orthopaedic surgery: [in the past 6 months] **NO** ☐ **YES** ☐

		Sites:
radiation synovioorthesis	☐	
arthroscopic synovectomy	☐	
synovectomy (surgical)	☐	
arthrodesis	☐	
arthroplasty	☐	
tenotomy	☐	
wedge-osteotomy	☐	
excision of cysts	☐	
excision of orthopedic material etc.	☐	
fracture	☐	
others:_____	☐	

B. Dental procedures: [in the past 6 months] **NO** ☐ **YES** ☐

Type (Specify):
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

C. Other surgical procedures: [in the past 6 months] **NO** ☐ **YES** ☐

Type (Specify):
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

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Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 6/A

Arthropathy assessment

CHILDREN

(for patients older than 16 years GO TO Section 6-B)

Hemophilia Joint Health Score

	Ankle L R	Elbow L R	Knee L R	other
Swelling: 0:none; 1:mild; 2:moderate; 3:severe	☐☐	☐☐	☐☐	_____
Duration (swelling): 1:≤1 month; 2:>1month	☐☐	☐☐	☐☐	_____
Muscle atrophy: 0:none; 1:mild; 2:severe	☐☐	☐☐	☐☐	_____
Axial alignment: measured only at knees and ankle 0:within normal limits 1:outside normal limits (see guidelines)	☐☐	☐☐	☐☐	_____
Crepitus of motion: 0:none; 1:mild; 2:severe	☐☐	☐☐	☐☐	_____
Flexion loss: 0:no loss; 1:loss of ≤ 10°; 2:loss of 11° to 20°; loss of >20°	☐☐	☐☐	☐☐	_____
Extention loss: from hyperextention 0:no loss; 1:loss of ≤ 10°; 2:loss of 11° to 20°; 3:loss of > 20°	☐☐	☐☐	☐☐	_____
Instability: 0:none; 1:present and significant joint laxity	☐☐	☐☐	☐☐	_____
Joint pain on motion: 0:no complaint of pain; 1:complaint of pain; 2:complaint of pain with wincing 3:wincing and attempts to withdraw	☐☐	☐☐	☐☐	_____
Gait*: 0:normal walking, running, galloping, skipping, stairs 1:normal walking, abnormal (running, galloping, skipping or stairs) when stressed 3:abnormal walking *Abnormalities:limping, walking with foot turned out, walking on side of foot, no push off, walking on toes, uneven strides, no/uneven weight shifting, abnormal running, galloping, skipping or stairs	☐☐	☐☐	☐☐	_____
Strength: (using modified Kendall 5 point scale)-within available ROM 0:holds test position against strong pressure (5) 1:holds test position against slight 7 moderate pressure (-4 to +4) 2:holds test position against slight pressure (3 to +3) 3:unable to move through available ROM 4:no muscle contraction	☐☐	☐☐	☐☐	_____
Total	☐☐	☐☐	☐☐	_____

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Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 6/B
Arthropathy assessment
ADULTS

(for patients younger than 17 years GO BACK TO Section 6-A)

Orthopaedic Joint Score (WFH modified)

	Ankle L R	Knee L R	Elbow L R	Shoulder L R	Hip L R
Swelling (0:none; 2:present; 3:chronic)	☐☐	☐☐	☐☐	☐☐	☐☐
Muscle atrophy (0:no; 2:yes [>2 cm])	☐☐	☐☐	☐☐	☐☐	☐☐
Crepitus on motion (0:absent; 1:present)	☐☐	☐☐	☐☐	☐☐	☐☐
Loss of Range of motion (0:<10%; 1:10-33%; 2:≥33%)	☐☐	☐☐	☐☐	☐☐	☐☐
Flexion contracture (0:no; 1:<15°; 2:≥15°)	☐☐	☐☐	☐☐	☐☐	☐☐
Instability (0:none; 1:present, not interfering; 2:function deficit or bracing	☐☐	☐☐	☐☐	☐☐	☐☐

Presence of chronic pain (in the past 6 months)
(Definition: pain present without an apparent bleed, recurrent at least twice a week and lasting >3 hours without treatment) **NO** ☐ **YES** ☐

Deambulation: normal ☐ bracing ☐ cane ☐ crutch ☐ wheel chair ☐ others ☐

Axial deformity

Left knee
☐0 (0-7° valgus) ☐1 8-15° valgus or 0-5° varus ☐2 normal ≥15° valgus or >5° varus

Right knee
☐0 normal (0-7° valgus) ☐1 8-15° valgus or 0-5° varus ☐2 ≥15° valgus or ≥5° varus

Left elbow
☐0 (0-7° valgus) ☐1 8-15° valgus or 0-5° varus ☐2 normal ≥15° valgus or ≥5° varus

Right elbow
☐0 normal (0-7° valgus) ☐1 8-15° valgus or 0-5° varus ☐2 ≥15° valgus or ≥5° varus

Left ankle
☐0 no deformity ☐1 ≤10° valgus or ≤5° varus ☐2 ≥10° valgus or ≥5° varus

Right ankle
☐0 no deformity ☐1 <10° valgus or <5° varus ☐2 ≥10° valgus or ≥5° varus

Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 7
Treatment modality

A. Age at first infusion: ☐☐☐ months

B. Is the patient currently on home treatment: **NO** ☐ **YES** ☐

C. Who has *mainly* administered the therapy in the past 6 months:

self administered ☐ a family member ☐

physician at the center ☐ nurse at the center ☐

general practioner ☐ nurse at hometown ☐ other hospital ☐

D. How is the patient treated? **On demand, only** ☐ **On prophylaxis** ☐

If the patient is on prohylaxis:

D.1. Is the patient on primary prophylaxis? NO ☐ YES ☐ start ☐☐☐ months

-> the answer *"YES"* must meet all the following criteria:

1. Started *before* the 2nd bleed or *before* the age of two ☐
2. Regularly administered at least 2 times a week ☐
3. Continuosly administered at least 45 weeks a year ☐

(respectively 23 weeks in the past 6 months)

Dosage per administration: ☐☐☐ IU/Kg No. of administration per week ☐☐

D.2. Is the patient on secondary prophylaxis? NO ☐ YES ☐ start ☐☐☐ months

-> the answer *"YES"* must meet all the following criteria:

1. Started *after* the 2nd bleed or *after* the age of two ☐
2. Regularly administered at least 2 times a week ☐
3. Continuosly administered at least 45 weeks a year ☐

(respectively 23 weeks in the past 6 months)

Dosage per administration: ☐☐☐ IU/Kg No. of administration per week ☐

D.3. Has the patient been on intermittent prophylaxis in the past 6 months ?

NO ☐ YES ☐

-> the answer *"YES"* must meet all the following criteria:

1. Regularly administered at least 2 times a week ☐
2. Continuosly administered less than 45 weeks a year ☐

(respectively 23 weeks in the past 6 months)

Dosage per administration: ☐☐☐ IU/Kg No. of administration per week ☐☐

D.4. Weeks on prophylaxis in the past 6 months: ☐☐ weeks

E. Venous access type in the past 6 months:

1. peripheral vein ☐
2. arterovenous fistula ☐
3. central line ☐ Port-a-cath ☐
   Broviac/Hickman ☐
   Other (specify) ☐ _____

Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 8
Type of product

A. Types of products used in the past 6 months	**No. infusions/ injections**	**Total consumption**
☐ DDAVP commercial name _____	☐☐	☐☐☐☐☐ mg
☐ Fresh frozen plasma commercial name _____	☐☐	☐☐☐☐☐ ml
☐ cryoprecipitate commercial name _____	☐☐	☐☐☐☐☐ ml
☐ plasma derived FVIII/FIX concentrate commercial name _____	☐☐	☐☐☐☐☐☐☐☐ IU
☐ recombinant FVIII/FIX concentrate commercial name _____	☐☐	☐☐☐☐☐☐☐☐ IU
☐ prothrombin complex concentrate commercial name _____	☐☐	☐☐☐☐☐☐☐☐ IU
☐ activated prothrombin complex concentrate commercial name _____	☐☐	☐☐☐☐☐☐☐☐ IU
☐ recombinant FVIIa commercial name _____	☐☐	☐☐☐☐☐ mg

E. Need for blood transfusions in the past 6 months?

NO ☐ **YES** ☐ If YES: packed red cells ☐ total units: ☐☐☐☐

whole bloods ☐ total units: ☐☐☐☐

F. Drugs used for HIV treatment in the past 6 months **NO** ☐ **YES** ☐

If yes, specify :	**Drug**	**Posology**	**Days on treatment**
1			
2			
3			
4			
5			
6			

G. Drugs used for hepatitis treatment in the past 6 months **NO** ☐ **YES** ☐

If yes, specify :	**Drug**	**Posology**	**Days on treatment**
1			
2			
3			
4			
5			

Patient initials ☐☐ Centre number ☐☐ Patient number ☐☐☐☐

SECTION - 9
Medical visits

Please, answer to each question

A. Number of visits at the Hemophilia Center in the past 6 months

None ☐ programmed ☐☐ for bleedings ☐☐

B. Number of visits at the general practitioner's in the past 6 months

None ☐ haemophilia-related ☐☐ for other problems ☐☐

C. Number of days of assisted physio-therapy in the past 6 months

None ☐ at home ☐☐ in a center ☐☐

D. Number of visits at psychoterapist/psychologist in the past 6 months

None ☐ private ☐☐ public ☐☐

E. Number of hospitalisation in the past 6 months

None ☐ haemophilia-related ☐☐ for other problems ☐☐

F. Number of days of hospitalization in the past 6 months

None ☐ haemophilia-related ☐☐☐ for other problems ☐☐☐

E.1. Of these how many days in an **Intensive Care Unit**

None ☐ haemophilia-related ☐☐☐ for other problems ☐☐☐

G. Number of school/work/normal life days lost in the past 6 months

None ☐ haemophilia-related ☐☐☐ for other problems ☐☐☐

H. No. of school/work/normal life days lost by patient's care-givers in the past 6 months:

None ☐ haemophilia-related ☐☐☐ for other problems ☐☐☐

I. Number of visits at other specialists outside the haemophilia centre in the past 6 months

specialist:

_____	No.		public	or private	
_____	No.		public	or private	
_____	No.		public	or private	

personal costs for private visits *in the past 6 months*: _____ Euros