HEMOPHILIA
PATIENTS WELFARE SOCIETY
RAWALPINDI CHAPTER

# HAEMOPHILIA HANDBOOK

Developed by Haemophilia Patients Welfare Society
Rawalpindi Pakistan

# EDUCATIONAL BOOKLET
# FOR
# HEALTH CARE PROFESSIONALS

**Edited by**
**Professor Tahira Zafar, MRCPath, FRCPath**

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***This document is an educational guideline & should be taken as such. The ultimate judgment must be made by the physician in the light of all the circumstances presented by the individual patient.***

**Dedicated to the Haemophilia Community, hoping that it will impact their lives positively, now & in future!**

## Preface to the First Edition

I have been involved with looking after Haemophilia & other Inherited Bleeding Disorders (IBD'S) for over 3 decades, both in Pakistan and overseas (United Kingdom). These patients, here in Pakistan, first present to the primary care physicians who, due to the rarity of these disorders, are not well aware of the issues & challenges associated with these disorders & their management. This causes a delay in appropriate treatment resulting in complications which can be fatal at times.

This handbook is designed for the Health Care professionals to provide them with a frame work to act when they come across patients with IBD's. It also gives them the details of whom to contact & where to refer these patients when the initial emergency is taken care off. This book should, by no means, be taken to replace the standard principles of care but rather as an adjunct to them, with the physicians looking after these patients taking the ultimate responsibility of care.

It has been an arduous task compiling this book & I am grateful to God, who gave me strength, courage and patience and to my friends & colleagues who gave me their unwavering support & help in the write up & enabled me to finish it up.

I would like to express my deep gratitude to World Federation of Haemophilia (WFH), who through the Development Grants Project (DGP) provided the necessary funds to publish this book.

I am also extremely grateful to Muhammad Laiq Khan for his efforts in designing and formatting of the handbook.

Finely I acknowledge with gratitude, the support provided by my family, my husband Prof. Asif Zafar, who provided constant advice & encouragement, my children Sarah & Ali & grandchildren Rahimeen, Ahmad & Zayn who kept me going & made it possible for me to pull it all through.

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# CHAPTER 1

## HAEMOPHILIA CARE IN PAKISTAN

**CHAPTER 1**

# HAEMOPHILIA CARE IN PAKISTAN

**Munawar Sher Khan[1, 2], Hasan Raza [1], Tahira Zafar[1, 2]**

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Haemophilia patients were initially looked after at the Thalassemia Centers run by Fatimid Foundation, which was also the designated National Member Organization (NMO) of the World Federation of Haemophilia. Haemophilia Patients Welfare Society (HPWS) developed in the 1990's, catered to the needs of Haemophilia Community, through its independent Chapters in Karachi, Lahore, Rawalpindi & Peshawar (**Annexe 1**). Within a decade the NMO status moved from Fatimid to HPWS (WFH Congress, 2000, Montreal, Canada) & was shared by the chapters in rotation.

All Haemophilia Patients Welfare Societies have affiliated Haemophilia Treatment Centre's( **HTC : Annexe 2** ) which look after the medical needs of the patients with Inherited Bleeding Disorders through their Centre doctors, their Medical Advisory Board (MAB) and associated Haemophilia Friendly Hospitals (HFH's)

In 2018 **Haemophilia Federation of Pakistan (HFP: Annexe 1)** was formed as a National umbrella organization to coordinate between WFH, the Haemophilia Patient Welfare Societies (HPWS) and the Government. It consists of members elected to represent the adult patients with inherited bleeding disorders and selection of a parent from each HPWS to represent minors with bleeding disorders. Presidents of each HPWS are also on the HFP Committee.

HFP's Mission is to improve & sustain care of people with Inherited Bleeding Disorders in the Country through national & international collaboration. HFP has formed a National Registry of all Haemophilia patients registered with HPWS in Karachi, Lahore, Rawalpindi & Peshawar

## CHAPTER 1

**Summary of Nationally Registered Patients with HFP**

| Sr. # | Diagnosis | Number of Patients |
|---|---|---|
| 1 | FVIII | 1755 |
| 2 | FIX | 329 |
| 3 | VWD | 321 |
| 4 | F VII | 32 |
| 5 | FXIII | 24 |
| 6 | FX | 23 |
| 7 | GT | 20 |
| 8 | FV | 19 |
| 9 | BSS | 2 |
| 10 | Un Diagnosed | 3 |
| | **Total** | **2643** |

## HAEMOPHILIA PATIENTS WELFARE SOCIETY RAWALPINDI (HPWS RWP)

The Haemophilia Patients Welfare Society Rawalpindi is a dynamic voluntary, non-profit philanthropic organization established in 1999 by a group of medical professionals and patients.

### Mission

To establish an integrated community based service network aimed at improving the overall health status of Patients with Inherited Bleeding Disorders by providing them with quality care and support.

### Objectives

- To provide information and guidance about the disease to patients, families, care givers, public and health authorities
- Increasing the number of diagnosed patients
- Lab facilities for accurate diagnosis.
- Development of treatment guidelines & protocols
- To provide timely and adequate treatment to patients
- To provide publications about the disease
- To raise funds for the medical treatment of these patients
- To support the women and children of these families for better education and improved income

**Summary of patients registered with the Society (31st Dec 2019)**

| Haemophilia Patients Welfare Society Rawalpindi | | | | |
|---|---|---|---|---|
| Total Patients | | | 1117 | |
| Males = 941 | | | Females = 176 | |
| Sr. # | Diagnosis | Number of Patients | Diagnosis | Number of Patients |
| 1 | FVIII | 639 | vWD | 94 |
| 2 | FIX | 123 | GT | 36 |
| 3 | vWD | 86 | FV | 9 |
| 4 | GT | 25 | FVII | 8 |
| 5 | FVII | 19 | Fx | 7 |
| 6 | FV | 9 | FXIII | 5 |
| 7 | FXIII | 9 | BSS | 1 |
| 8 | FX | 6 | SPD | 1 |
| 9 | BSS | 1 | FI | 1 |
| 10 | SPD | 1 | FIX | 1 |
| 11 | Un Diagnosed | 23 | Un Diagnosed | 13 |

**vWD** von Willebrand Disease **GT** Glanzmann's Thromboasthenia
**SPD** storage pool disease **BSS** Bernard Soulier Syndrome

## HAEMOPHILIA TREATMENT CENTRE RAWALPINDI

The Haemophilia Treatment Centre (HTC) of HPWS Rawalpindi is an outpatient facility which looks after all the medical needs of the Haemophilia community by its well-trained Medical & Nursing staff (Medical officer, nurses, and consultants). It has a comprehensive Medical Advisory Board (**MAB: Annexe 3**) with specialists covering all aspects of Inherited Bleeding Disorders who volunteer free services to the patients. The indoor treatment facilities are provided by a network of Haemophilia Friendly Hospitals (**HFH: Annexe 4**) in the twin cities of Rawalpindi & Islamabad.

## CHAPTER 1

### Services

- Medical checkup ,MO/Consultant
- Treatment (as per Policy)
- Referrals to & consultations by our Medical Advisory Board (MAB) &relevant Doctors at Haemophilia Friendly Hospitals (HFH)
- Admission in HFH's if required & provision of protocols & haemostatic cover per requirement
- 24 hour on call service for emergencies
- Emergency care per policy
- Physiotherapy sessions
- Counseling
- Training to prepare factors & infuse factors
- Awareness activities, Seminars & workshops
- Lab diagnosis
- Management of medical issues
- Provision of timely & adequate treatment
- Development of medical literature, protocols & guidelines
- Continuing Medical Education & training of doctors, nurses & paramedics
- Research

The patients have to be registered with the HTC.

### Requirements for registration:

### Blood tests

- Complete Coagulation Profile
- Factor level
- HB sAg
- HCV
- Other tests like Blood CP, LFTs, etc. if required.

### Documents

- B- Form / CNIC of Patient
- Parents CNICs
- 2 passport size pictures of Patient

- Home address or (Proof of residential documents if the patient is foreign national)
- Phone No. / Email

## CONTACT DETAILS

### HPWS Rawalpindi

1st Floor, Thalassemia House

Tipu Road Rawalpindi

Tel: 8432751, 8432752

E mail: hpwsrwp@gmail.com

**Contact person**: Naveed Inderayas 0344 5093127

### HTC Rawalpindi

1st Floor, Thalassemia House

Tipu Road Rawalpindi

Tel: 8432751, 8432752

**Contact person:** Alamgir Abbasi 0332 8733220

# CHAPTER 2

## INHERITED BLEEDING DISORDERS

CHAPTER 2

# INHERITED BLEEDING DISORDERS

**Tahira Zafar[1, 2], Lubna Zafar[1, 3] Humera Siddique[4]**

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[3] DHQ Hospital, Mardan

A bleeding disorder results when blood cannot clot properly causing prolonged bleeding. For blood to clot normally; clotting factors & platelets are required. Deficiency or abnormal function of these result in a bleeding disorder. When the deficiency is genetic, the disorder is called Inherited Bleeding Disorder

Platelets are the first line of defense against an injury. Platelet aggregation results in formation of a primary haemostatic plug which stops bleeding but is friable and unstable. This is strengthened by fibrin deposition & cross linking due to activation of clotting factors, secondary haemostatic plug. This is solid & stable.

In inherited bleeding disorders there is either deficiency of clotting factors or abnormality of platelet function resulting in prolonged bleeding which can affect any part of the body and can occur spontaneously, in severe deficiencies. In mild cases however, the prolonged bleeding happens after trauma or surgery

## TYPES

### Common Bleeding Disorders

Haemophilia A (F VIII deficiency)

Haemophilia B (F IX deficiency)

von Willebrand Disease (vWD Type I)

### Rare Bleeding Disorders:

Von Willebrand Disease (vWD Type III)

Coagulation factors deficiencies, Factor I, II, V, VII, X, XI & XIII

Platelet function disorders e.g. Glanzmann's Thrombasthenia, Bernard Soulier Syndrome

These are uncommon in the western world but not so uncommon in Pakistan & other countries where consanguineous marriages are practiced.

## GENETICS

### X LINKED DISORDERS

When the defective gene is on X chromosome, males suffer from disease as they have only one X chromosome. Females on the other hand have two X chromosomes so with one defective gene they are carriers as their normal X chromosome compensates by producing enough factors.

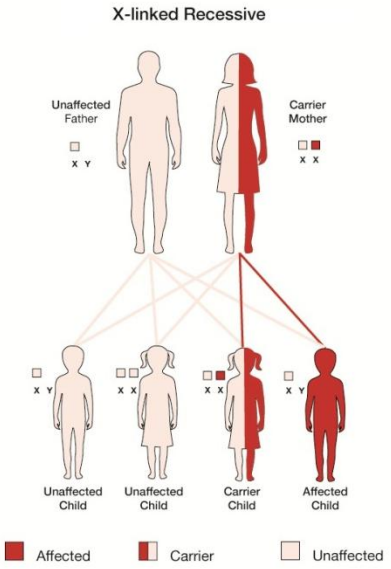



**Fig 1: Haemophilia A & B are X Linked disorders**

### AUTOSOMAL DISORDERS

Males and females have similar pairs of autosomes (one from each parent.) So autosomal disorders are seen in both genders.

## Autosomal dominant

Autosomal dominant: one copy of a mutant gene on one chromosome, from one parent, produces the disease.

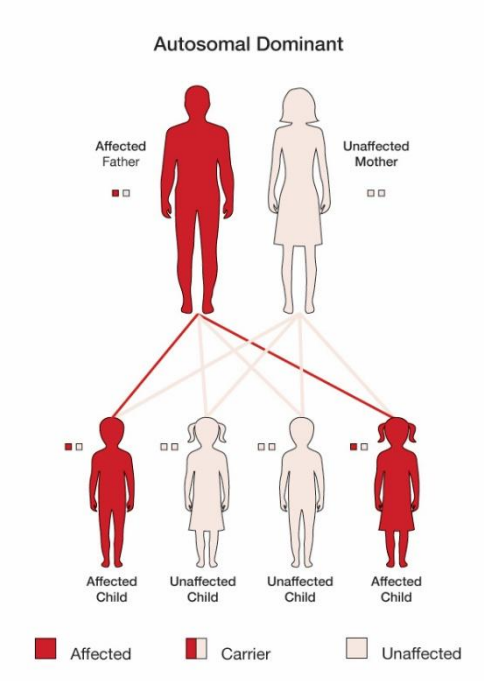



**Fig 2: Most cases of vWD Type I & 2 are autosomal dominant disorders**

## Autosomal recessive

Autosomal recessive diseases require that the affected individual has two copies of the mutant gene, one from each parent.

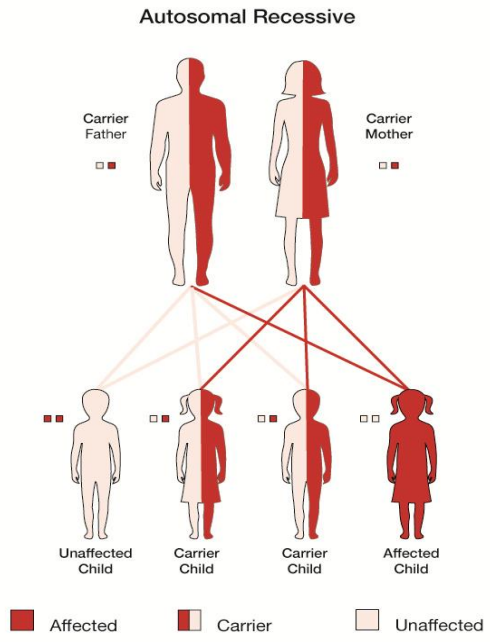



**Fig 3: vWD Type 3, Coagulation factors I, II, V, VII, X, XI & XIII deficiency and Platelet function defects are autosomal recessive**

## DIAGNOSIS OF INHERITED BLEEDING DISORDERS

### Haemophilia

### vWD

### Rare Bleeding Disorders (Platelet Function Disorders, Deficiency of Factor I, II, V, VII, X, XI & XIII)

A detailed medical history, family history & pattern of bleeding provide important clues to diagnosis. Suspected cases should be referred to a haematologist who would order appropriate tests to diagnose the case. Where the diagnosis is **documented** there is **no need to repeat the diagnostic investigations**

### Screening tests (first line)

- Platelet count
- Bleeding time (BT)
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT )
- Thrombin time (TT) in some cases

The screening tests, if normal, help to rule out a bleeding disorder in most cases. However in case of abnormal results diagnosis has to be confirmed by doing several other tests.

### Diagnostic tests (second line)

- Mixing studies (using adsorbed plasma or aged serum)
- Factor Assays
- Platelet function tests
- Clot Lysis test

These help in confirmation of specific bleeding disorders

## Diagnosis of Haemophilia A & B

### Screening Tests:

- **Platelet count** Normal
- **BT** Normal
- **PT** Normal
- **aPTT** **Prolonged**
- **TT** Normal

### Diagnostic tests

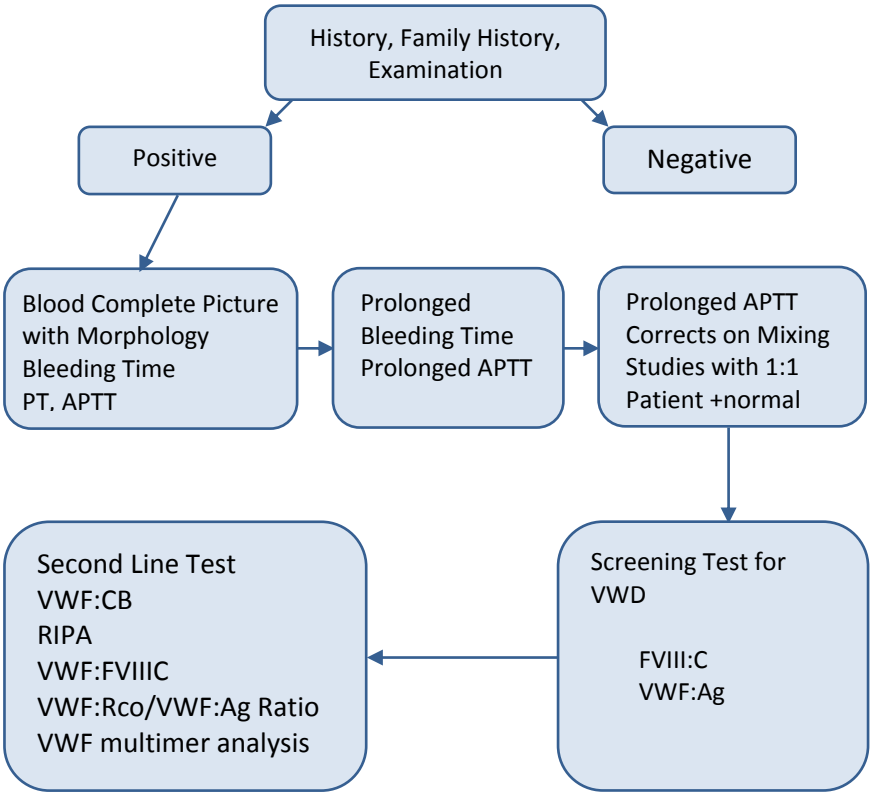
- **Mixing Studies** (using normal, adsorbed or aged plasma)
- **Pooled Plasma:** This is mixed in a 1:1 ratio with patient's plasma and APTT is repeated.
    - Correction : factor deficiency
    - No correction: inhibitor of coagulation. In such cases, inhibitor screen is performed
- **Aged Plasma:** (No factor V and VIII). This is mixed in a 1:1 ratio with Patient's serum and APTT is repeated.

  - Correction: Haemophilia B
  - No correction: Haemophilia A.
- **Adsorbed plasma:** No factor II, VII, IX, X.) this is mixed in a 1:1 ratio with Patient's serum and APTT is repeated.
  - Correction : Haemophilia A
  - No correction : Haemophilia B
- **Factor Assays**
  - Low F VIII levels : Haemophilia A
  - Low F IX levels : Haemophila B

## Diagnosis of von Willebrand Disease

- **BT** **Prolonged** (in almost all patients)
- **aPTT** May or may not be prolonged (depending upon the type of vWD).
- **VWF Ag and vWF activity** Done to diagnose vWD.
- **vWF Ag levels** are done to check severity of disease
- **Platelet function studies** showing poor or no response to ristocetin

For more detailed workup of Vwd, following algorithm should be followed:




## Diagnosis of Rare Bleeding Disorders

- **Platelet Function Disorders**

Platelet count Normal

BT Prolonged

PT Normal

aPTT Normal

Platelet functions Abnormal

- **Factor XIII deficiency**

| | |
|---|---|
| Platelet count | Normal |
| BT | Normal |
| PT | Normal |
| aPTT | Normal |
| Clot lysis | Abnormal |

**In Labs not doing Clot lysis test, FXIII deficiency can be missed**

- **Factor VII deficiency**

| | |
|---|---|
| Platelet count | Normal |
| BT | Normal |
| PT | Prolonged |
| aPTT | Normal |
| FVII levels | Low |

- **Other Factor Deficiencies (**Factor I, II, V, X, XI )

Diagnosed using a combination of PT, aPTT, mixing studies and factor levels

## PRINCIPLES OF TREATMENT

The main aim of treatment in inherited bleeding disorders is to prevent & treat bleeding according to the factor deficiency. Treatment should be prompt & adequate. To do this it is extremely important to have documented accurate diagnosis.

Never go by the verbal statement of the patients or the attendants. If there is no proof of the diagnosis, patient should be reinvestigated.

Patients registered with Haemophilia Patients Welfare Society carry an identification card indicating their diagnosis, the severity of disease, inhibitor status and the type of treatment they are taking. Contact details of their HTC and consultant haematologist are also on the card. This helps in appropriate management in emergency situations.

**The general management should be done as follows:**

- Close liaison is essential between the treating hospital & HTC
- Whenever possible, specific factor deficiency should be treated with specific factor concentrates. The treatment should be prompt & adequate
- Where clotting factors concentrates are limited, adjunctive treatments should be used. These include the use of fresh frozen plasma (FFP), cryoprecipitate and antifibrinolytic agents
- Platelet concentrates are used for platelet function disorders
- In case of joint bleeds use of protection (splint), rest, ice, compression and elevation (PRICE) is very useful. For further details please refer to Chapter on Joint & muscle issues in Haemophilia
- Patients positive for inhibitors should be treated with by passing agents
- Both psychological and social support must be provided to patients as well as their families.
- A physiotherapist who has experience of haemophilia patients should advise on musculoskeletal health & fitness. Please refer to chapter on physiotherapy
- Aspirin & non-steroidal anti-inflammatory drugs (NSAID's) should be avoided. Paracetamol is a safe alternative
- Intramuscular injections to be avoided

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# CHAPTER 3

# HAEMOPHILIA

# HAEMOPHILIA

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[2] Frontier Medical College, Abbotabad
[3] DHQ Hospital, Mardan

Haemophilia is an X-linked inherited bleeding disorder that is caused by a deficiency of coagulation factor VIII or IX in the body. Since these factors are responsible for completing secondary haemostasis and thereby stabilizing the clot, the cascade is left incomplete due to their deficiency. The unstable clot then dislodges/disintegrates, resulting in prolonged bleeding.

## GLOBAL FACTS AND FIGURES

- Haemophilia is the commonest inherited bleeding disorder.
- Around 400,000 people are affected worldwide.
- The estimated number of potential patients in Pakistan is around 13600. Of these only 2400 patients are nationally registered and are being cared for at the Haemophilia Treatment Centres (HTCs)
- Haemophilia A represents 80-85% of the total Haemophilia population.

## TYPES

There are two types of Haemophilia:

- Haemophilia A (Classic Haemophilia) caused by Factor VIII deficiency
- Haemophilia B (Christmas Disease) caused by Factor IX deficiency

## GENETICS

Genes for both Factor VIII and Factor IX are located on the long arm of chromosome X (Xq28). The disease is inherited in an X-linked recessive manner. Since females carry a set of two X chromosomes, they will not

present with disease (phenotype) unless the Factor VIII/IX gene on both X chromosomes are affected. Therefore, phenotypic presentation of disease occurs only in:

- Males ($X^hY$)
- Homozygous Females ($X^hX^h$)
- Heterozygous Females with X chromosome inactivation ($X^hX^i$)
- Most frequent mutation found in Pakistani Haemophilia patients is the Point Mutation. One study carried out on 92 Haemophilia A patients reports a prevalence of 42% (Table 1). Another study carried out on 34 Haemophilia B patients reports a prevalence of 74% (Table 2).

**Table 1: Mutations Reported for Haemophilia A in Pakistan**

| Point Mutation | | | | Inversion | | Frame shift | | Del of exons | No Mutation |
|---|---|---|---|---|---|---|---|---|---|
| **Missense** | Nonsense | Splice Site | Promoter | Inv 22 | Inv 1 | Nucleotide deletion | Nucleotide duplication | 01 | 11 |
| **18** | 17 | 03 | 01 | 18 | 01 | 19 | 03 | | |

**Table 2: Mutations Reported for Haemophilia B in Pakistan**

| Point Mutation | | | | Frame Shift | |
|---|---|---|---|---|---|
| Missense | Nonsense | Splice Site | Branch Point | Nucleotide Deletion | Nucleotide Duplication |
| 17 | 04 | 02 | 02 | 07 | 02 |

Both FVIII & FIX genes can develop new mutations and result in Haemophilia without a family history (in 1/3 cases)

## INHERITANCE

Two most common presentations of Haemophilia gene inheritance are as follows:

### Example 1: Mother has a Haemophilia Gene

When mother is a carrier of one haemophilia gene and the other allele is functional, chances of inheritance are as follows:

| Father \ Mother | $X^h$ | X |
|---|---|---|
| X | $X^hX$ | XX |
| Y | $X^hY$ | XY |

Where

$X^h$: X chromosome with haemophilia gene
X: X chromosome with normal gene
Y: Y chromosome

As is shown in this example, each son has a 50% chance of inheriting the haemophilia gene and be affected by Haemophilia. Each daughter also has a 50% chance of inheriting the haemophilia gene but she will be a carrier only.

### Example 2: Father has a Haemophilia Gene

When father has a Haemophilia gene (and therefore, has Haemophilia), chances of inheritance are as follows:

| Father \ Mother | X | Y |
|---|---|---|
| $X^h$ | $XX^h$ | $XX^h$ |
| Y | XY | XY |

Where

$X^h$: X chromosome with haemophilia gene
X: X chromosome with normal gene
Y: Y chromosome

As is shown by the above example, none of the sons will inherit the haemophilia gene and therefore none will have Haemophilia. On the other hand, all daughters will inherit the haemophilia gene but they will be carrier only.

**Note:** Coagulation Factor VIII and IX genes are both prone to new mutations and as many as 1/3 of all Hemophilia cases are the result of spontaneous mutation where there is no prior family history.

(For more details please refer to: Introduction to inherited Bleeding Disorders)

## CHAPTER 3

## Pathophysiology

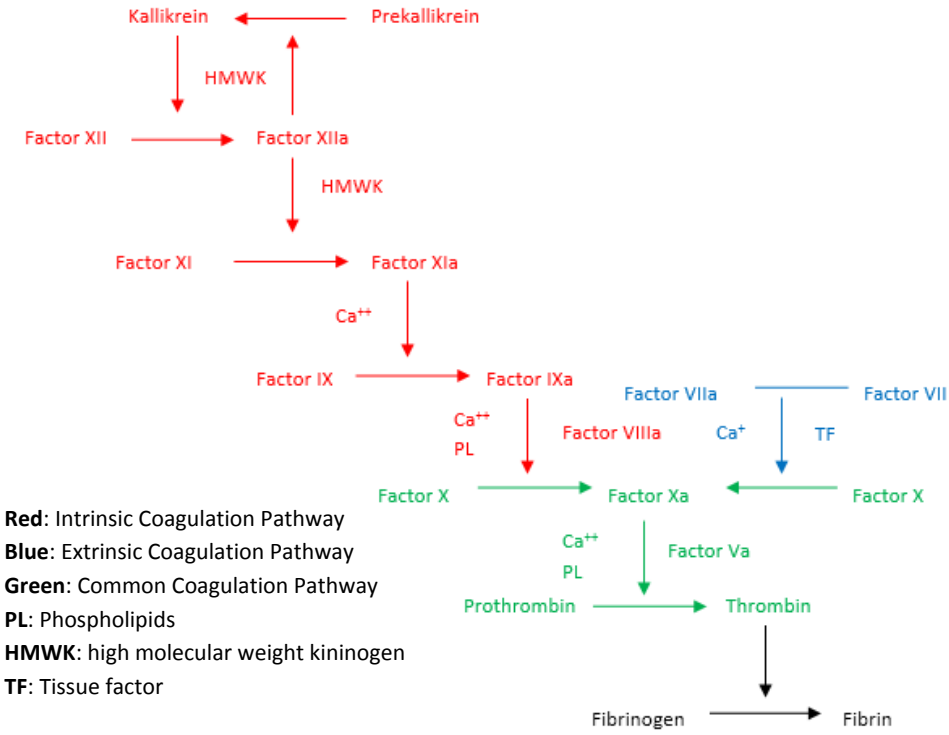


**Figure 1: The Coagulation Cascade**

## Deficiency of Factor VIII/IX

Activated coagulation Factor VIII and IX together form the Tenase complex in the intrinsic pathway of coagulation. Decreased Tenase activity due to a lack of either Factor VIII or IX ultimately leads to decreased conversion of fibrinogen into fibrin. Due to a lack of fibrin in the clot, it is unstable, has increased susceptibility to fibrinolysis and easily dislodges, especially in areas of increased blood flow, thereby leading to prolonged bleeding and poor wound healing.

## CLINICAL FEATURES

Bleeding tendency is the characteristic phenotype in Haemophilia. The severity of bleeding generally correlates with clotting factor levels (Table 3).

**Table 3: Clinical Classification of Haemophilia**

| Classification | Factor VIII Level | Clinical Features |
|---|---|---|
| Severe | ≤1% of normal (≤0.01 U/ml) | Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge |
| Moderate | 1–5% of normal (0.01–0.05 U/ml) | 1. Occasional spontaneous bleeding<br>2. Prolonged bleeding with minor trauma or surgery |
| Mild | 6–30% of normal (0.06–0.30 U/ml) | 1. Spontaneous bleeding is rare<br>2. Severe bleeding with major trauma or surgery. |

**Time of First Presentation:** Although bleeding can occur at any time, most frequent first presentations of Haemophilia are:

- Excessive bleeding after circumcision , very common presentation in Pakistan in neonates
- Excessive bruising from an early age
- Bleeding into joints/muscles when a child starts crawling/ walking

Patients with mild forms may not bleed excessively until they undergo major trauma or surgery. Most heterozygous females usually have more than 50% of factor levels and do not present with excessive bleeding even after trauma/surgery. However, those with X chromosome inactivation may have low factor levels. Therefore, measuring factor levels is necessary in all carriers in order to avoid the danger of excessive bleeding after surgery and child birth etc.

A study of 30 obligate carriers at Haemophilia Treatment Centre Rawalpindi showed only 3 had factor FVIII levels below 50% of the normal. Of these 3 females, 2 carriers were unmarried with FVIII levels 33% & 37% of the normal and gave only history of epistaxis. Third carrier female had FVIII level 26.1% of normal presented with history of menorrhagia and postpartum hemorrhage.

## CHAPTER 3

**Frequent Sites of Bleeding:** Bleeding in Haemophilia most commonly occurs internally, into the joints or muscles (Table 4).It also occurs in the oral cavity ( mouth , gums ) & genitourinary tract(haematuria) Bleeding at certain sites (intracranial, neck, throat, GIT) can be life threatening and requires immediate management.

**Table 4: Frequency of Bleeding Sites in Haemophilia**

| Site Of Bleeding | Approximate Frequency |
|---|---|
| Haemarthrosis<br>-more common into hinged joints: ankles, knees, and elbows<br>-less common into multi-axial joints: shoulders, wrists, hips | 70%–80% |
| Muscle | 10%–20% |
| Other major bleeds | 5%–10% |
| Central nervous system (CNS) | <5% |

**Haemarthrosis** accounts for 70-80% of bleeds in Haemophilia.

(For further details please refer to: Joint & muscle issues in Haemophilia)

## LABORATORY DIAGNOSIS

### Screening tests:

- **Complete Blood Count (CBC) Normal**

(Decreased hemoglobin only in prolonged bleeding)

- **Bleeding Time (BT) Normal**
- **Prothrombin Time (PT) Normal**
- **Activated Partial Thromboplastin Time (APTT) Prolonged**

### Diagnostic tests:

#### Correction Studies

- **Pooled Plasma:**

  Correction Factor deficiency
  No Correction Inhibitors

- **Aged Plasma:** (No Factor V & VIII)

| | |
|---|---|
| Correction | Haemophilia B |
| No Correction | Haemophilia A |

- **Adsorbed plasma:** (No Factor II, VII, IX, X)

| | |
|---|---|
| Correction | Haemophilia A |
| No Correction | Haemophilia B |

### Factor Assay

The confirmed deficient factor is then assayed for determining the severity of disease.

(For Further details please refer to: Introduction to Inherited bleeding disorders)

## MANAGEMENT

### Acute Bleeding

- Must be treated promptly & adequately preferably within two hours. If in doubt, treat.
- Patients often experience an aura of tingling sensation before the manifestation of physical signs.
- During an episode of acute bleeding, an assessment for identification of the site of bleeding should be made and appropriate clotting factor should be administered.
- Life threatening bleeding episodes especially in the head, neck, chest, and gastrointestinal tract must be promptly treated with factors, even before diagnostic assessment is completed.
- Close liaison should be maintained with the surgical department that will assess whether patient needs to be operated upon.
- The World Federation of Hemophilia (WFH) recommends the following factor replacement protocol in countries with significant resource constraint (Table 6).

## CHAPTER 3

**Table 6: Plasma Factor Peak Level and Duration of Administration (When there is Significant Resource Constraint) in the Event of Acute Haemorrhage**

| Type of Haemorrhage | Haemophilia A | | Haemophilia B | |
|---|---|---|---|---|
| | Desired level IU/dL | Duration (Days) | Desired level IU/dL | Duration (Days) |
| **Joint** | 10–20 | 1–2 may be longer if response is inadequate | 10–20 | 1–2 may be longer if response is inadequate |
| **Superficial muscle**/no neuro vascular compromise (except iliopsoas) | 10–20 | 2–3, sometimes longer if response is inadequate | 10–20 | 2–3, sometimes longer if response is inadequate |
| **Iliopsoas and deep muscle** with neurovascular injury, or substantial blood loss<br>Initial<br><br>Maintenance | 20–40<br><br>10–20 | 3–5, sometimes longer as secondary prophylaxis during physiotherapy | 15–30<br><br>10–20 | 3–5, sometimes longer as secondary prophylaxis during physiotherapy |
| **CNS/Head** | 50–80 | 1–3 | 50–80 | 1–3 |
| Initial | 30–50 | 4–7 | 30–50 | 4–7 |
| Maintenance | 20–40 | 8–14 | 20–40 | 8–14 |
| **Throat and Neck** | | | | |
| Initial | 30–50 | 1–3 | 30–50 | 1–3 |
| Maintenance | 10–20 | 4–7 | 10–20 | 4–7 |
| **Gastrointestinal** | | | | |
| Initial | 30–50 | 1–3 | 30–50 | 1–3 |
| Maintenance | 10–20 | 4–7 | 10–20 | 4–7 |
| **Renal** | 20–40 | 3–5 | 15–30 | 3–5 |
| **Deep laceration** | 20–40 | 5–7 | 15–30 | 5–7 |

**CHAPTER 3**

## HAEMOSTATIC AGENTS

### Factor Concentrates

- Factor VIII and IX concentrates are the treatment of choice for Haemophilia A and B respectively. May be recombinant or plasma derived.
- When selecting product, following must be addressed:
  **Product purity** Percentage of the desired ingredient, relative to other ingredients present (low purity product may give rise to an allergic reaction).
  **Viral inactivation** Heat treatment (HBV, HCV, HIV, HAV)
  Solvent /detergent treatment (HBV, HCV, HIV)
  Use of both treatments is preferred over using one
- In the absence of an inhibitor, each IU/kg of Factor VIII and IX concentrate infused intravenously will raise plasma levels to approximately 2 IU/dl and 1 IU/dl respectively.
- **Dose calculation**:
  - Haemophilia A: Patient's weight (kg) x desired rise in factor VIII levels (IU/dl) x 0.5
  - Haemophilia B: Patient's weight (kg) x desired rise in factor IX levels (IU/dl)
- Half life of factor VIII and IX is approximately 8-12 and 18-24 hours, respectively.

### Fresh Frozen Plasma (FFP)

- Contains all coagulation factors.
- One ml of FFP contains 1 unit of factor activity.
- Usual starting dose is 15-20 ml/kg
- It is difficult to achieve factor VIII and IX levels higher than 30 and 25 IU/dl, respectively with FFP alone.
- Is not subjected to viral inactivation and, therefore, there is an increased risk of viral transmission, especially with repeated transfusions.
- Due to concerns about its safety and quality, its use can only be justified in countries with significant resource constraints.

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### Cryoprecipitate

- Contains significant quantities of factor VIII, VWF, fibrinogen, and factor XIII but not factor IX or XI.
- One ml of cryoprecipitate contains 3-5 IU of factor VIII activity
- Usual dose is 1 bag(30-40mL)/10kg body weight
- Preferred over FFP for treatment of Haemophilia A.
- Not subjected to viral inactivation and, therefore, there is an increased risk of viral transmission, especially with repeated transfusions.
- Due to concerns about its safety and quality, its use can only be justified in countries with significant resource constraints.

### Tranexamic Acid

- An antifibrinolytic agent that inactivates the conversion of plasminogen into plasmin.
- Useful as an adjunctive therapy for maintaining clot stability in Haemophilia patients.
- Usual dose is 10ml/kg intravenous or 20ml/kg orally 3-4 times daily.
- Particularly useful in controlling bleeding from skin and mucosal surfaces (oral bleeding from eruption/shedding of teeth, menorrhagia, epistaxis)
- Contraindicated in haematuria where insoluble clots/haematomas may be formed and in thoracic surgeries

### Fibrin Glue

- Contains fibrinogen, thrombin, and factor XIII.
- The fibrinogen–factor XIII mixture is placed on the injury site and clotted with a human thrombin solution containing calcium. As a result, the fibrin clot is cross linked and anchored to the tissue.
- Can be used as an adjunctive therapy to maintain local haemostasis following dental surgery, circumcision, orthopedic surgery and removal of pseudo tumor etc

## Desmopressin (DDAVP)

- A synthetic analogue of vasopressin.
- Boosts plasma levels of factor VIII and von Willebrand Factor.
- May be a treatment of choice in patients with mild-moderate Haemophilia A, but not effective in Haemophilia B.
- One dose of 0.3 µg/kg body weight, intravenous or subcutaneous, can boost factor VIII level three to six fold.
- Particularly useful in the treatment and prevention of bleeding in Carriers.

## Not available in Pakistan

## Inhibitors

- Development of IgG antibodies that neutralize clotting factors.
- Lifetime risk of development of inhibitors is:

Severe Haemophilia A 20-30%

Mild-moderate Haemophilia A 05-10%
Haemophilia B <5%

- Median age of development of inhibitors is:
  Severe Haemophilia A 03 years
  Mild-moderate Haemophilia A 30 years
- Development of inhibitors in patients with mild-moderate Haemophilia changes their disease phenotype to 'Severe' due to neutralization of endogenously synthesized coagulation factors.
- Inhibitor screening is essential in:
  - All patients prior to surgery
  - Once every 6-12 months
  - Failure to respond to factor replacement in a previously responsive patient
  - All patients undergoing intensive factor replacement for more than five days
- Depending on their levels, inhibitors are divided into:
  Low responding: persistently <5 BU/ml
  High responding: ≥5 BU/ml (tend to be persistent)

- Titres of high responding inhibitors may fall when not challenged for long time, however, an anamnestic response will generate within 3-5 days of factor re-exposure.
- Some low responding inhibitors are transient and may disappear within 6 months of documentation.
- A low responding inhibitor may be dealt with a much higher dose of factor replacement, part of which will neutralize the inhibitor.
- A high responding inhibitor that has fallen to low levels may be treated the same as above until the development of anamnestic response.
- A high responding inhibitor with levels ≥5 BU/ml will not be effectively managed without continuous ultra-high infusion therapy.

## Alternative Therapeutic Agents for treatment of Inhibitors

Factor VIII Inhibitor Bypassing Activity (**FEIBA**)

- Is a bypassing agent
- Contains factors II, IX, and X, mainly non-activated, and factor VII, mainly in the activated form
- FEIBA is given in doses of 50-100IU/kg every 6-12 hours in most hemorrhagic episodes.

Recombinant factor VIIa (rVIIa)

- Is a bypassing agent
- Contains factor VIIa manufactured by Recombinant technology.
- Can safely be given in doses of 90-120 µg/kg or higher every 2 to 3 hours in most hemorrhagic episodes

Prothrombin Complex Concentrates (**PCC**) and their activated forms (**APCC**)

- These contain factor II, IX and X, some versions also contain factor VII.

In short, several approaches to treatment of factor VIII/IX inhibitors are available (Table 9):

**Table 9: Treatment of Inhibitors in Haemophilia A/B patients**

| Type of Patient | Initial Titre | Minor Haemorrhage | Major Haemorrhage |
|---|---|---|---|
| Low Responder | < 5 BU | rVIIa, FEIBA, PCC | High dose fVIII, rVIIa, FEIBA, PCC |
| High Responder | ≥ 5 BU | rVIIa, FEIBA, PCC | rVIIa, FEIBA, plasma exchange |

### Immune Tolerance Induction (ITI)

- One of the therapies for 'Haemophilia patients with inhibitors' is to give factor concentrate regularly over a period of time until body is trained to recognize the treatment product without reacting to it.
- When successful, the inhibitors disappear and patient's response to factor concentrates returns to normal.
- Majority of people who undergo ITI therapy will see an improvement within 12 months, but more difficult cases can take two years or longer.
- Studies for devising an optimum dosage and the effect of brand or type of factor concentrate on ITI therapy are still underway.

## TRANSFUSION TRANSMITTED INFECTIONS

- In countries with significant resource constraint, the use of FFP and cryoprecipitate is still common.
- The above haemostatic agents are not subjected to viral inactivation and therefore, there is an increased risk of viral transmission, especially with repeated transfusions.
- All Haemophilia patients must be tested for HBV, HCV and HIV every 6-12 months.
- All Haemophilia patients without immunity must receive an anti-HBV vaccination. Protective seroconversion must be re-checked after vaccination. Patients who do not seroconvert should be revaccinated with double the anti-HBV vaccine dose.
- The diagnosis, counseling, treatment and monitoring of above infections should be the same as in the non-Haemophilia Population.

## CHAPTER 3

## HOME TREATMENT

**Is provided:**

- To HTC attending patients who need extended treatment of their bleeds.
- To patients on a regular prophylactic regimen
- Patients aged 10 years and above or their attendants are trained to infuse factor concentrates at Haemophilia Treatment Centres (HTC).

## PROPHYLAXIS

Prophylaxis of Bleeding in Haemophilia is of two types:

**Intermittent**

- Treatment given to prevent bleeding for short period of time, such as, during and after surgery. (Discussed under Management of Surgery)

**Continuous**

- Regular infusion of factor concentrates to prevent bleeding in Haemophilia patients.

**Table 10: Types of Continuous Prophylaxis in Haemophilia**

| Type of Prophylaxis | Definition |
|---|---|
| Primary Prophylaxis | Regular continuous treatment, started before the second large joint bleed and age of 3 years |
| Secondary Prophylaxis | Regular continuous treatment, started after two or more large joint bleeds but before the onset of joint disease |
| Tertiary Prophylaxis | Regular continuous treatment, started after the onset of joint disease to prevent further damage |

- Treatment of choice for all severely affected Haemophilia patients.
- Usual dose of factor concentrates is 25-40 IU/kg two-three times per week.
- Markedly decreases the frequency of haemophilic arthropathy and other long-term effects of haemorrhagic episodes.
- Is very expensive and not practical in countries with significant resource constraints.

## LOW DOSE PROPHYLAXIS (LDP) PROJECT IN PAKISTAN

- A number of studies in developing countries have shown an improved quality of life with the use of a lower dose of prophylaxis (LDP).
- LDP was started in Pakistan in 2017 and 25 severely affected Haemophilia patients are enrolled in the study.
- Factor concentrates are given to these patients in a dose of 20 IU/kg IV every week.
- This project is supported by the WFH Humanitarian Aid Program (HAP) and is led by Haemophilia Foundation Pakistan (HFP) & Haemophilia Patients Welfare Societies (HPWS) in collaboration with their Haemophilia Treatment Centres (HTC).

## VACCINATION OF CHILDREN WITH HAEMOPHILIA

- Haemophilia patients have an increased risk of acquiring hepatitis B from repeated transfusions and at least the same risk as the general population of acquiring other vaccine-preventable diseases.
- Because of the risk of hematomas, there is great concern about the use of vaccine that can be administered intramuscularly only.
- There are also speculations that vaccines may induce the development of inhibitors against factor concentrates however, these are not substantiated by unequivocal clinical data.
- The Medical and Scientific Advisory Council (MASAC) Vaccine Working Group has developed a set of recommendations which have been approved by The National Hemophilia Foundation (NHF). These are:

### Centers for Disease Control and Prevention (CDC) Guidelines

- It is highly recommended that Haemophilia patients continue to follow the American Academy of Pediatrics (AAP) and Centres for Disease Control (CDC)'s vaccine recommendation route and schedule for their age.

## CHAPTER 3

### Protocol for Administration of Vaccines

- A fine-gauge needle (≤ 23 gauge caliber) should be used.
- At the site of injection, firm pressure should be applied for at least 2 minutes without rubbing.
- Patient's attendant and nurse must be aware about the risk of haematoma at the injection site.
- The patient's attendant must be guided to promptly call the HTC in the event of hematoma development.
- Aspirin and NSAIDS (such as ibuprofen, naproxen sodium) should be avoided because of the potential risk of bleeding. Acetaminophen is a safe alternative.
- In patients receiving prophylaxis treatment for Haemophilia, vaccination could be given within 24 hours of prophylaxis to decrease the risk of prolonged bleeding.

### Vaccines that can be given subcutaneously

Vaccines that have been tested and demonstrated to be effective when administered either intramuscularly or subcutaneously include: **Pneumococcal polysaccharide (PPSV), Polio inactivated (IPV), Hepatitis A, and Hepatitis B**

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# CHAPTER 4

# JOINT AND MUSCLE ISSUES IN HAEMOPHILIA

# JOINT AND MUSCLE ISSUES IN HAEMOPHILIA

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Bleeding in joints is characteristic of severe and to a lesser extent moderate Haemophilia. Other than Haemophilia joint bleeding can also be seen in Factor X Deficiency, vonWillebrand Disease Type III and Type 2N. In severe Haemophilia, 90% of bleeding episodes involve musculoskeletal system, 80% 0f these being in the joints. Tissue factor pathway inhibitor seems to play role in making joints increasingly susceptible to bleeding.

**Table 1: Frequency of Bleeding Sites in Hemophilia**

| Site Of Bleeding | Approximate Frequency |
|---|---|
| Haemarthrosis | 70%–80% |
| Muscle | 10%–20% |
| Other major bleeds | 5%–10% |
| Central nervous system (CNS) | <5% |

## JOINT BLEEDS

Although any joint can be affected, the weight bearing joints such as knees, elbows and ankles are most vulnerable to mechanical trauma and subsequent bleeding. Data of Haemophilia treatment Centre of Haemophilia Patients' Welfare Society Rawalpindi shows the following distribution of Joint bleeds:

**Table 2: Distribution of Joint bleeds**

| Joint Involved | Episodes of Haemarthrosis No (%) |
|---|---|
| Knee Joint | 310(47.83) |
| Elbow | 90(13.88) |
| Ankle | 80(12.34) |
| Toe | 18(2.77) |
| Hip | 15(2.31) |
| Wrist | 11(1.69) |
| Fingers | 10(1.54) |
| Shoulder | 02(0.30) |

## CHAPTER 4

## PATHOPHYSIOLOGY

### Three stages of haemophilic arthritis:

Acute Haemarthrosis
Chronic synovitis
Degenerative arthritis

The synovium has very limited capacity of absorbing blood. Therefore, the first incidence of Haemarthrosis may be somewhat tolerated. However, subsequent episodes result in formation of blood breakdown products that the synovial membrane cannot remove. Among these, hemosiderin plays major role in activating the production of pro inflammatory cytokines such as IL-1, IL-6 and TNF which promote inflammation in the form of increased vascularity and hypertrophy of synovial tissue making it friable and more prone to haemorrhage, thereby generating a vicious cycle of bleeding and inflammation. The articular cartilage also undergoes destruction through direct contact with blood and synovium associated inflammation. These two processes result in degenerative arthritis that progresses until joint is completely destroyed.

**Table 3: Haemophilic Arthrosis**

| Acute Haemarthrosis | Chronic Haemarthrosis |
|---|---|
| Associated with severe pain | Not associated with pain |
| Joint is maintained in a position of comfort (typically in flexion) and has a fluid characteristics | Synovium is palpable as a soft tissue firmness |

## CLINICAL EVALUATION:

### Symptoms

Patient first experiences an aura of mild discomfort that progresses into pain over the next few minutes to hours. The affected joint is swollen, warm and has limited movement. Patient may have mild fever. All of these are signs of synovitis.

### Clinical examination

Joint health is measured using different scoring systems
**The Functional Independence Score in Hemophilia (FISH) – 2007** (Poonnoose PM, Padankatti S, Macaden AS, Srivastava A; Christian Medical College, Vellore, India) Developed as a performance-based

assessment tool to objectively measure an individual's functional ability. It is intended to measure what the person with disability *actually does.* It is safe to perform and complements other scores that measure body structure and function

**World Federation of Hemophilia Physical Examination Score (also called the Gilbert Score)** Authors/developers Gilbert M, and the Orthopedic Advisory Committee of WFH. It is primarily designed for adults and children with established arthropathy. It may be used Interventions when there is a need for orthopedic intervention, or as an outcome measure of physiotherapy

**Haemophilia Joint Health Score (HJHS)** (Feldman BM, Funk S, Hilliard P, Van Der Net J, Zourikian N, Berstrom B-M, Engelbert RHH, Abad A, Petrini P, Manco-Johnson M, and the International prophylaxis Study Group).The HJHS measures joint health, in the domain of body structure and function (i.e. impairment), of the joints most commonly affected by bleeding in haemophilia: the knees, ankles, and elbows. It is primarily designed for children with haemophilia aged 4-18 years with mild joint impairment (e.g. treated with prophylaxis). It can be used when there is a need for orthopaedic intervention, or as an outcome measure of physiotherapy

## Imaging Studies

- Magnetic Resonance Imaging is the gold standard and more sensitive than Radiography for detecting haemophilic arthropathy and particularly soft tissue changes.
- Imaging scoring systems commonly used are the Pettersson score, the European MRI scale, the Arnold–Hilgartner score and the Denver MRI scale
- Radiological stages of haemophilic arthropathy in the Arnold-Hilgartner Classification are :

**Table 4: Arnold- Hilgartner classification of Haemophilic Arthropathy**

| Stage | Radiologic Findings |
|---|---|
| Stage 0 | Healthy joint |
| Stage 1 | Soft tissue swelling. No skeletal abnormality. |
| Stage 2 | Some osteoporosis and epiphyseal overgrowth. No cysts and no narrowing of cartilage space. |
| Stage 3 | Early subchondral bone cysts. Joint space irregularities. |
| Stage 4 | Prominent bone cysts with marked narrowing of joint space. |
| Stage 5 | Fibrous joint contractures, obliteration of joint space and extensive enlargement of epiphyses with substantial disorganization of the joint. |

## TARGET JOINTS

A joint which has had recurrent bleeding for four or more times in the past six months. Patients with severe Haemophilia are more prone to develop a target joint. Target joint should be treated aggressively with appropriate factor replacement to interrupt the vicious cycle of inflammation, swollen synovium and recurrent bleeding.

## MUSCLE/SOFT TISSUE BLEEDING

- Any muscle can be affected but the large weight bearing muscle groups of the thigh, calf, posterior abdominal wall and buttocks are most vulnerable.
- The resultant haematoma may cause local pressure effects on the surrounding structures
    - A common example is entrapment of femoral nerve caused by iliopsoas bleeding. This is presented with a triad of groin pain, hip flexure and cutaneous sensory loss over femoral nerve distribution.
    - A retroperitoneal haematoma may cause ureteric obstruction and compromise renal function.
    - Pharyngeal & retropharyngeal haematoma may obstruct the airways.
    - Bleeding into a compartment may cause compartment syndromes by compressing the arterial vasculature resulting in ischemic muscle atrophy.

- The iliopsoas haemorrhage may be life threatening if it is associated with high volume of blood loss in the retroperitoneal space.

## MANAGEMENT

**RICE:** Rest, Ice, Compression and Elevation

- **Rest:** Important to give rest to the bleeding joint Use of crutches, slings, splints or pressure bandages for joint support can help in reducing pain Lower limb bleeds benefit from bed rest for one day, elevation when sitting for 3-4 days and use of wheel chair or crutches when ambulating. Joint to be mobilized as soon as the pain improves to avoid muscle atrophy and limitation of movement.
- **Ice:** Constricts blood vessels and decreases pain. Wrap crushed ice or ice cubes in a wet towel and leave it in place for 5 minutes. Repeat the procedure 3-4 times daily with 10 minutes interval between the treatments. Treatment by frozen gel packs is same as the treatment with ice packs. Avoid direct contact with skin. Best results are when it is done within the first 48 hours
- **Compression:** This can minimize swelling, limit bleeding & provide support to the joint. Joint can be wrapped in an elastic bandage.
- **Elevation-** Raising the injured part above heart level will decrease pressure in the area and help minimize bleeding and swelling.

In acute phase, all therapies that impede the haemostatic process, such as **massages and heat sources, are contraindicated**

### Analgesics/Pain Killers

Paracetamol or acetaminophen or milder opioid analgesics can be used. Dose of Paracetamol: 325 to 650 mg, 1 tab 2-3 times daily. NSAIDs can aggravate bleeding therefore are contraindicated.

## CHAPTER 4

### Anti-inflammatory treatment:

Since NSAIDS are contraindicated, the more modern COX-2 inhibitors, will not affect primary haemostasis &may be assessed. Use of Intra-articular corticosteroid injection has been described for chronic synovitis. Systemic corticosteroids may exert side effects but may be considered in severe inflammatory reactions refractory to other treatments.

**Intramuscular injections should not be prescribed.**

**Opiates:** If pain is not relieved, following medicines can be used:

**Table 5: Opiate Analgesics**

| Drug | Adult dose | Paediatric dose |
|---|---|---|
| Co-Proxamol | 2 tabs 3-4 times daily | Not recommended |
| Codeine | 30-60 mg every 4-6 hours | 0.5 – 1.0 mg/kg every 4 hours |
| Temgesic | 0.8 mg every 6 hours | Not recommended |
| Tramadol | 60-100 mg every 6 hours | Not recommended |
| Pentazosine | 30-60 mg I/V 3-4 hours; 50 mg P.O 3-4 hours | 6-12 years: 25 mg 3-4 hourly |

## FACTOR CONCENTRATES

Joint & muscle bleeds are treated by replacing the missing factors. The requirement for factors depends on the type of bleed.

**Table 6: Factor requirements:**

| Type of Haemorrhage | Haemophilia A | | Haemophilia B | |
|---|---|---|---|---|
| | Desired level IU/dl | Duration (Days) | Desired level IU/dl | Duration (Days) |
| Joint | 10–20 | 1–2 may be longer if response is inadequate | 10–20 | 1–2 may be longer if response is inadequate |
| Superficial muscle/no neuro vascular compromise (except iliopsoas) | 10–20 | 2–3, sometimes longer if response is inadequate | 10–20 | 2–3, sometimes longer if response is inadequate |
| Iliopsoas and deep muscle with neurovascular injury, or substantial blood loss | | 3–5, sometimes longer as secondary prophylaxis during physiotherapy | | 3–5, sometimes longer as secondary prophylaxis during physiotherapy |
| Initial | 20–40 | | 15–30 | |
| Maintenance | 10–20 | | 10–20 | |

**Dose calculation:**

**Factor VIII**= Body weight (in kg) X Desired factor VIII level in IU/dl X 0.5
**Factor IX** = Body weight (in kg) X Desired Factor IX level in IU/dl X1.1

**Alternate treatments**

In the absence of factor concentrates the blood components which can be used are: Fresh Frozen Plasma (FFP), Cryoprecipitate, and Prothrombin Complex Concentrates (PCC)

**Table 7: Alternate Treatments**

| | Haemophilia A | Haemophilia B |
|---|---|---|
| FFP | 10-15 ml/kg every 12 hours | 10-15 ml/kg every 24 hours |
| Cryoprecipitate | 1 bag/10 kg every 12 hours | No factor IX present |
| PCC | No factor VIII | Loading: 20-30 IU/Kg<br>Maintenance: 15 IU/Kg/day |

## ARTHROCENTESIS (JOINT ASPIRATION)

**Joint aspiration:**

- Done to remove load of blood after a joint bleed.
- It can help relieve pain and spasm and speed up rehabilitation.

Should only be performed under following conditions:

- When the joint is extremely swollen and painful.
- A joint which has not improved even after 2-3 days of treatment.
- Aspiration should always be done under aseptic conditions.
- Aspiration from elbow, knee and ankle can be done in OPD.
- Aspiration of hip and shoulder joints should be done under radiographic control in the operation theatre by an orthopedic surgeon.
- Whenever aspiration is done, the factor levels should be 30-50% for at least 2-3 days.
- If factors are unavailable, aspiration should not be done.
- Aspiration should not be done if there is an infection.

## CHAPTER 4

Arthrocentesis usually in unnecessary & is only useful when the joint is severely distended or when resolution of Haemarthrosis is delayed despite adequate replacement therapy. The systematic use of joint aspiration best be avoided, due to risk of infections and other complications. In most of the cases joint aspiration is performed in ignorance, rather than as an option.

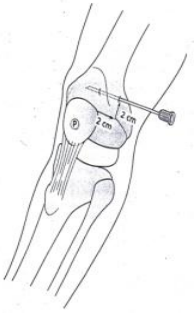
### Synoviorthesis (Non-surgical Synovectomy):

Synoviorthesis is percutaneous, intra-articular injection of a certain material with the aim of "Stabilizing" (Orthesis) the synovium of a joint (Synoviorthesis) by producing fibrosis. This can be done by radioisotopes (yttrium, dysprosium, rhenium, or phosphorus) or by chemical agents (rifampicin or oxytetracycline). Radiosynovectomy is more reliable in causing synovial fibrosis but in Pakistan we mostly use Rifampicin as it is cheap and easily available.

### Rifampicin Synoviorthesis

Main advantages of Rifampicin Synoviorthesis is that less factor coverage is required, very negligible chances of infection and stiffness and can be performed in one sitting , on an outpatient basis

| Technique of Rifampicin Synoviorthesis |
|---|
| **Day 01**<br>Capsule Transamine 15 mg/kg tds; Continue for 5-7 days |
| **Day 02**<br>-Factor concentrate F VIII -20 IU/kg I/V stat<br>-Proposed site is infiltrate by injection Lignocaine 10 ml, attempting to anaesthetize not only skin but also the deeper tissues down to and including joint capsule and synovium<br>-Injection Rifampicin<br>Knee 600 mg intra-articular<br>Elbow 300 mg intra-articular<br>-Splint the joint-rest<br>Ice treatment -2 4 to 48 hours |
| **Day 08 and later**<br>-If required six consecutive injections of Rifampicin at weekly intervals can be given |




**Knee Synoviorthesis through supra-patellar lateral route**: Injection is made above the lateral corner of the patella (p) and directly into supra-patellar pouch

| Rifampicin Synoviorthesis: Results at Haemophilia Treatment Centre Rawalpindi |
|---|
| **Number of Patients**<br>Twenty |
| **Factor Deficiency**<br>Factor VIII Deficiency- 19;-Von Willebrand Disease - 01 |
| **Age**<br>Range: 8-26 years ; Mean 13 years |
| **Follow up**<br>Six months |
| **Treatment**<br>Injection Rifampicin (600mg), given intra-articularly by an orthopaedic surgeon under factor cover (Pre and Post procedure infusion of factor concentrates as per weight). |
| **Results**<br>In 70% (n=14) only single dose of injection Rifampicin was used while in remaining patients two doses were given |
| **Outcome**<br>Excellent= 16; Good = 03;Failed = 01 |

## SURGICAL SYNOVECTOMY:

Can be performed as an open procedure or with arthroscopy.
More effective in younger patients with radiologically less advanced joint arthropathy.

## CHAPTER 4

## ARTHROSCOPIC SYNOVECTOMY

In advanced countries it is the treatment of choice in treating synovitis. It is performed under direct vision, and hence helps to visualize the proliferated synovium more objectively. It helps in removing affected synovium to the maximum extent. Recovery is faster with adequate factor replacement. In 3rd world countries may not be preferred to Synoviorthesis as it is more invasive and requires more factor infusion for management

**Table 8: Synoviorthesis versus Synovectomy**

| Synoviorthesis | Surgical Synovectomy |
|---|---|
| Inexpensive | Expensive |
| Simple | Complex |
| Less invasive | Invasive |
| Lower risk of infection | High risk of infection |
| No general anaesthetic | General anaesthetic |
| Less amount of factor concentrate is required | Factor concentrate is required in excessive amounts |

**Joint Debridement:**

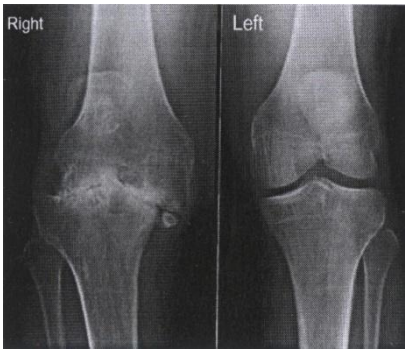
Minimally invasive surgery done to removes synovitis and loose cartilage from the joint. Helps in extending pain-free, functional life of the joint.

**Arthrodesis (Fusion):**

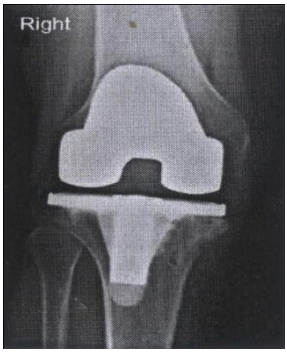
Performed at the ankle joint. The painful joint is removed and bones are fused.

## TOTAL KNEE REPLACEMENT (TKR) IN HAEMOPHILIA

In developed world it is recommended now in patients of hemophilia with severe arthropathy. Studies have found that using the latest techniques of continuous infusion of clotting Factor have significantly helped to reduce the complication rates and have achieved results which match those of the non-haemophilic population undergoing TKR.




**Severe right knee arthropathy in severe hemophilia. Left is spared**




**Same subject following total knee replacement on right side**

## REHABILITATION

Start early in order to prevent loss of function.

(Please refer to Physiotherapy Chapter)

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# CHAPTER 5

# PHYSIOTHERAPY IN HAEMOPHILIA

CHAPTER 5

# PHYSIOTHERAPY IN HAEMOPHILIA

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## PHYSIOTHERAPY

Physiotherapy is a medical field, which helps, treats conditions such as chronic or acute pain, soft tissue injuries, cartilage damage, arthritis, gait disorders and physical impairments typically of musculoskeletal, cardiopulmonary, neurological and endocrinological origins. This is done by using evidence-based kinesiology, electrotherapy, shockwave modality, exercise prescription, joint mobilization and health education. Physiotherapy can reduce swelling, pain in the affected joint, and improve its mobility.

Physiotherapist is a certified medical professional who helps patients with physical problems or deformities caused by illness or injury by using physical methods, heat treatment, and various physical exercise interventions. They facilitate the reinstatement of flexibility of muscles and joints and thus prevent future complications

## HAEMOPHILIA AND PHYSIOTHERAPY

Major impact of haemophilia is on joints so the physiotherapist plays a very important role in health, fitness & care of the hemophiliacs. It is therefore extremely important that a dedicated Physiotherapist, who understands the complications caused in joints and muscles due to haemophilia, be in regular contact with patients. It is important to consider the following points:

- Parents should be counseled about the need for exercise to build muscles, which will help to prevent bleeds**.**

- Weakness of the muscles caused by loss of movement due to recurrent bleeding in a joint can cause permanent disability. Exercises can improve the strength of the muscles and mobility of the joint
- Different exercises are advised to avoid the damage caused to affected area by haemophilia
- It is important for patients with haemophilia to know that unaffected joints can be strengthened with the help of different exercises
- Clear instructions on how to do exercises should be given so as not to exert the unaffected muscles causing further deterioration. Suddenly increasing any, weightlifting or vigorous exercise can increase injury risks**.**
- Any sign of bleed during physiotherapy should be taken as an indication to slow down, but not to stop physiotherapy altogether. The case should be referred to the HTC for treatment after which physiotherapy should be started slowly. Some patients will need haemostatic cover during physiotherapy to prevent bleeding.
- If surgery is needed to treat the affected joint, even then physiotherapy cannot be ignored because it is important to know what exercises to do and at what time. Physiotherapy can improve the results of the surgery. Surgery is only indicated when the condition of the joint is not improving even after regular exercises.

## JOINTS IN HAEMOPHILIA

The most affected joints due to bleeding in haemophilia are **elbow, knee and ankle**. This is because they are more mobile and experience more weight than other joints in the body.

These joints are joined by strong muscles, which are weakened when there is loss of movement due to bleeding in the joint. The affected joint hinders the mobility of other joints as well. Lack of exercise causes permanent joint deformity.

**When pain, swelling and warmth** of the bleeding area is reduced it is important start physiotherapy which will bring the joints back to their **normal function**

## HAEMOPHLIC ARTHROPATHY- ROLE OF EXERCISES

The physiotherapist should start these exercises and then train the parents/patient to do them so that they can be continued at home with follow up visits to the Physiotherapy Centre.

The exercises for Knee, ankle & elbow are listed below. For other affected joints, advice should be sought from the specialist physiotherapist

### KNEES

#### Quadriceps

Tighten thigh muscles. Try to raise heel off the bed or floor by pushing the knee down. The kneecap should move slightly upwards. Relax fully.

**Note**: start with 5 times every hour and increase to 10, 15, 20 etc. do this exercise also with other leg.

#### Straight leg raise

Lie on back or sit with legs straight ahead. Tighten the thigh muscles, push the knee down, and raise the heel. Keeping the leg as straight as possible, raise it to 45 degrees (half way) and count to three. Lower the leg. Relax and repeat the exercise.

**Note:** start with five times every hour and increase to 10, 15, 20 etc. do this exercise also with the other leg.

#### Hamstrings

Lie prone; put a small cushion or roll of towel under the lower leg. Bend the knee as far as possible. Lower the leg slowly to the starting position and relax

**Note:** Start with five times and increase to 10, 15, 20 etc. do it also with the other leg.

## CHAPTER 5

## ANKLES

### Ankle circles

Draw a circle in the air with foot. First: clockwise and then anticlockwise. Do it five times each way and repeat with other foot.

### Ankle movements (dorsi-and plantar flexion)

Sit with a cushion underneath the knee. Pull the front part of feet upwards. Push the front of your feet away and downwards. Repeat 5 times.

### Standing on tiptoes

Stand behind a chair and hold it with both hands for stability. Rise to standing on tiptoes, stand again on both feet, and relax. Raise front part of feet and stand on heels. Stand on both feet and relax. Repeat this exercise 5 times.

## ELBOWS

### Flexion

Start with your arms at your sides, hand palms facing forward. Bend your arms slowly; trying to touch your shoulders, lower arms to starting position. Repeat 5 – 10 times.

### Pronation and supination

Hold arms with elbows bent in 90 degrees flexion. Turn palms facing down repeat 5 – 10 times.

### Extension

Lie prone on a bed near the edge with upper arm resting on the bed and the lower arm hanging down. Extend the arm and count to three. Return to the starting position slowly and relax. Repeat 5, 10, 15, 20 times.

### Isometric exercises

Start with a light exercise putting stress on muscles instead of putting stress on joints. This exercise is beneficial for those joints in which pain is felt during movement or those muscles, which are weak. Pain during exercise is an indication that the muscle is over-exerted or bleeding has started

## USE OF SPLINTS IN HAEMOPHILIC ARTHROPATHY

A splint is a piece of medical equipment used to keep an injured body part from moving and to protect it from any further damage. The aim of application of splints in established synovitis is:

**A)** Prevention of deformities

**B)** Correction of deformities

**C)** Support the limb in resting and weight bearing

**D)** Applying a distributed compression over the affected areas

**E)** Minimizing the effects of trauma by protective and shock absorbing action

## IMPORTANT POINTS

- Create awareness about value of physiotherapy for joint & muscle health
- Parents should be trained to exercise the young child while older children should be taught to do the exercises themselves so that they take this responsibility themselves.
- To have treatment & prophylactic factor cover if there is a bleed after physiotherapy
- Affected area can affect a non-affected area, for example, an affected knee joint can cause backache. Physiotherapy can help in keeping a better posture.
- Better joint & muscle health can prevent disabilities and help the patient to grow normally.
- Proper use of a splint or support is essential. For example, crutches should be held in a proper way if required for walking otherwise it can be harmful.
- Safe sports should be encouraged while dangerous to be avoided

## CHAPTER 5

## SPORTS IN HAEMOPHILIA

**Safest:** Walking, hiking, cycling, swimming, badminton, table tennis, Golf

**Most Dangerous:** Boxing, Wrestling, Power lifting, Football, Hockey, Cricket with a hard ball.

The parents should be encouraged to discuss the sport their child wants to start with the HTC & physiotherapy team so that a calculated, safe decision can be made.

**Haemophilia is an inherited lifelong disorder but disability is not. Prompt & adequate treatment and regular physiotherapy can help develop patients normally, bringing them in the streamline as useful members of the society**

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# CHAPTER 6

# SURGERY IN PATIENTS WITH HAEMOPHILIA

# SURGERY IN PATIENTS WITH HAEMOPHILIA

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## DISEASE PHENOTYPE

Prolonged bleeding is the characteristic phenotype in Haemophilia. The severity of bleeding generally correlates with clotting factor levels. Although bleeding can occur at any time, most frequent first presentations of Haemophilia are:

- Excessive bleeding after circumcision , very common presentation in Pakistan
- Bleeding into joints when a child starts crawling/ walking

Patients with mild forms may bleed only when they have major trauma or surgery.

Surgery in patients with Haemophilia may result in excessive haemorrhage, the most feared complication.

## PRINCIPLES OF SURGICAL CARE

### Pre op

- Surgery must be planned as an elective procedure.
- Surgery must be performed earlier in the week in order to avoid weekends.
- Pre-operative inhibitor screening is essential
- Patient's positive for inhibitors should be treated with alternative therapeutic agents. These include Factor VIII

Inhibitor Bypassing Activity (FEIBA), recombinant factor VIIa (rVIIa), Prothrombin Complex Concentrates (PCC) and their activated forms (APCC).

- A written down plan of haemostatic cover is to be obtained from the HTC and stuck in patient's surgical notes.
- Whenever possible, specific factor deficiency should be treated with specific factor concentrates. They should be made available, prior to surgery from the HTC.
- Where clotting factors concentrates are limited, adjunctive treatments should be used. These include the use of desmopressin (DDAVP not available in Pakistan), fresh frozen plasma (FFP), cryoprecipitate and antifibrinolytic agents (tranexamic acid).
- Start tranexamic acid the night before the operation.

## Peri- operative

- On the day of surgery patient must be put first on the surgical list.
- At the time of induction of anaesthesia, Factor Concentrates must be infused per protocol to raise factor levels so as to avoid the anticipated bleeding (Table 1).

**Table 1**: **Plasma Factor Peak Level and Duration of Administration (When There is Significant Resource Constraint) Pre- and Post-Operatively (WFH guidelines)**

| Type of Haemorrhage | Haemophilia A | | Haemophilia B | |
|---|---|---|---|---|
| | Desired level IU/dl | Duration (Days) | Desired level IU/dl | Duration (Days) |
| Major Surgery | | | | |
| Pre-Operative | 60–80 | | 50–70 | |
| Post-Operative | 30-40<br>20-30<br>10-20 | 1-3<br>4-6<br>7-14 | 30-40<br>20-30<br>10-20 | 1-3<br>4-6<br>7-14 |
| Minor Surgery | | | | |
| Pre-Operative | 40-80 | 1-5 depending on the type of procedure | 40-80 | 1-5 depending on the type of procedure |
| Post-Operative | 20-50 | | 20-50 | |

- Adequate local haemostatic measures must be ensured and surgery must be performed with precision in order to avoid local causes of bleeding.
- All invasive diagnostic procedures (such as lumber puncture, endoscopy with biopsy, arterial blood gas determination etc.) must be covered with adequate factor replacement

**Post-operative**

- Post-surgery, factors must be maintained at desired levels per protocol i.e., 1-14 days depending on the type of surgery. (Table 1)
- Surgical procedures may be classified as major or minor. A major surgical procedure is defined as one that requires haemostatic support for periods exceeding 5 consecutive days.
- Close monitoring for any bleeding
- Depending upon the severity of post-operative pain, intravenous morphine or oral opioid/ paracetamol/acetaminophen may be used.
- Intramuscular administration of any drug and oral administration of anti-platelet drugs (Aspirin and other Non-Steroidal Anti Inflammatory Drugs) must be avoided.
- Effectiveness of haemostasis is analyzed by the operating surgeon/Anaesthetist using criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (Table 2).

**Table 2: Definition of Adequacy of Haemostasis for Surgical Procedures**

| | |
|---|---|
| **Excellent** | Intra-operative and post-operative blood loss similar (within 10%) to the non-haemophilic patient.<br>• No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND<br>• Blood component transfusions required are similar to non-haemophilic patient |
| **Good** | Intra-operative and/or post-operative blood loss slightly increased over expectation for the non-haemophilic patient (between 10-25% of expected), but the difference is judged by the involved surgeon/Anaesthetist to be clinically insignificant.<br>• No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND<br>• Blood component transfusions required are similar to the non-hemophilic patient |
| **Fair** | Intra-operative and/or post-operative blood loss increased over expectation (25-50%) for the non-haemophilic patient and additional treatment is needed.<br>• Extra (unplanned) dose of FVIII/FIX/bypassing agents needed OR<br>• Increased blood component (within 2 fold) of the anticipated transfusion requirement |
| **Poor/none** | Significant intra-operative and/or post-operative blood loss that is substantially increased over expectation (>50%) for the non-haemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than Haemophilia<br>• Unexpected hypotension or unexpected transfer to ICU due to bleeding OR<br>• Substantially increased blood component (> 2 fold) of the anticipated transfusion requirement |

**Notes:**

- Apart from estimates of blood loss during surgery, data on pre- and post-operative haemoglobin levels and the number of packed red blood cell units transfused may also be used, if relevant, to estimate surgical blood loss.

- Surgical haemostasis should be assessed by an involved surgeon and/or Anaesthetist and records should be completed within 72 hours following surgery.

## EMERGENCY SURGERY

- In case of an emergency the hospital staff (or patient's attendant) contact HTC & discuss the case with Medical Officer who guides them about the haemostatic cover directly or after an advice by the Consultant.
- In case of an out-of-hours emergency, the HTC Coordinator is informed about the patient condition & the nature of surgery. The HTC Coordinator informs Consultant on call and according to their advice an emergency treatment is given. The treatment is also documented in patient's notes with the name of the consultant who advised it. A written down surgical plan is provided on the next working day.

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# CHAPTER 7

# WOMEN WITH INHERITED BLEEDING DISORDERS

CHAPTER 7

# WOMEN WITH INHERITED BLEEDING DISORDERS

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## INTRODUCTION

The general perception is that only males suffer from inherited bleeding disorders because Haemophilia, an X- linked bleeding disorder affects males and is much more common as compared to vWD and other disorders seen in women. Thus women with inherited bleeding disorders are often ignored. It is important to understand that inherited bleeding disorders are present in both men and women.

According to statistics of Pakistan‘s Haemophilia Treatment Centres and HFP, von Willebrand (vWD) disease is the second most common bleeding disorder after Haemophilia. Since vWD is an autosomal disorder, both genders are affected.

**The inherited bleeding disorders in women include:**

- Von Willebrand Disease(vWD Type I,II,III )
- Coagulation factors deficiencies Factor I, II, V,VII, X, XI & XIII
- Platelet function disorders e.g. Glanzmann’s Thrombasthenia, Bernard Soulier Syndrome
- Haemophilia carriers (symptomatic carriers, rare )
- Haemophilia i.e. factor VIII and IX (very rare)

## CHAPTER 7

### SIGNS AND SYMPTOMS

Mostly sign and symptoms of bleeding disorders are similar in males and females. However females have symptoms related to menstrual cycle and childbirth as well.

- Heavy or prolonged menstrual flow
- Recurrent nose and gum bleeds
- Easy bruising / petechial haemorrhages
- Bleeding from digestive tract or urinary tract
- Prolonged bleeding after cuts, dental extraction or surgery
- Excessive bleeding during childbirth and puerpurium
- Recurrent abortions
- Bleeding into joints, muscles and brain

Bleeding can be spontaneous i.e. without any apparent cause if the disease is severe or after injury or trauma, in mild to moderate cases.

### DIAGNOSIS

A female suspected of having a bleeding disorder should be referred to a hematologist who after carefully reviewing the medical and family histories and a detailed physical examination, will order relevant laboratory tests to determine if she has a bleeding disorder.

### SCREENING TESTS (FIRST LINE)

These include

- Platelet count
- Bleeding time (BT)
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT )
- Thrombin time (TT) in some cases

The screening tests if normal help to rule out a bleeding disorder in most cases. However in case of abnormal results diagnosis has to be confirmed by doing several other tests.

## DIAGNOSTIC TESTS (SECOND LINE)

- Mixing studies (using adsorbed plasma or aged serum)
- Factor Assays
- Platelet function tests
- Clot Lysis test

These help in confirmation of specific bleeding disorders
(For details please refer to: Introduction to inherited bleeding disorders)

### von Willebrand Disease (vWD)

vWD is an autosomal disorder, thus both male and female are affected. It is caused by a deficiency of von Willebrand Factor (vWF). vWF is a protein in the blood essential for the formation of the platelet plug. When there is not enough vWF in the blood or the factor does not work correctly, clots form slowly and poorly.

## PATHOGENESIS

Clotting of blood is dependent upon coagulation factors (proteins) in blood as well as platelets and vWF.
vWF interacts with GpIb on platelets surface, thus forming a bridge between platelets and collagen in the basement membrane. If vWF is deficient, this results in poor primary hemostatic plug formation. (Fig-4)
Another function of vWF is that it protects factor VIII in blood from degradation so in vWD patient factor VIII may be low in plasma.

## PRESENTING SYMPTOMS

Usually bleeding occurs from mucous membranes like nose, mouth and digestive tract. In females heavy and prolonged menstrual bleeding may be the presenting symptom.
(See sign and symptoms given above)

## CHAPTER 7

## CLASSIFICATION

There are three main types of vWD. Type I and 2 are autosomal dominant; whereas type3 is autosomal recessive (such individuals have inherited a gene for vWD from both parents)
Type I and type 2 are usually mild to moderate diseases whereas type 3 is considered to have a severe deficiency of vWF and factor VIII as well. For detailed classification see Table 1

**Table 1: CLASSIFICATION OF VWD**

| Type | Abnormalities | Clinical course | Laboratory Findings | Inheritance | Frequency |
|---|---|---|---|---|---|
| **Type I** | | | | | |
| Quantitative Defect | Partial deficiency of VWF | Mild to moderate | VWF Level 5-30% of normal | Autosomal dominant 60-80% | More common in west |
| **Type II Qualitative Defect** | | | | | |
| 2A | Decrease VWF dependent platelet adhesion | Moderate to severe | VWF level variably low, loss of HWM multimers | Autosomal dominant | 15-20% |
| 2B | Increase VWF & platelet adhesion | Moderate to severe | Low VWF level, Thrombocytopenia | Autosomal dominant | |
| 2M | Decrease VWF dependent platelet adhesion | Moderate to severe | Low VWF level, Normal HWM multimers | Autosomal dominant | |
| 2N | Decrease VWF & factor VIII affinity | Moderate to severe | VWF level normal with markedly low FVIII | Autosomal dominant | |
| **Type III** | | | | | |
| Quantitative Defect | Complete deficiency of VWF | Severe | Markedly low or absent VWF level and Factor VIII | Autosomal recessive | common in Pakistan, rare in west |

## DIAGNOSIS

A detailed medical history, family history & pattern of bleeding provide important clues to diagnosis.

The investigations include: BT, PT, aPTT, platelet function tests,VWF Ag and vWF activity

**(For details please refer to:** Introduction to inherited bleeding disorders)

## MANAGEMENT

### General measures

- Good oral hygiene
- No intra muscular injection
- No antiplatelet (aspirin) & non-steroidal anti-inflammatory drugs(NSAID's)
- Avoid Contact sports
- Nasal packing soaked with Inj. tranexamic acid for nose bleed
- Gargles with Inj. tranexamic acid for gum bleeds
- Tranexamic acid Capsules /injections very useful in cases of external bleeding

### Specific treatment

- vWF replacement (Haemate P, Alphanate) is treatment of choice
- Factor VIII concentrate (intermediate purity,Koate)
- DDAVP (Desmopressin) (not available in Pakistan)

### Option other than factor replacement.

- FFP
- Cryoprecipitate
- Platelet concentrates in some cases

## MANAGEMENT ISSUES

### Heavy Menstrual Bleeding (HMB)

HMB is one of the most common symptoms for women with bleeding disorders. It is defined as bleeding that last for more than seven days or a blood loss of more than 80 ml during the menstrual cycle.

### Treatment

Treatment options are those for menorrhagia in general with addition to factor replacement therapy

- Tablet Ponstan forte : One tablet 500mg TDS X 3 - 5 days
- Tranexamic acid (anti fibrinolytic agent) 500 mg X TDS X 5 Days , may be increased up to 1000 mg TDS
- Oral Contraceptive Pills (OCPs)
- Famila 28, 1 tablet daily continuously for 6 months or more (doctor's discretion)
- Primolut N tablet, 1 tablet TDS. Dose can vary from patient to patient. (maximum 2 TDS)
- Mirena IUD (for married women) Levonorgestrel releasing intra uterine system
- Factor replacement
- General measures like iron supplements may be required if patient is anemic. Transfusion of RCC is also useful in this situation if anemia is severe (Hb<7g/dl)

## DYSMENORRHEA

Painful menstrual bleed is common in women and girls with bleeding disorder. It can result from the increased volume of bleeding and incomplete clots forming in uterus.
Some women experience pain in the middle of their cycle during ovulation. This is called mittelschmerz.

### Treatment

- Tablet Ponstan forte 500mg TDS X 3 to 5 days.
- Tablet Calcium once daily
- Mirena (Married women) Levonorgestrel releasing intra uterine system

## CONCEPTION / FERTILITY

If a woman uses hormonal therapy to control excessive menstrual bleeding, this treatment will interfere with her ability to conceive. Patients have to stop taking hormonal therapy with factor cover for HMB. They need to be covered with Factors/FFP during menstruation.

**CHAPTER 7**

## PREGNANCY AND CHILDBIRTH

Miscarriage is more common in women with bleeding disorders and some women require regular factor/FFP cover during pregnancy. Higher hormone levels in pregnancy may stimulate increased levels of plasma clotting factors which drop soon after delivery. The delivery needs to have haemostatic cover to prevent post partum haemorrhage. Close liaison between the haematologist & obstetrician is essential
SOPs for management of patient during pregnancy, childbirth (normal delivery / C-section) are available at the HTC.

## PRENATAL DIAGNOSIS

Prenatal diagnosis is done in a fetus before it is born. If the fetus is affected by a disorder the parents have the choice to get the pregnancy terminated. Chorionic villus sampling (CVS) is done at 12 – 14 weeks of gestation and is available at many centres in Pakistan. Prenatal diagnosis of inherited bleeding disorders is very expensive and is available only in a few laboratories in Pakistan.

## RARE BLEEDING DISORDERS

These are autosomal recessive disorders and are not so rare in Pakistan because of consanguineous marriages

### Factor I or fibrinogen deficiency

This can present with excessive bleeding from umbilical cord. Patients have frequent nose bleeds, bleed after minor bumps and scrapes or when teeth come out. Cryoprecipitate and FFP are used to treat the deficiency of factor I.

### Factor II deficiency

People with Factor II deficiency may experience easy bruising, nose bleeds, bleeding after child birth or surgery. Treatment options are FFP and prothrombin complex concentrates.

### Factor V deficiency

It has also been called parahemophilia, since hemarthrosis can occur with severe deficiency. Patients may have spontaneous bleeding from gums, gastrointestinal tract, or even in the brain. In some patients bleeding time may be increased and platelet function may also be affected. FFP is used for its treatment. Platelet transfusion can also be used.

### Factor VII deficiency

Factor VII deficiency can present as intra cranial bleeding at birth. Women with factor VII deficiency can experience heavy menstrual bleeding, spontaneous nose bleeds, or gum bleeding, as well as bleeding into gastrointestinal and urinary tract. Factor VII concentrates and FFP are used for its treatment.

### Factor X deficiency

Patients with severe Factor X deficiency may have bleeding from umbilical cord at birth. Women might experience heavy menstrual bleeding. Easy bruising, spontaneous nosebleeds and bleeding into gastrointestinal tract is common. Prothrombin Complex Concentrate and FFP are used for its treatment.

### Factor XI deficiency

Factor XI deficiency is usually diagnosed after injury-related bleeding, and symptoms tend to be mild. Nearly 50% of people with Factor XI deficiency report no bleeding problems.

### Factor XIII deficiency

Patients present with poor wound healing, umbilical stump bleeding and intracranial haemorrhage. Bleeding after surgery or injury can be serious and without treatment, can last for days or weeks. Recurrent miscarriages in females are common & need to be given prophylactic Cryoprecipitate/FFP during pregnancy. These individuals fail to form firm, solid blood clots. Clot lysis test is used for its diagnosis.

It is treated by FFP or Cryoprecipitate as Factor XIII concentrate is not available in the country.

## PLATELET FUNCTION DISORDERS

### Glanzmann Thrombasthenia (GT)

It is characterized by impaired platelet function .It is caused by an abnormality in the gene coding glycoprotein IIb/IIIa, a receptor which is present on the surface of platelets, also called the fibrinogen receptor. (Fig-1)

Symptoms of this disorder usually include abnormal mucocutaneous bleeding including menorrhagia, which may be severe. Prolonged bleeding if not treated may be life threatening.

### Bernard–Soulier syndrome (BSS)

It is characterized by deficiency of glycoprotein Ib (GpIb), the receptor on platelets for vWF. (Fig4). In affected individuals, platelets are unusually large and fewer in number than usual (a combination known as macrothrombocytopenia). People with BSS tend to bruise easily and have an increased risk of nosebleeds (epistaxis). Women with BSS often have heavy or prolonged menstrual periods (menorrhagia).

## DIAGNOSIS

- Blood CP (Particularly platelet count)
- Bleeding time (prolonged)
- Coagulation profile (PT and APTT are normal )
- Platelet function studies are needed for confirmation

## MANEGEMENT OF BLEEDING IN PLATELET FUNCTION DISORDER

### General measures

As mentioned above

### Specific measure

No specific treatment available, so mostly platelet concentrates infusions are given if needed. Activated factor VII (i.e. Novoseven, Aryoseven) is useful in uncontrolled bleeding

## CHAPTER 7

### Carriers of Haemophilia

- Carriers of Haemophilia may or may not have more than 50% factor activity.
- Those with less factor activity may face haemostatic challenges depending on their factor levels.

### TYPES

**Obligate carriers** necessarily have the haemophilia gene.
Detected through detailed family history (pedigree analysis).

- All daughters of a father with Haemophilia,
- Mother of two or more sons with Haemophilia
- Mother of one son with Haemophilia and one other family member with known Haemophilia gene (carrier/disease)

**Possible carriers** Possibility of a haemophilia gene
Detected by mutation analysis or by direct sequencing of factor VIII/IX gene.

- Daughter, sister, mother, maternal grandmother, aunt, niece and female cousin of a carrier
- Mother of one son with Haemophilia but no other family member with known Haemophilia gene (carrier/disease)

### Prenatal diagnosis of Haemophilia

- An important aspect of reproductive choices for women in families with Haemophilia.
- Also beneficial for appropriate obstetric management during labor and delivery because prolonged labor, invasive monitoring techniques and instrumental deliveries should be avoided in affected fetuses to minimize potential fetal and neonatal haemorrhagic complications.
- Is done after confirmation of a male foetus
- Carriers whose mutation has been identified, can get fetal DNA tested for Haemophilia via: **Chorionic Villus Sampling** at 10-12 weeks of gestation
  **Amniocentesis** at 16-20 weeks of gestation

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# CHAPTER 8

# DENTAL ISSUES IN HAEMOPHILIA

CHAPTER 8

# DENTAL ISSUES IN HAEMOPHILIA

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## INTRODUCTION

Haemophilia patients are special patients from dental point of view as the routine dental treatment such as even an extraction can be life threatening. Therefore management of haemophilic patients should always be in a setting of a specialized unit with appropriate clinical expertise and laboratory support. The very high cost of treatment should be kept in mind. When planning any dental work, management strategies should be such as to reduce the need of prophylactic coagulation factor cover.

The characteristic oral presentation of Haemophilia is gingival and post-extraction hemorrhages. In addition to this children can bleed during eruption and falling of teeth and post injury. Frenulum bleeding is quite common in toddlers. Oral bleeding is more frequently seen in severe Haemophilia and von Willebrand disease (vWD).

Poor oral hygiene can also result in local bleeding. Daily cleanliness and regular dental checkups can help minimize bleeding episodes and avoid treatment. Dental treatment should be done very carefully & by a dentist who knows about Haemophilia and its complications.

The Dental Department should liaison closely with Haemophilia Treatment Center (HTC) in cases of dental issues and where a procedure needs to be carried out should get a written plan for Factor cover and provision of the required factors. The factors should be infused pre & post treatment along with adjuvant treatment (tranexamic acid) per protocol.

## CHAPTER 8

## GENERAL DENTAL CARE

- Brushing twice daily, after breakfast and before going to bed. This will prevent gum disease.
- Always use a soft, round tipped brush made of nylon.
- Always use a brush which can reach the ends of teeth easily and change brush after every three months.
- USE Toothpastes containing fluoride.
- Dental checkup twice a year.
- If possible, stop bottle feeding.
- Healthy diet, vegetables, fruits, wheat, meat and milk.
- Avoid sugary stuff, candies, toffees, chocolates, biscuits, sugary & fizzy drinks etc.
- Fissure sealant can be applied to the premolars & molars to prevent collection of food.
- Taking good care of teeth can prevent cavities and other dental issues.

## MAIN DENTAL DISEASES AFFECTING THE HAEMOPHILIA PATIENTS

- Dental carries which is not attended timely will lead to Endodontics treatment or Extraction
- Periodontitis or Gingivitis

Both the above are preventable diseases if attended timely. Early detection of carries is only possible if the patient is having regular 6 monthly dental checkups. Carious teeth if attended timely can be restored and no factor replacement is needed. Otherwise if the tooth is grossly carious causing severe pain, then the pulp/nerve is exposed which leads to Endodontic treatment, which has to be carried out with Factor concentrate cover on the first visit. However on the following visit factor replacement is not required.

## TEETHING ISSUES

Children with bleeding disorders can bleed heavily when new teeth are growing or when teeth fall. Milk Teeth start coming at the age of 6 months & start falling at the age of 5 years while Permanent teeth start coming out at the age of 6 years and continue till the age of 12 years.

### Prevention & management of bleeding during teething

- Teeth, should be allowed to fall naturally & not touched & pulled.
- Mix transamine capsule with water to make a paste and apply it on the affected area to help stop bleeding.
- Advise to avoid, using straw, eating hard things and gargling.
- If bleeding does not stop with local measures please refer the child to the HTC for infusion of factor concentrates.

## DENTAL BLEEDS

Bleeding can cause anxiety for the children because there are numerous blood vessels in the mouth which can cause heavy bleeding. Adults can also bleed from mouth and this is one of the common presentations in patients with vWD.

Transamine can be applied directly to the site of bleeding.

In case of excessive bleeding the child should be referred to the HTC for factor infusion.

### Care during oral wound healing

Wounds in mouth take 2 – 3 weeks to heal. HTC to provide factor cover if required Patient to be advised soft chilled food and very gentle cleaning of teeth.

## CHAPTER 8

### Plan for Dental procedures

Factors are needed before scaling, tooth filling, removing teeth, root canal or any other dental surgery. A proper factor cover plan should be obtained from the HTC before any such procedure. The factors concentrates should be available prior to procedure and infused pre & post procedure per protocol.

### CONTROL OF DENTAL PAIN

Dental pain can usually be controlled with paracetamol Aspirin should not be used due to its anti-platelet effect. The use of any non-steroidal anti-inflammatory drug (NSAID) should also be avoided.

### PERIODONTAL AND GUM DISEASES

Usually patients with hemophilia have periodontal/gum problems. There is inflammation and bleeding of the gums. For such patients we need to plan scaling.

Prior to the treatment, infection and inflammation have to be settled by prescribing metronidazole and antibiotics. This will reduce the infection and inflammation. Before starting the procedure, factor is given, scaling and polishing is performed. Sometimes scaling has to be carried out in 3 to 4 visits.

### DENTURE

There are no problems in providing routine prosthetic procedures such as removable dentures for a patient with hemophilia.

### ORTHODONTICS

Previously orthodontics was avoided in patients with bleeding disorders. Currently the bands are prefabricated and can be replaced by tubes and the technique is not multiband but multibrackets bonded directly or indirectly, thereby reducing the possible damage to the gingival tissue.

## DENTAL SURGERY

Surgical treatment, including a simple dental extraction, must be planned to minimize the risk of bleeding, excessive bruising, or hematoma formation.

The following points will help prevent problems:

- Emergency, unplanned surgical treatment is rarely required as pain & bleeding can often be controlled. All treatment plans must be discussed with the HTC.
- All the measures to reduce the risk of infection to be taken (administration of antibiotics, topical antiseptic mouthwashes like Chlorhexidine and Povidine-iodine.
- Oral infections Antibiotics should be considered for all patients so that unplanned surgical treatment is avoided. Penicillin along with Metronidazole is effective in treating dental infections. The treatment should continue for 5–7 days.
- Dental emergencies, however rare, can occur .It is important to coordinate with HTC and deal with it accordingly. Treatment should not be carried out without prior planning to prevent prolonged bleeding in patients with inherited bleeding disorders.
- Extreme care during dental procedures in using saliva ejectors & placement of X- ray films, to prevent damage to the oral mucosa and also measures to reduce intraoperative and postoperative hemorrhage must be undertaken.
- Local anesthesia. No restriction to the type of local anesthesia.
- Aspirin, its derivatives & NSAID's to be avoided.
- Absorbable sutures are recommended if needed.
- Hemophiliacs may be the carriers of hepatitis B or C viruses. Necessary tests and precautionary measures are essential. All invasive surgical interventions should have Factor concentrate cover.

## CHAPTER 8

## DENTAL ANESTHETIC TECHNIQUES

- Buccal Infiltration
- Intra-papillary
- Intra-ligamentary
- Inferior dental nerve block

After infiltration the patient can be left for 5 to 10 minutes before carrying out the treatment in order to achieve adequate anesthesia. The extraction has to be very atraumatic, the goal is 'keyhole surgery' with least possible interference with the gingiva and periodontium.

After the extraction a pack soaked in transamine is placed on the socket and patient is asked to bite on it. Sometimes absorbable gelatin sponge is packed in the socket.

## INSTRUCTIONS TO BE FOLLOWED POST EXTRACTION

- The patient should be observed for 24 hours after the extraction.
- The patient should be given strict instructions to have only cold and very soft diet.
- No vigorous mouth rinses should be done.
- Avoid use of straw.
- Usage of transamine capsule should be continued for at least 5 days after the extraction.
- Do not touch the wound.
- Do not take aspirin as it would prolong the bleeding time.
- The patient's blood pressure may increase due to worry and pain, hence it should be monitored. A suitable analgesic and benzodiazepine will help to reduce the pain, anxiety and blood pressure.
- Post op follow up for bleeding is essential. If bleeding continues the case to be discussed with the HTC consultant so that additional Factor concentrates, if required, can be provided.

## CHAPTER 8

## COMPLICATIONS FOLLOWING A DENTAL EXTRACTION

- Early bleeds: within 24 hours of extraction, there must be some mucosal damage so the wound has to be cleaned and packed with fibrin plug and Factor replacement/ FFP may be required.
- Late bleeds is within 2 to 5 days. This might occur due to infection and antibiotics may be required.
- Recurrent bleeding: If the above have failed the use of coagulation factors should be considered.

It is a great dilemma in Pakistan that dental services are not readily available to Haemophilia patients. With the above information, it is hoped that the much-needed awareness in dental surgeons shall arise so that proper dental services are provided to all haemophilic patients. Moreover it is imperative that in far flung areas the existing dental facilities are upgraded in assistance with Hemophilia Patients Welfare Society in order to cater to all suffering patients and their families.

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# CHAPTER 9

# LIFE THREATENING BLEEDS IN INHERITED BLEEDING DISORDERS

CHAPTER 9

# LIFE THREATENING BLEEDS IN INHERITED BLEEDING DISORDERS

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## INTRODUCTION

Inherited bleeding disorders (IBDs) are uncommon as compared to other causes of bleeding, incidence being only 3-5%. These include Haemophilia A, Haemophilia B, von Willebrand disease (vWD)and also the rare bleeding disorders which include deficiencies of clotting factors I, II, V, VII, X, XI, XIII, combined factors V and VIII , Glanzmann's thrombasthenia (GT) and Bernard–Soulier syndrome (BSS ).Abnormal bleeding is the commonest manifestation in inherited bleeding disorders (IBD). These are very heterogeneous ranging from petechial bleeds to subarachnoid haemorrhage depending upon the cause.

## MAJOR BLEEDING

**Major bleeding**, according to the International Society of Thrombosis and Haemostasis (ISTH) criteria, includes a clinically overt bleeding that is fatal or associated with a reduction in haemoglobin of at least 2 g/dl, a transfusion of at least 2 units of blood or packed cells, or occurs in a critical area or organ (intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal bleeding, intraocular bleeding, or pericardial bleeding).

## CLINICALLY RELEVANT NON-MAJOR (CRNM) BLEEDING

**Clinically relevant non-major (CRNM) bleeding** is defined as an overt bleeding that did not meet the criteria for major bleeding, but is associated with a medical intervention, unscheduled contact with a physician (in person or by telephone), interruption or cessation of study

treatment, or discomfort for the subject including pain or impairment of activities of daily living.

## TYPES OF BLEEDING ON THE BASIS OF SEVERITY

Severity of bleeding varies subjectively.

### Mild:

Mild events are defined as events when the subject is aware of signs and symptoms, but the signs and symptoms are easily tolerated.

### Moderate:

Moderate events are defined as events that caused enough discomfort to interfere with activities of daily living.

### Severe:

Severe events are defined as events that caused subjects to be unable to perform normal daily activities.

### Life threatening:

Life-threatening events are those that pose an immediate risk of death.

Life threatening bleeding includes intracranial bleeding, severe postpartum haemorrhage, severe post traumatic bleeding, iliopsoas bleeding, haematomas in critical areas, severe bleeding occurring in surgical procedures, gastrointestinal bleeding, intra-abdominal bleeding, bleeding in respiratory tract, pericardial, peritoneal, pleural bleeding and any other bleeding which causes haemodynamic compromise that includes any major bleed.

Post traumatic bleeding or bleeding after an accident that causes massive haemorrhage is also included in life threatening bleeding. Massive haemorrhage is defined as loss of more than one blood volume within 24 hours (around 70 ml/kg, >5 liters in a 70 kg adult) 50% of total blood volume lost in less than 3 hours or bleeding in excess of 150 ml/minute.

**Table I - Minor or mild bleeds (do not need any medical intervention)**

| |
|---|
| Small cuts |
| Scratches |
| Superficial ecchymosis |
| Small haematomas |
| Uncomplicated haemarthrosis |
| Symptomatic haematomas in non-critical areas |
| Bleeding associated with therapeutic procedures like dental procedure, arthrocentesis, dressing change, bone marrow biopsy, removal of stitches and drains |
| Easily controlled nose bleeds |
| Gum bleeding |
| Petechiae/purpura that is localized to 1 or 2 dependent sites, or is sparse/non-confluent |
| Oropharyngeal bleeding, epistaxis <30 min duration |

**Table II –Clinically relevant non- Major bleeds (CRNM) (needs medical intervention)**

| |
|---|
| Profuse epistaxis or oropharyngeal bleeding >30 min |
| Symptomatic oral blood blisters, i.e. bleeding or causing major discomfort |
| Multiple bruises, each >2 cm or any one >10 cm |
| Diffuse Petechiae/purpura |
| Haematuria |
| Abnormal bleeding from invasive or procedure sites |
| Unexpected vaginal bleeding saturating more than 2 pads with blood in a 24-h period |
| Macroscopic bleeding in cavities |
| Retinal bleeds without visual impairment |
| Gastrointestinal bleeding like haematemesis, malena, fresh blood in stool |
| Hemoptysis |
| Musculoskeletal bleeding |
| Soft tissue bleeding not requiring red cell transfusion within 24 h of onset and without haemodynamic instability |

## CHAPTER 9

**Table III – Major or Severe bleeds (requiring immediate intervention)**

| |
|---|
| Any bleeding requiring red cell transfusion in 24 hours of onset but without haemodynamic instability |
| Grossly visible bleeding in body cavity |
| Cerebral bleeding without signs and symptoms and noted on CT scan |

**Table IV – Life threatening bleeds**

| |
|---|
| Non-fatal cerebral bleeding with neurological signs and symptoms |
| Retinal bleeds with visual impairment |
| Any debilitating bleeding ,GI ,PPH etc. |
| Bleeding causing haemodynamic instability (hypotension, >30 mmHg change in systolic or diastolic blood pressure) |
| Fatal bleeding from any source |
| Post-partum haemorrhage |
| Massive bleeding after trauma |

## MANAGEMENT OF LIFE THREATENING BLEEDING

- **Minimal time elapsed:**

Patient should be transported immediately to an appropriate facility where severe bleeding can be managed and where blood bank also works in close liaison with the emergency department. A multidisciplinary team should be involved in management including surgeon, radiologist, gynaecologist and orthopaedic surgeon. **Haemophilia treatment centers (HTCs) and clinics should not deal with such cases.**

**Rationale:** Not all the hospitals provide appropriate services to a bleeding patient and not all hospitals work in collaboration with blood banks. It is of utmost importance for a bleeding patient to be in such a hospital where he can receive immediate critical intervention along with appropriate tests and imaging. The time elapsed between the onset of fatal bleeding and intervention should be minimal. This is generally seen that severely bleeding patients die within 24 hours of onset of bleeding if not treated in time.

- **Initial assessment:**

History should be taken from the patient if he/she is conscious or from the attendant available. The extent of the bleeding and the site of the bleeding should be checked immediately. Vitals should be taken at the entry of the patient.

**Rationale**: The past medical history, site of the bleeding and the vital are of prime importance because the subsequent treatment is based on this information. If the diagnosis of the patient is known then the specific treatment can be started immediately like factor VIII concentrates in Haemophilia A patients should be arranged and given immediately. Similarly, the site of bleeding is important as in case of severe limb bleeding a tourniquet can save the limb.

Pulse, blood pressure, respiratory rate and conscious level of the patient should be checked to see if the patient is in shock and mental state of patient is to be assessed for any CNS bleeds.

## GENERAL MEASURES

- **Intravenous line and fluid replacement:** I/V line should be maintained immediately and fluid replacement therapy should be started at once. The recommended fluid is isotonic crystalloid, 0.9% saline should not be used in excess. Ringer's lactate should be avoided in patients with severe CNS bleeds. The use of colloids should be restricted due to the adverse effects on haemostasis. Patient should undergo immediate bleeding control procedure unless initial resuscitation measures are successful.
- **Imaging: Important to treat the patient before these investigations:** If the site of bleeding is internal and cannot be localized then patient should undergo immediate imaging like ultrasonography or CT scan to pinpoint the bleeding site, for example, CNS bleeding, intra-abdominal bleeding like iliopsoas bleeding. Patients with intra-thoracic, intra-abdominal or retroperitoneal bleeding and haemodynamic instability. Keep the patient warm to maintain **normothermia.**
- Monitor **urinary output**.

- Send the **baseline tests** immediately like blood complete picture, urine R/E, serum lactate and base deficit to estimate and monitor the extent of bleeding and shock.
- Intravenous **tranexamic acid** should be started at a loading dose of 1 g infused over 10 min, followed by I/V Infusion of 1 g over 8 hours.
- **Red blood cells, platelet concentrates and fresh frozen** plasma should be arranged and should be given in case of shock and also depending upon the cause of the bleeding i.e. the disease.
- A target **systolic blood pressure** of 80–90 mmHg until major bleeding has been stopped.
- In the presence of life threatening hypotension, administration of **vasopressors** in addition to fluids should also be given to maintain target arterial pressure i.e. ≥80 mmHg.
- **Recombinant Factor VII** can be used in severe and life threatening bleeding.

## SPECIFIC MEASURES

These measures should be according to the disease of the patient.

**Haemophilia treatment centers should be contacted for arrangements of concentrates.**

- **Haemophilia A and B:**
  - These patients should be given Factor VIII and Factor IX concentrates immediately.
  - In urgent situations cryoprecipitates or FFPs can also be given if the factor concentrates are not available

- **von Willebrand disease (vWD):**
  - von Willebrand factors (vWF) should be arranged immediately. These contain a combination of vWF & FVIII.
  - In case of unavailability of vWF concentrates, Intermediate purity Factor VIII concentrates (Koate) can be used as it does contain vWF as well.

- **Fibrinogen deficiency:**
  - Fibrinogen concentrates are the best choice. Not available in Pakistan
  - FFPs & Cryoprecipitates can be given & are the main treatment option in Pakistan

- **Factor II, V, X, XI and XIII deficiency:**
  - FFPs are the best and the only source for these inherited bleeding disorders
  - In case of Factor II (Prothrombin), Factor VII and Factor X prothrombin complex concentrates are the best choice but they are not easily available and are expensive.

- **Factor VII deficiency**
  - rFVII is available and is used in this deficiency. Very expensive
  - If rFVII cannot be used because of expense or unavailability, FFP should be used

## CONGENITAL FUNCTIONAL PLATELET DISORDERS

- These include Bernard Soulier disease, Glanzmann's Thrombasthenia and storage pool defects of platelets.
- Platelet concentrate transfusion is the therapy of choice but platelet alloimmunization remains the main adverse effect of this therapy. To avoid this adverse effect these patients are mostly treated with oral or I/V tranexamic acid and they show good response as well.
- Recently thrombopoietin receptor agonists (TPOR) like eltrombopag and romiplostim has shown some promising results but needs validation.

**Table V – Treatment choices in Inherited Bleeding Disorders**

| Disorder | 1st choice | 2nd choice | 3rd choice | Adjuvant measure |
|---|---|---|---|---|
| **Haemophilia A** | Recombinant FVIII concentrates | Plasma derived FVIII concentrates | Cryoprecipitate/ FFPs | Tranexamic acid |
| **Haemophilia B** | Recombinant FIX concentrates | Plasma derived FIX concentrates | FFPs | Tranexamic acid |
| **Fibrinogen deficiency** | Fibrinogen concentrates | FFPs | - | Tranexamic acid |
| **Prothrombin deficiency** | PCC | FFPs | - | Tranexamic acid |
| **Factor V deficiency** | FFPs | - | - | Tranexamic acid Platelet concentrates* |
| **Combined Factor V and Factor VIII deficiency** | FVIII concentrates FFPs | FFPs | - | Tranexamic acid Platelet concentrates* desmopressin |
| **Factor VII deficiency** | Recombinant FVII concentrates | FFPs | - | Tranexamic acid |
| **Factor X deficiency** | PCC | FFPs | - | Tranexamic acid |
| **Factor XI** | FXI concentrates | FFPs | - | Tranexamic acid~ |
| **Factor XIII deficiency** | FXIII concentrates | FFPs | - | Tranexamic acid |
| **Platelet disorders** | Platelet concentrates | TPOR | - | Tranexamic acid |
| **VWD** | VWF concentrates | FFPs | - | Tranexamic acid |

*Platelet alpha granules contains factor V

~Tranexamic acid is not given in urogenital and oropharyngeal bleeding

PCC prothrombin complex concentrates, FFP, TPOR thrombopoietin receptor agonists,

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# CHAPTER 10

# PSYCHOSOCIAL ISSUES IN INHERITED BLEEDING DISORDERS

CHAPTER 10

# PSYCHOSOCIAL ISSUES IN INHERITED BLEEDING DISORDERS

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## INTRODUCTION

Individuals with haemophilia face a number of psychosocial challenges and need help to face these issues. A good family support with a solid academic foundation is essential for a child with haemophilia.
This will help them grow up as normal, confident & useful members of the Society with complete social integration.

## COPING WITH DIAGNOSIS, PARENTS AND FAMILY

A key issue that arises early on is coping with the diagnosis by parents and family members. They need help to accept the diagnosis and understand that though hemophilia is a lifelong chronic condition it is just one aspect of an individual's life. The counselor needs to show empathy for emotional reactions that often affect parent's feelings such as distress, depression, anger, feelings of guilt, fear, uncertainty, helplessness, sadness and loneliness and help them to manage them.

Parents should be encouraged to educate themselves about the disorder and know first-aid/ home treatment measures. This helps them to get over the fear of unknown and to have a control of the disease. The Haemophilia Society has useful publications on different aspects of haemophilia in Urdu & English, which should be passed on to all parents.

Parents should be advised how to strike a balance between constant attention to situations potentially dangerous to health and the development of normal activities. They should not blame and punish the child or react with excessive anxiety in response to an injury or an accident as the child may not inform parents immediately in future. This could lead to an emergency rather than the bleed being controlled by less costly and simple treatment to start with.

## THE SPORTS ISSUE

Sports not only build self-confidence but also help in developing strong muscles and coordination. This helps to protect joints and leads to fewer spontaneous bleeding episodes. Exercise can also teach these children about what to do when they get hurt. There are, however, limitations to what can & what can't be done. The parents & later on the child should be counseled on setting limits on the sports. Most contact sports such as football, hockey, boxing and wrestling are not recommended. Swimming, specific indoor exercises, walking and hiking are useful.
There are many alternatives to sports that are just as enjoyable and helpful in building self-esteem and a sense of accomplishment. Non-sports related hobbies or skills developed in the school-age years often become fulfilling, lifelong pursuits. Examples include: Painting, Music, Photography, Stamp collecting, Debating, Model building and Board games.

## BALANCING CARE WITH CONFIDENCE BUILDING, THE EARLY YEARS

Parents play a vital role in developing the child's self-esteem as it is important to balance vigilance and overprotectiveness and they need to be guided about developing the child's confidence in basic activities such as crawling, walking, running and playing.

**Parents need to know about:**

- The degree of liberties and limitations, taking into consideration level of maturity and psychological readiness.
- The encouragement of indoor games and activities e.g. book

reading, block building, jigsaw puzzles and to limit the use of computers, mobile phones or TV watching as these activities damage brain development in young children.

- About admission in Montessori or nursery classes as this will give the child a chance to interact with other children and adults and become more independent. This will also help the parents and the child to gain experience in answering questions about haemophilia. In no way should the condition of the child be kept hidden.

## IMPORTANCE OF SCHOOLING & SELF CARE, THE PRE-ADOLESCENT CHILD

Parents should be made aware that schooling plays an extremely important role in the development of the child and his future as useful member of the society. All children should therefore attend school. An open relationship with the school and with the child's teachers should be established & they should be given information about haemophilia & what to do in case of an accident or bleed .The Society has developed a letter for the school & has literature on basics of haemophilia, both in English & Urdu, which should be passed on to the school at the time of admission.

The child should be encouraged to take an active role in the management of his bleeding disorder and being responsible for his health and avoiding dangerous situations and taking of risks.

Anger and denial might cause increase in risk-taking and attempts to avoid appropriate treatment as the child is dealing with his feelings about physical changes and health issues. He should be taught at an early age, through knowledge about his disease, to differentiate between when to accept what the majority does or wants and when to defend his own decisions to avoid risky situations. This will help him cope with his disease and the social pressures.

## CHAPTER 10

## SELF ESTEEM & RELATIONSHIPS, THE ADOLESCENT

Most of the counselling for adolescents is the same as mentioned in the other sections, but adolescence is often a difficult time of transition into adulthood and a position of responsibility & therefore guidance is essential to cope with these stressful years by:

- Not taking risks with health and safety and avoiding appropriate treatment.
- avoiding peer pressure and learn to say" NO".
- Undertaking academic and vocational pursuits that do not involve significant physical risk.
- Facing common adolescent challenges such as self-esteem issues and relationships.
- Developing a growing responsibility for therapy (including psychotherapy if & when required) and self-care, and gradually reducing parental supervision while the therapy process progresses. A key component of self-care is communicating the existence of injuries and/or accidents & getting prompt treatment.

## WORK ISSUES IN ADULTS

An early diagnosis and access to a multi care Haemophilia Treatment Centre helps to develop not only good physical health but also confidence and independence which leads to a well-rounded adult. They, however still face the following issues:

- **Disclosure**: Most adults have shared their diagnosis, and often their associated complications, with friends and family. In terms of disclosing to their employers and coworkers, this varies based on the individual's preference, privacy issues, treatment needs, the degree of physical impairment, and past experiences with disclosure in the workplace. However it is better if they are encouraged to disclose their status in case of an emergency at work.
- **Increasing physical impairment:** this can result in significant lifestyle changes and reversal of roles within a family. These changes in abilities, functions, and difficulty in finding or keeping a job are a major loss for adult patients who have

overcome so many obstacles to achieve independence and they often suffer from low self-esteem and depression. Encourage them and their families to let them retain part of the decision-making process about their health care and their overall life as this is important to adults with hemophilia.

- Encourage the individuals to participate in social or support groups for people with hemophilia & have close liaison with their HTC and the Haemophilia Society.

## SIBLING RIVALRY

Siblings of children with haemophilia often feel ignored by their parents because the haemophiliac child requires so much attention. To avoid a feeling of not being loved in these siblings parents should be advised to:

- Educate siblings about haemophilia.
- Encourage siblings to discuss haemophilia openly with them and their brother.
- Include siblings in the general care of the child if they are of an age where they can help.
- NOT blame or punish siblings if the child bleeds.
- Listen carefully to their children when they talk about haemophilia and to be sure that what they are saying is correct.
- Must be consistent with rules and discipline methods for all their children.
- Spend time alone with each child so that they don't feel neglected.

## PSYCHOSOCIAL ISSUES IN FEMALES WITH INHERITED BLEEDING DISORDERS

The bleeding problems in females are similar to males in early life but the real issues which affect their psychosocial health begin with menarche and then continue throughout their child bearing age.

### 1. Heavy Menstrual Bleeding (HMB), unable to cope with the stress

Lack of awareness about the disease, heavy menstrual bleeding, which is difficult to cope with, not taken seriously, late diagnosis & the

importance in bleeding disorder community being given to males, who form the major bulk of the disease, are the major factors making the young females feel **Isolated, anxious, angry & frustrated .** What adds to this is the inability to discuss these with friends, family and even their doctor due to the cultural settings, shyness & embarrassment .The following measures can help:

- **Education & awareness**
  Parents & patients should be encouraged to educate themselves about the disease so that they not only know about it but know first-aid/ home treatment measures. This helps them to get over the fear of unknown and take control of the disease. The publications of HPWS Rawalpindi (in Urdu as well) can be very useful in this regard.
- **Communication**
  Females should form their own groups as communication with other women with similar Problems can help to cope with the stress. Talking with their extended family & sharing the information they have about the in disease, if they can overcome the inhibitions, can be useful as it can lead on to the diagnosis in other members of the family.
- **Female empowerment:** The ability to decide for themselves & take responsibility for their welfare gives female the confidence to overcome the stress.
- **Liaison with the medical team**
  This will provide added help & support & discussion of any issues which the family can bring up

## 2. Marriage: Coping with disease disclosure & related Issues (conception & Pregnancy)

Most of the marriages are arranged & if it is outside family, it is very difficult for the parents to disclose the disease to the other family because of the fear of rejection. If the diagnosis is kept a secret then it causes lots of problems & loss of trust between families & the couple later on. It can result in separation/divorce.

Communicating with other married females & their parents and learning from experiences can help. This can also be discussed with the medical team who can provide them information about the disease &

the help & care which can be provided.

Difficulties in conception, miscarriages & post partum haemorrhage are other causes of stress for the females & the families. Here again, communicating & learning from others & the help and support provided by the medical team can go a long way in improving the psychosocial status

Females have come a long way from the time when they were told not to get married & then not to have children, if they did. This has helped a lot to build up their morale & confidence. The knowledge of females in the Inherited Bleeding Disorders group getting married & having successful pregnancies has provided a lot of hope & has helped to lift the enormous pressure.

## FURTHER READING


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# ANNEXURE

## ANNEX 1: HAEMOPHILIA FEDERATION OF PAKISTAN

## ANNEX 2: HAEMOPHILIA TREATMENT CENTRES (HTC'S)

## ANNEX 3: MEDICAL ADVISORY BOARD

## ANNEX 4: HAEMOPHILIA FRIENDLY HOSPITALS & THEIR CONTACT DOCTORS

**ANNEX 1**

# HAEMOPHILIA FEDERATION OF PAKISTAN

**10, JAIL ROAD, INSIDE CHUGTAI LAB, OLD BUILDING, GULBERG V, LAHORE**

**Contact Persons:**

Masood Fareed Malik 0300-4008088
**mfmalik@hemophilia.org.pk**
Faizan Baig 0306 6655578
**faizan.baig@outlook.com**

## HAEMOPHILIA PATIENT WELFARE SOCIETIES

| SR # | HPWS | Contact Person | Contact Information | Postal address |
|---|---|---|---|---|
| 1. | Rawalpindi | Dr Munawar Sher Khan | 0300 5003706<br>051 8432751<br>051 8432752<br>hpwsrwp@gmail.com | 1st Floor , Thalassaemia House, Opposite RMC, Tipu Road Rawalpindi |
| 2. | Lahore | Dr Shahla T Sohail | 0300 8433881<br>042 35717632<br>Infor@pakhpws.org | 10, Jail Road, Inside Chugtai Lab, Lahore |
| 3. | Karachi | Raheel Ahmed | 0333 2221844<br>raheelhpws@hotmail.com | Ground Floor Usama Arcade, Eidgah Ground, Nazimabad 3, Karachi |
| 4. | Peshawar | Syed Shabistan | 0345 8862517<br>091 5711721<br>Syedhemo8@yahoo.com | 8 Khyber colony no. 2, Tehkal Payaan, Main University Road, Peshawar |

**ANNEX 2**

## HAEMOPHILIA TREATMENT CENTRES (HTC'S)

| SR # | HTC | Contact Person | Contact Information | Postal address |
|---|---|---|---|---|
| 1. | PIMS Islamabad | Dr Zahida Ahmed | 0333 5456646<br>drzahidaahmed@gmail.com | PIMS HTC, New Emergency |
| | | Dr Tazeen Anwar | 0301 2648589<br>051 9261170<br>tazeen.anwar@gmail.com | Children HTC |
| | | Neha Imtiaz | 0343 5268275 | |
| | | Ibrar Hussain | 0336 5208756<br>ibrar922@gmail.com | |
| 2. | Rawalpindi | Dr Bilquis Sohail | 0333 5341240<br>051 8432751<br>drbilquissohail@gmail.com | 1st Floor , Thalassaemia House, Opposite RMC, Tipu Road Rawalpindi |
| | | Alamgir Abbasi | 0332 8733220<br>051 8432752<br>aagkhan81@gmail.com | 1st Floor , Thalassaemia House, Opposite RMC, Tipu Road Rawalpindi |
| 3. | Lahore | Dr Shahla T Sohail | 0300 8433881<br>042 35717632<br>Infor@pakhpws.org | 10, Jail Road, Inside Chugtai Lab, Lahore |
| 4. | Karachi | Raheel Ahmed | 0333 2221844<br>raheelhpws@hotmail.com | Ground Floor Usama Arcade, Eidgah Ground, Nazimabad 3, Karachi |
| 5. | Peshawar | Syed Shabistan | 0345 8862517<br>091 5711721<br>Syedhemo8@yahoo.com | 8 Khyber colony no. 2, Tehkal Payaan, Main University Road, Peshawar |

**ANNEX 3**

# HAEMOPHILIA PATIENTS WELFARE SOCIETY RAWALPINDI

## Medical Advisory Board

| SR# | Name | Designation | |
|---|---|---|---|
| 1 | Prof. Tahira Zafar | Consultant Haematologist | **Chairperson** |
| 2 | Prof. Lubna Zafar | Consultant Haematologist | **Deputy Chairperson** |
| 3 | Dr. Nadeem Ikram | Consultant Haemotologist | **Member** |
| 4 | Prof. Asif Zafar | Consultant Surgeon | **Member** |
| 5 | Dr. Qasim Ali | Consultant Surgeon | **Member** |
| 6 | Dr. Sarah Zafar | Consultant Ophthalmologist | **Member** |
| 7 | Dr Khalid Aslam | Consultant Orthopaedic Surgeon | **Member** |
| 8 | Prof. Riaz Sheikh | Consultant Orthopaedic Surgeon | **Member** |
| 9 | Prof. Nouman Maqbool | Consultant Orthopaedic Surgeon | **Member** |
| 10 | Prof. Naeem Zia | Consultant Surgeon | **Member** |
| 11 | Prof. Humaira Bilqees | Consultant Gynaecologist | **Member** |
| 12 | Dr. Erum Naeem | Consultant Gynaecologist & Sonologist | **Member** |
| 13 | Dr. Zahida Ahmed | Dental surgeon | **Member** |
| 14 | Dr. Ayesha Farid | Consultant Psychiatrist | **Member** |
| 15 | Dr. Farkhanda Nazli | Consultant Rehab Medicine | **Member** |

**ANNEX 4**

# HAEMOPHILIA FRIENDLY HOSPITALS & THEIR CONTACT DOCTORS

| Hospital | Name | Designation |
|---|---|---|
| **Benazir Bhutto Hospital Rawalpindi** | Dr. Nadeem Ikram | Consultant Haematologist |
| | Dr. Ranaa Zeeshan | Consultant Haematologist |
| | Prof. Riaz Sheikh | Consultant Orthopedic Surgeon |
| | Prof. Naeem Zia | Consultant Surgeon |
| | Dr. Moazzma Ahmed | Senior Physiotherapist |
| | Dr. Ayesha Fareed | Consultant Psychiatrist |
| | Dr Humera | Consultant Gynaecologist |
| **PIMS Hospital Islamabad** | Dr. Zahida Ahmed | Consultant Dental surgeon |
| | Prof.Syeda Batool | Consultant Gynaecologist |
| | Dr. Tazeen Anwaar | Medical officer Haemophilia Centre |
| | Dr. Riaz Khattak | Medical Officer Haemophilia Centre |
| | Dr. Bisma | Senior Physiotherapist |
| **Holy Family Hospital Rawalpindi** | Dr. Qasim Ali | Consultant Surgeon |
| | Prof. Atifa Shuaib | Consultant Haematologist |
| | Prof.Humera Bilqees | Consultant Gynaecologist |
| **Attock Refinery Hospital Morgah Rawalpindi** | Dr. Noman Maqbool | Consultant Orthopedic Surgeon |
| **AFIP/ AFBMTC Rawalpindi** | Brig. Assad Abbasi | Consultant Haematologist |
| | Lt. Col. Helen Robert | Consultant Haematologist |
| | Maj. Saima Saad | Consultant Haematologist |
| | Brig Qamar un Nisa | Consultant Haematologist |
| | Col Mehreen | Consultant Haematologist |
| **Quaid e Azam International Hospital Rawalpindi** | Dr. Khalid Aslam | Consultant Orthopedic Surgeon |
| **Shifa International Hospital Islamabad** | Dr. Ayesha Junaid | Consultant Haematologist |
| **Al-Shifa Eye Trust Rawalpindi** | Dr. Sarah Zafar | Consultant Ophthalmologist |
| **Ahmad Medical Complex** | Dr Erum Zia | Consultant Gynaecologist & Sonologist |

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