Challenges of Comprehensive Haemophilia Care Management

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Singapore General Hospital
Congenital Coagulation Disorders

- Haemophilia A
- Haemophilia B
- von Willebrand’s Disease
- Isolated Clotting Factor Deficiencies
Fibrin Clots

Thrombin

Xa + Va

IXa

VIIa

Xla

Xla

von Willebrand’s Disease

Haemophilia A

Haemophilia B

IX

XIa

VIIa

VIIa
Ten point statement of European Principles of Haemophilia Care

1. Haemophilia Co-ordinating Organisations with supporting local Organisations
2. National Haemophilia Patient Registry
3. Provision and Maintenance of Comprehensive Care Centres (CCCs) and Haemophilia Treatment Centres (HTCs)
4. Partnership in the Delivery of Haemophilia Care
5. Access to Safe and Effective Concentrates at Optimum Treatment Levels
6. Access to Home Treatment & Delivery
7. Access to Prophylactic Therapy
8. Access to Specialist Services and Emergency Care
9. Management of Inhibitors
10. Education and Research
Importance of the National Haemophilia Registry

- Key information on haemophilia and related disorders
- Accurate assessment of disease prevalence.
- Analysis of standards and outcome of care.
- Tool for auditing clinical and laboratory services.
- Help for development of better quality of care.
- Resource planning and allocation.
- Comprehensive and effective surveillance systems.

EU Interdisciplinary Working groups- IDWGs
The Goals of Treatment of Haemophilia

- To prolong life and to minimise disability: **Access to therapy**
- To facilitate social and physical well-being: **Comprehensive care**
- To help each patient achieve full potential whilst causing no harm! **Safety**

SGH HAEMOPHILIA CENTRE:

COMPREHENSIVE HAEMOPHILIA CARE

• National Haemophilia Registry
• Reference Coagulation Laboratory
• Carrier Detection, Prenatal Diagnosis and Genetic Counselling
• Haemophilia Walk-In Clinic
• Home Treatment Programme
• Orthopaedics Care and Hepatitis Management
• Ancillary Care and Psychosocial Support
Multi-Disciplinary Care

- Haematologists
- Paediatricians
- Dental Surgeons
- Orthopaedic Surgeons
- Gastroenterologist
- Obstetrics & Gynae
- Physiotherapists
- Social Welfare Workers
Challenges of Haemophilia Management

1. **Data**
   - Manual Record ➔ National Haemophilia Registry

2. **Diagnosis**
   - Functional Assay/ Pedigree study ➔ Molecular Diagnosis

3. **Treatment**
   - Cryoprecipitate ➔ Plasma-derived Factor ➔ Recombinant Factor
   - On demand Treatment ➔ Prophylaxis Treatment
   - Outpatient Treatment ➔ Home Treatment
   - Proband Treatment ➔ Prenatal Diagnosis & Counselling

4. **Inhibitor**
   - Factor Swarm/Bypass ➔ FIX Complex/FEIBA or Factor VIIa ➔ Immune Tolerance

5. **Target Joints**
   - Isotope Synovectomy ➔ Total Joint Replacement

6. **Hep C Infection**
   - Interferon only ➔ Interferon + Ribavarin ➔ Peg-Interferon + Ribavarin

7. **Research**
   - Gene Therapy ➔ Endothelial/Liver Transplant ➔ Modified FVIII (future)
DEVELOPMENT OF SGH HAEMOPHILIA DATA RECORDS

Manual Records

National Haemophilia Registry

International Hemophilia Training Center Directory of WFH

17 Jun 1963

1 Aug 1995

13 Dec 2002
## Prevalence of Haemophilia in Asia

Data adapted from
World Federation of Hemophilia
Report on the Annual Global Survey 2006

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>HemA&amp;B/100,000</th>
<th>VWD/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>222,781,000</td>
<td>0.5</td>
<td>0.0</td>
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<td>Malaysia</td>
<td>25,347,000</td>
<td>4.1</td>
<td>1.4</td>
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<td>Philippines</td>
<td>83,054,000</td>
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<td>4,326,000</td>
<td>4.7</td>
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<td>Thailand</td>
<td>64,233,000</td>
<td>1.9</td>
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<td>Viet Nam</td>
<td>84,238,000</td>
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<td>0.0</td>
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<td>Mean</td>
<td></td>
<td><strong>2.3</strong></td>
<td><strong>0.5</strong></td>
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<tr>
<td>China</td>
<td>1,315,844,000</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Japan</td>
<td>128,085,000</td>
<td>3.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Korea</td>
<td>47,817,000</td>
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<td>0.2</td>
</tr>
<tr>
<td>India</td>
<td>1,103,371,000</td>
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<td>0.0</td>
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<tr>
<td>Bangladesh</td>
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<td>0.0</td>
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<td>Sri Lanka</td>
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<td>Pakistan</td>
<td>157,935,000</td>
<td>0.9</td>
<td>0.0</td>
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<tr>
<td>Nepal</td>
<td>27,133,000</td>
<td>0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td><strong>1.5</strong></td>
<td><strong>0.1</strong></td>
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NATIONAL HAEMOPHILIA REGISTRY
Prevalence of Haemophilia in Singapore

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Count</th>
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<tbody>
<tr>
<td>Haemophilia A</td>
<td>194</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>36</td>
</tr>
<tr>
<td>von Willebrand’s Disease</td>
<td>72</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>302</strong></td>
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</tbody>
</table>
DEMOGRAPHICS

Haemophilia B (n=36) 12%

VWD (n = 72) 24%

Haemophilia A (n = 194) 64%

~ 1 / 20,000

Singapore population: 3,789,300 (Citizens & permanent residents)
Approx: 5.2 million if include foreigners
• Age Group
- Severity

Haemophilia A (n = 194)
- Mild 35%
- Moderate 34%
- Severe 31%

Haemophilia B (n = 36)
- Mild 45%
- Moderate 33%
- Severe 22%

VWD (n = 72)
- Type 1 47%
- Type 2 30%
- Type 3 23%
The Singapore Haemophilia Registry facilitates:

- Early treatment of the disorder to prevent joint complications e.g. radioisotope synovectomy
- Early treatment of the transfusion-related complications e.g. hepatitis C treatment
- Treatment of clotting factor inhibitors
- Prenatal diagnosis and genetic counselling
- Social and financial counselling
- Research and Publications

Outcome: Better quality of life for haemophilia patients
CHALLENGES IN DIAGNOSIS

- Disease
- Carrier

Coagulation Study

Pedigree Study

Genetic Study
Haemophilia A & B

**Qualitative test**: Activated partial thromboplastin time (aPTT)

**Quantitative test**: Factor and Inhibitor Assay

<table>
<thead>
<tr>
<th>Severity</th>
<th>VIII:C(%)</th>
<th>IX:C(%)</th>
<th>Joint Bleed</th>
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<tbody>
<tr>
<td>Severe</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>+++</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 to &lt;5</td>
<td>1 to &lt;5</td>
<td>+</td>
</tr>
<tr>
<td>Mild</td>
<td>5 to 25</td>
<td>5 to 25</td>
<td>+/-</td>
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</tbody>
</table>
FVIII Estimation Problems in Mild Haemophilia A

• Up to 1/3 of patients with mild haemophilia A may have discrepant 1-stage and chromogenic assay levels

• Use of 1-stage only FVIII assay will:
  - underestimate the severity of many patients
  - fail to identify 10-5% of patients with mild haemophilia
  - may over-diagnose some patients with haemophilia

• Recommend to do both 1-stage and chromogenic FVIII assay to investigate for mild haemophilia with bleeding disorder
### von Willebrand’s Disease

**Qualitative test**: Ristocetin cofactor activity, low dose ristocetin induced platelet aggregation

**Quantitative test**: vWF Ag assay

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>RistoCoF</th>
<th>vWF Ag</th>
<th>low RIPA</th>
<th>VIII:C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>low</td>
<td>low</td>
<td>absent</td>
<td>low</td>
</tr>
<tr>
<td>2A</td>
<td>low/normal</td>
<td>low/normal</td>
<td>absent</td>
<td>low/normal</td>
</tr>
<tr>
<td>2B</td>
<td>low/normal</td>
<td>low/normal</td>
<td>present</td>
<td>low/normal</td>
</tr>
<tr>
<td>3</td>
<td>very low</td>
<td>very low</td>
<td>absent</td>
<td>low</td>
</tr>
</tbody>
</table>
Type 1 is most common form of VWD

Mechanisms include: decreased VWF synthesis, decreased VWF secretion, Increased VWF clearance

VWF and its propeptide (VWFpp) are released in 1:1 ratio
- ↓VWFpp = reduced synthesis/secretion
- ↑VWFpp/VWF:Ag = increased clearance
- Normal ratio = increased retention/decreased secretion
Results & Implications of VWF Propeptide Study

In 262 confirmed as Type 1 VWD cases
- 58 Type 1C = 22%
- 12 Type 1 severe (VWF AG = 1-5 IU/dL), majority of cases were Type 1C
- Majority of patients with VWF:AG <20 IU/dL were Type 1C

Rapid clearance in these patients may preclude use of DDAVP

Critical Importance Of VWF Propeptide (VWFpp) In The Diagnosis Of Type 1 Von Willebrand Disease (VWD)
Sandra L. Haberichter, Ph.D., Pamela A. Christopherson, Veronica H. Flood, MD, Joan Cox Gill, MD, Daniel B. Bellissimo, Kenneth D. Friedman, M.D., Robert R. Montgomery, MD and The Zimmerman Program Investigators (ASH 2013 Abstract)
Challenges in Genetic Testing

Spectrum of Haemophilia Mutations:

> 2100 different Factor 8 mutations

> 1100 different Factor 9 mutations

Mutation detection rates ~ 90%
Common Gene Mutation in Severe Haemophilia A - Intron 22 inversion
Haemophilia A & B

Gene Analysis by

- Restriction Fragment Length Polymorphism (RFLP)
- Variable Number of Tandem Repeat (VNTR)
- Polymerase Chain Reaction (PCR)
- Southern Blotting
- Gene Sequencing

Indications:
- Family Study
- Prenatal Diagnosis
• Prenatal Diagnosis & Genetic Counselling

• Prenatal diagnosis is possible for female Haemophilia A and B carriers

• To date, SGH has performed carrier screening and prenatal diagnosis with genetic counselling in:

  Haemophilia A : 53 family members (23 pregnancies)
  Haemophilia B : 11 family members (4 pregnancies)
Current Haemophilia Therapy:

SAFE and EFFECTIVE

But ......
Limitations to Current Haemophilia Treatment:

- Inconvenient: repeated intravenous infusions
- Immunogenic: 15-25% inhibitor incidence in Haemophilia A
- Costly
- Only available to ~30% of all haemophiliacs
CHALLENGES IN TREATMENT

- **Blood Product** Replacement Therapy
  
  Fresh Frozen **Plasma**
  
  Cryoprecipitate
  
  Viral inactivated **Factor Concentrates**
  
  Recombinant **Factor Concentrates**
## CRYOPRECIPITATE

**Advantages**

1. Smaller donor pool and hence less donor exposure risk.
2. Presumably cheaper.

**Disadvantages**

1. Storage: Freezer is required.
2. Preparation: Time consuming.
3. Infusion: 10-20 mins is required.
4. Purity: Other proteins present, allergic reactions more common.
5. Safety: Inactivation of virus not possible; “windows period”.

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## FACTOR VIII CONCENTRATE

**Advantages**

1. Storage: Only ordinary refrigerator.
2. Preparation: A few mins to reconstitute.
3. Infusion: Only a few mins.
5. Stability: May be stored up to 2yrs under refrigeration.

**Disadvantages**

1. Large donor pool was used in manufacturing Factor VIII concentrates.
2. Presumably more expensive.
### Factor Usage per Capita

Data adapted from
World Federation of Hemophilia
Report on the Annual Global Survey 2006

<table>
<thead>
<tr>
<th>Country</th>
<th>FVIII per capita</th>
<th>FIX per capita</th>
</tr>
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<tbody>
<tr>
<td>Bangladesh</td>
<td>0.005</td>
<td>0.000</td>
</tr>
<tr>
<td>Indonesia</td>
<td>0.015</td>
<td>0.000</td>
</tr>
<tr>
<td>Japan</td>
<td>2.272</td>
<td>0.304</td>
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<td>Korea</td>
<td>2.105</td>
<td>0.330</td>
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<td>Malaysia</td>
<td>0.404</td>
<td>0.197</td>
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<tr>
<td>Nepal</td>
<td>0.012</td>
<td>0.002</td>
</tr>
<tr>
<td>Pakistan</td>
<td>0.002</td>
<td>0.000</td>
</tr>
<tr>
<td>Philippines</td>
<td>0.010</td>
<td>0.000</td>
</tr>
<tr>
<td>Singapore</td>
<td>0.751</td>
<td>0.104</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>0.620</strong></td>
<td><strong>0.134</strong></td>
</tr>
<tr>
<td>Australia</td>
<td>4.614</td>
<td>0.759</td>
</tr>
<tr>
<td>New Zealand</td>
<td>5.020</td>
<td>0.875</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>4.817</strong></td>
<td><strong>0.817</strong></td>
</tr>
<tr>
<td>Belgium</td>
<td>5.759</td>
<td>0.537</td>
</tr>
<tr>
<td>Finland</td>
<td>4.445</td>
<td>0.446</td>
</tr>
<tr>
<td>France</td>
<td>5.125</td>
<td>0.967</td>
</tr>
<tr>
<td>Germany</td>
<td>6.772</td>
<td>0.861</td>
</tr>
<tr>
<td>Greece</td>
<td>2.587</td>
<td>0.362</td>
</tr>
<tr>
<td>Hungary</td>
<td>5.080</td>
<td>0.498</td>
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<tr>
<td>Italy</td>
<td>5.164</td>
<td>0.861</td>
</tr>
<tr>
<td>Portugal</td>
<td>3.023</td>
<td>0.629</td>
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<tr>
<td>Spain</td>
<td>3.760</td>
<td>1.393</td>
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<tr>
<td>Sweden</td>
<td>6.775</td>
<td>0.771</td>
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<tr>
<td>Switzerland</td>
<td>3.753</td>
<td>0.707</td>
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<tr>
<td>United Kingdom</td>
<td>4.245</td>
<td>0.771</td>
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<tr>
<td><strong>Mean</strong></td>
<td><strong>4.707</strong></td>
<td><strong>0.652</strong></td>
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<tr>
<td>Canada</td>
<td>4.283</td>
<td>1.138</td>
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<tr>
<td>United States</td>
<td>5.365</td>
<td>1.341</td>
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<tr>
<td><strong>Mean</strong></td>
<td><strong>4.824</strong></td>
<td><strong>1.240</strong></td>
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</tbody>
</table>
Changing Trend

**Timing** of factor replacement therapy
- On demand ➔ Prophylaxis

**Administration** of factor replacement therapy
- IV Bolus ➔ ?Continuous

**Place** of factor replacement therapy
- Hospital ➔ Home
Reconstitution is Easy

Sterile Diluent + Factor = Factor for Infusion

as soon as possible
Early Treatment

Traumatic bleed

Spontaneous bleed

Adapted from WFH Website
BENEFITS OF HOME TREATMENT

1. Less short term and long term damage due to delayed treatment.

2. A more “normal” life

3. Reduced medical costs.

4. Psychological benefits.

RECORD KEEPING

1. The Product used
   • name of product
   • amount given
   • batch lot number

2. The treatment itself
   • date and time
   • indications
   • person administering
   • immediate side effects
   • any difficulties
   • effectiveness
Challenges in Treatment of Inhibitors

Alloantibodies against foreign factors infused

Incidence of Inhibitors

Haemophilia A
17%
(only 6% persists)

Haemophilia B
0%

von Willebrand Disease
0%

Treatment strategies:

- Reduction of inhibitors
  - Inhibitor swarming with factors
  - Plasma exchange
  - Immune Tolerance

- Bypass of inhibitors
  - Factor IX prothrombin complex
  - FEIBA
  - Recombinant factor VII
Choice of Factor for Haemophilia A with Inhibitors

- Inhibitor <5BU, Minor bleed: Factor 8 Swarm or PCC
- Inhibitor >5BU, Minor bleed: PCC or FEIBA
- Inhibitor +, Major Bleed or Surgery: FEIBA or F7a

Immunotolerance done in SGH patients

Haemophilia A, Severe, Low Responder x 2 patients

- World Federation of Haemophilia Protocol: 1
- Modified Bonn Protocol: 1

Both were successful with no further inhibitor demonstrated, and patients reverted to use of Factor 8.
TREATMENT of Target Joints

- **Joint Problems**
  - Haemarthrosis
  - Cold compress
  - Joint aspiration if necessary
  - Surgical synovectomy
  - Isotope synovectomy
  - Physiotherapy & aids
  - Corrective Osteotomy
  - Arthrodesis
  - Arthroplasty and implants
• **Target Joints:**

<table>
<thead>
<tr>
<th>Radionuclide Used</th>
<th>1997-2001</th>
<th>2002-2004</th>
<th>2006-now</th>
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<tbody>
<tr>
<td>P32</td>
<td>Rhenium 88</td>
<td>Yttrium -90</td>
<td></td>
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</table>

**Radionuclide Synovectomy**

- **Knee**
  - No of Cases: 31
  - Response: 27 (87%) significant improvement, 4 with no difference

- **Ankle**
  - No of Cases: 7
  - Response: 5 (71%) significant improvement, 2 with no difference

- **Elbow**
  - No of Cases: 5
  - Response: 3 (60%) significant improvement, 2 with no difference

<table>
<thead>
<tr>
<th>Total Joint Replacement</th>
<th>Knee</th>
<th>Elbow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>1</td>
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</tbody>
</table>

Adapted from WFH Website
Challenges in the Treatment of Transfusion-transmitted Infections

**Hepatitis and HIV Markers in Haemophilia**

<table>
<thead>
<tr>
<th>Marker</th>
<th>No. tested / Total Tested</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV IgG</td>
<td>18 / 81</td>
<td>22</td>
</tr>
<tr>
<td>HBs Ag</td>
<td>5 / 130</td>
<td>4</td>
</tr>
<tr>
<td>HCV Antibody</td>
<td>68 / 166</td>
<td>41</td>
</tr>
<tr>
<td>↑ ALT/AST in HCV+ Pts</td>
<td>29 / 65</td>
<td>45</td>
</tr>
<tr>
<td>HIV antibody</td>
<td>0 / 160</td>
<td>0</td>
</tr>
</tbody>
</table>
Summary of Hepatitis C Treatment

- 10 complete responses
  [genotypes 1, 1a(3pts), 1b(2pts), 1a 1b, 2b, 3a(2pts)]
- 4 responses but relapse
  [genotypes 1b, 1b 4a, 3, 3a]
- 2 failed treatment
  [genotypes 1b]
- 1 did not complete treatment
  [genotype 3,4]
- 1 still on treatment
  [genotype 1a]
ANCILLARY CARE & PSYCHOSOCIAL SUPPORT

Haemophilia Alert Card: To be carried with patients all the time

Vaccination: Vaccinated against HBV & HAV

Schooling: School staff should be informed of child’s disease, minimise contact sports

Dental Care: Dedicated dental surgeon

Physiotherapy: Provide facility and dedicated physiotherapist

Genetic Counselling: Provide risk assessment for subsequent pregnancies.

Social and Financial Support: Social workers & Haemophilia Society
RESEARCH PUBLICATIONS

Genetic research


Clinical Research


9. MUSFIH (Musculoskeletal Function in Haemophilia in Developing Countries) Multicentre Study.

GENE THERAPY

Haemophilia as a unique model
Haemophilia Gene Therapy

Viral Gene Transfer
- Retrovirus
- Adenovirus
- Adeno-associated virus

Cell-based Gene Transfer
- Embryonic stem cells
- Adult stem cells
- iPS cells

Mutation Repair
- Zinc finger nucleases
- TALENs
- Crisp nuclease system

Non-viral Gene Transfer
- Hydrodynamic delivery
- Oral chitosan nanoparticles
- Targeted nanoparticle
FUTURE of Severe Haemophilia A Therapy (2015-2020)

- Plasma-derived FVIII
- Recombinant FVIII
- Recombinant FVIII + Recombinant vWF

- FVIII Conjugates e.g. PEG
- Novel Intrinsic Tenase
- FVIII Gene Transfer
- Modified FVIII e.g. fusion proteins, bispecific FVIII antibody mimetic

- Novel Adjunctive Therapies e.g. Antifibrinolysis, TFPI/PC/AT Inhibition
Haemophilia is a **Lifelong** Journey

Adapted from WFH Website
Thank You !