Haemophilia Care: Past, present and future

Dr Paula Bolton-Maggs
Executive Committee WFH
Consultant Haematologist
Manchester UK
Haemophilia – described in ancient texts

• For it is taught: if she circumcised her first child and he died (as a result of bleeding from the operation), and a second one also died, she must not circumcise her third child.

  – 4th century Rabbinic writings

Babylonian Talmud, 4th century
Yevamoth 64b
DIED]—In Frederick county (Virginia) Mr. Isaac Zoll, aged 19. His death was occasioned by a slight cut in one of his feet, with an ax. From the time of his receiving the wound, till he expired, no method could be devised to stop the bleeding: if the wound was bound up, the blood gushed out at his mouth or nostrils.—Five brothers to the above person have bled to death, at different periods, from the following accidents: One received a prick with a thorn—another, a scratch with a comb—a third, a prick with a needle—a fourth bruised his cheek against a stove—and the fifth received a cut in one of his thumbs. The father of the above persons has had two wives, and by each, several children; those who died in this singular manner were all of the first wife.—At Charleston,

Salem, Massachusetts Gazette, 1796
6 generations, 172 years, 20 haemophilic males
Later traced over 400yrs and 13 generations;
originating from UK in 1630

First pedigree of haemophilia published by Hay in 1813 in USA
Haemophilia - Past

- 1893 Wright: blood clotting time is prolonged
- 1911 Addis: addition of normal blood could correct the abnormal clotting
- 1840 Lane had described benefit of blood transfusion
- 1923 Feissly demonstrated superiority of plasma
- 1947 Pavlovsky observed that blood from one haemophiliac could correct the defect in another
- 1952 Biggs confirmed two types of haemophilia – report of Mr. Christmas
- 1950s Unravelling the coagulation pathways - several
Causes of death recorded for haemophilia by Carrol Birch, 1937 (98 cases)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No of cases</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operation</strong></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Circumcision</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lanced haematoma</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Trivial injuries</strong></td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Cut lip, bitten tongue, injuries to</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>finger, scalp etc.</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Internal bleeding</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lung haemorrhage</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Birth trauma and umbilical bleeding</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Only 6 patients survived to age 40 yrs
Haemophilia diagnosis

- ‘the number of cases in a given country depends upon the previous education of the medical men and the interest which they take in the disease’
  - Legg 1872
# Milestones in Haemophilia

<table>
<thead>
<tr>
<th>Time</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950s</td>
<td>Mainstay of treatment is FFP which often required stay in hospital&lt;br&gt;National haemophilia register established in UK under MRC&lt;br&gt;Haemophilia Society started</td>
</tr>
<tr>
<td>1964</td>
<td>Judith Pool discovers how to make cryoprecipitate for the treatment of haemophilia A</td>
</tr>
<tr>
<td>1968</td>
<td>Rosemary Biggs holds a tea party and the UKHCDO is started</td>
</tr>
</tbody>
</table>
History of haemophilia

- FFP was the mainstay of treatment until cryo was introduced in 1965
- The volumes required caused heart failure
  - Up to 1 litre twice a day for adults for 4-8 d
- Allergic reactions could be life-threatening
Historical recollections

• ‘My first patient with severe haemophilia had been to hospital 27 times and had seen 17 different doctors before he was 5 yrs old’ Peter Jones

• ‘A teenage haemophiliac had a tooth extracted and I held a swab to the socket intermittently for 18 days’ Stuart Douglas
## Milestones in Haemophilia

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<tr>
<td>1970s</td>
<td>Development and availability of concentrates allowed home treatment programmes. Establishment of haemophilia comprehensive care centres in many countries</td>
</tr>
</tbody>
</table>
| 1982-1984 | Sequencing of FIX gene  
Sequencing of FVIII gene                                                                                           |
| 1980s  | HIV and hepatitis viruses emerge as a major problem  
Heat treatment introduced  
Screening methods for these viruses in blood donors                                                        |
| 1990s  | Introduction of genetically engineered products                                                                                 |
Robert Massie – the patient perspective

• ‘When I was 12, two things happened which had an extraordinary impact.

• One was that in 1968, I was taught to self-infuse.

• Secondly, the factor VIII concentrates began to appear. These made an enormous difference because not only were they much more powerful, but the key piece was that they could be kept cool rather than frozen. That opened up an absolutely enormous vista for me to do things on my own because I could take my bottles of factor with me. Eventually they could be kept at room temperature..I could literally pack a back pack and go. I was able to give myself shots on camping trips or in the bathroom of a 747. Just at the moment of adolescence, when your life is expanding anyway, my ability to manage haemophilia improved in a way that allowed me this freedom.’

_from ‘The Gift of experience’, a collection of oral histories_
Haemophilia – the present

• In wealthy countries, good quality of treatment, nearly normal life
  – Recombinant products
  – Prophylaxis
  – No bar to surgery
  – Normal employment prospects and lifestyle
• In many countries, no or inadequate treatment
Prophylaxis for children

- Recommended as best therapy by
  - WHO 1994
  - UKHCDO 1994
  - USA National Hemophilia Foundation 1994
  - Canadian Hemophilia Society 1993
- Where it is not feasible, intensive ‘on demand’ therapy should be given.
Patterns of care in Western European Centres (PedNet group)

*Fig. 1. Boys treated and non-treated in Europe*

(Chambost and Ljung for PedNet, Haemophilia 2005: 11; 92-99)
Prophylaxis – when to stop?

• Study from van Creveld klinik

• 11/49 patients who stopped in early adult life
  – Started prophylaxis later
  – At a lower dose
  – Low bleed frequency
  – Joint scores no worse than those who continued

• Probably a milder phenotype
Surgery in Haemophilia

• Any surgical procedure can be performed in haemophilia
• There has been no attempt to evaluate the optimal dose to achieve haemostasis
• There is a complete lack of uniformity in practice

(Srivastava 2004)
Variable recommendations for treatment
Major surgery in Haemophilia A

<table>
<thead>
<tr>
<th>Desired level</th>
<th>Dose IU/kg</th>
<th>Duration (days)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-100</td>
<td>40-50</td>
<td>Not stated</td>
<td>Rizza 1981</td>
</tr>
<tr>
<td>80-100</td>
<td>40-50</td>
<td>10-14</td>
<td>Lusher 1999</td>
</tr>
<tr>
<td>80-100</td>
<td>40-50</td>
<td>12</td>
<td>Rickard 1995</td>
</tr>
<tr>
<td>50-150</td>
<td>50-60</td>
<td>Up to 17</td>
<td>Nilsson 1994</td>
</tr>
<tr>
<td>50-100</td>
<td>30-50</td>
<td>Until healing</td>
<td>Escobar 2003</td>
</tr>
</tbody>
</table>
### Lower doses for major surgery?

<table>
<thead>
<tr>
<th>Time</th>
<th>Desired level of FVIII C (%)</th>
<th>Desired level of FIX C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative</td>
<td>80-100</td>
<td>60-80</td>
</tr>
<tr>
<td>Days 1-3</td>
<td>20-40</td>
<td>15-30</td>
</tr>
<tr>
<td>Days 4+</td>
<td>15-30</td>
<td>10-20</td>
</tr>
</tbody>
</table>

18 patients with severe haemophilia, 20 surgical procedures; 1 bled d11 due to surgical cause. Duration 8-16d. Trough levels about 35%, lowest 11% with no bleeding.

• Guidelines (Rickard 1995) would lead to use of 50,000-80,000 units FVIII per patient
• This study used 12,000 to 20,000 units per patient
Inhibitor management

Great strides have been made in inhibitor therapy in the past two decades:-

- At least 80% of inhibitors can be eliminated by immune tolerance
- Bleeding can be treated far more effectively than before (FEIBA and rVIIa)
- Death rate has normalised.
- Morbidity and quality of life is almost as good as non-inhibitor pts and comparable to other chronic disease groups.
- This has been achieved at great financial cost. A small number of inhibitor patients are enormously expensive.
BUT Problems with haemophilia care in developing countries

- Inadequate knowledge
  - Education is essential
- Lack of laboratory diagnostic facilities
- Inadequate supply of affordable safe factor
What is the WFH?

- International non-profit organization founded 1963
- World Health Organization (WHO) recognition in 1969
- 113 National Member Hemophilia Organizations
- Extensive network of lay & medical volunteers
- Headquarters in Montreal, Canada (26 staff)
- Elected Executive Committee (15 members)
Today’s Reality

- 70% not diagnosed
- 75% not treated
- Many will die young or grow-up severely disabled
Our Mission

The World Federation of Hemophilia improves and sustains care for people with inherited bleeding disorders around the world.
45 Years - 2008

Accredited WFH National Member Organizations
- Americas
- Eastern Mediterranean and Africa
- South-East Asia and Western Pacific
- Europe
Treatment for all

A Vision for Improvement
The Vision

Treatment for All

• It means…
  – safe, effective treatment products are available for all people with inherited bleeding disorders.
  – proper diagnosis, management, & care by a multidisciplinary team of trained specialists.
  – expanding services beyond haemophilia, to those with von Willebrand disease, rare factor deficiencies & inherited platelet disorders.
Fewer than 10% of children with severe haemophilia attend school regularly. Only about 20% of adults are gainfully employed, leading to breakdown of the family.

Alok Srivastava
Severe haemophilia A aged 15 years from Libya
Inadequate treatment over several years

- Fixed flexion deformity
- Severe muscle wasting
- Swollen painful joints

Confined to a wheelchair, cannot walk
Cannot go to school
What future?
What is the future for this young man?

- Too late
- His joints cannot be rescued
- He will remain very disabled
- Unable to complete his education and poor prospects of long term employment
- Poor quality of life; dependent upon family

This outcome could have been prevented by adequate treatment
Leading a normal life with haemophilia

Social integration

Full education
Normal job prospects
Fully contributing member of the workforce
Reasons for Inadequate care

• Haemophilia not a government priority
• Inadequate infrastructure and diagnosis
• Inadequate education and training
• Poorly developed blood transfusion service
• High cost of replacement therapy

(Brian O’Mahony, Past President, WFH)
Haemophilia - global

- Survival is enhanced by network of treatment centres
- Survival is enhanced by use of replacement therapy
- Optimum survival is associated with replacement therapy = or greater than 1 unit per capita
WFH Global Survey 1999 – Relationship of Economic capacity and No of Adult Patients:

Small expenditure for haemophilia with input of expertise and training can make a significant difference, even with limited funding – a five-fold increase in survival into adulthood.
Russia – Increase in Factor VIII IU Per Capita

Haemophilia – new problems for wealthy countries

- New generation of young men with haemophilia who don't know what a bleed is
- How ‘normal’ should life be?
  - Sports restrictions?
- Transition of care in adolescence
- Prophylaxis – at birth? When should it stop?
- New problems to manage in old age
- Inhibitor management
  - Prevention
  - Treatment
Haemophilia and bleeding disorders in the under-developed countries

• Availability of reliable diagnosis
• Availability of treatment products
• Low priority in comparison with other medical needs
• High importance of genetic diagnosis and counselling because of the more severe clinical problems faced with inadequate treatment
• Cultural issues
# Strategies to Improve Clotting Factors

## Higher production
- **Increase secretion**
  - FVIII: A1 mutation (F309S)
  - FVIII: B domain variants (226aa/N6)

## Higher potency
- **Higher specific activity**
  - FVIIa: Novo NN1731 (V158D - E296V - M298Q)
  - FVIIa: FVIIaVEAY, FVIIaDVQ
  - FVII: E113A
  - FIX: R338A, Y1A, other muteins

- **Improved activation**
  - FVIII: (FVIII/HCII hybrid)

- **Increased membrane affinity**
  - FVIIa: Gla-domain (Maxy-7, other muteins)

- **Improved post-translational modifications**
  - FIX: Gla, sulfation, phosphorylation, glycosyl.

## Prolonged efficacy
- **PEGylation**
  - FVIIa, FIX, FVIII: GlycoPEGylation (Novo)
  - FVIII: Site-directed PEGylation (Bayer)
  - FVII, FIX: Random PEGylation (Baxter)

- **Hyperglycosylation**
  - FVIIa: Maxy-7 (T106N - V253N) (Bayer)
  - FVIII: Polysialylation +vWF (Baxter)

- **Fusion proteins**
  - FVIIa: FVIIa-albumin (CSL Behring); FIX-Fc (Biogen Idec)

- **FIX, FVIII polymorphism screening**

- **Liposome formulation (FVIIa, FVIII)**

- **Polymer-based delivery (FIX, FVIII)**

## Resistance to inhibitors
- **Protein sequence**
  - FVIII, FIX: Change sequence to make it less immunogenic

- **Hybrid proteins**
  - FVIII: Porcine-human hybrids

- **Resistance to inactivation**
  - Stabilized protein
    - FVIII: IR8; Disulfide bond-FVIII
  - Hybrid protein
    - Porcine-human hybrids (D318G/M337R)

## Resistance to inhibitors
- **Protein sequence**
  - FVIII, FIX: Change sequence to make it less immunogenic

- **Hybrid proteins**
  - FVIII: Porcine-human hybrids

- **Assess risks of immunogenicity, thrombogenicity**
Hope to see you there