World Haemophilia Day
19 April 2017, Straßbourg

Wildbad-Kreuth Initiative I - IV
EDQM Recommendations

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HAEMOSTASIS AND HAEMOPHILIA

60 YEARS ANNIVERSARY

1938  K. BRINKHOUS: FACTOR VIII
1952  R. BIGGS: HAEMOPHILIA B / CHRISTMAS DISEASE

R. MARX: ACC 76  1. COUMARIN ANTIDOT (PROTHROMBINCONCENTRAT) TO TREAT COUMARINBLEEDINGS!

1953  NOBELPRICE: CITRIC ACID CYCLE / COENZYM ME A LITERATURE: WINSTON CHURCHILL

1954  FIRST FACTOR VIII- CONCENTRATE /CRYOPRECIPITAT
1958  I.M. NILSSON: PROPYLACTIC TREATMENT

EARLY 1950: FOUNDATION OF NATIONAL SOCIETIES OF HAEMOPHILIA – UK, CANADA, GERMANY A.O.
50 yrs ago still only a small percentage of haemophilia pts. grew older than 40yrs

Marx, Prognose der Hämophilien und soziale Probleme, 1968

<table>
<thead>
<tr>
<th>Zeitpunkt</th>
<th>Autor</th>
<th>Prozentsatz der 40 und mehr Jahre alten Personen (abgerundet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1937</td>
<td>Birch (zit. nach Hecht) (schwere Hämophilie allein ?)</td>
<td>7%</td>
</tr>
<tr>
<td>1961</td>
<td>Deutsch</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>a) schwere Fälle (42)</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>b) mittlere und milde Fälle (60)</td>
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<tr>
<td>1965</td>
<td>Ahlberg</td>
<td>18%</td>
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<tr>
<td></td>
<td>Schwere, mittlere und milde Fälle zusammen (soweit vom Autor selbst untersucht) (157)</td>
<td></td>
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<tr>
<td>1968</td>
<td>Marx</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>a) schwere Fälle (92) – (1961–1968)</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>b) mittlere und milde Fälle (68) (1961–1968)</td>
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<tr>
<td></td>
<td>Deutsch – Ahlberg – Marx</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>zusammen – alle Hämophilie-Typen – (419 casus)</td>
<td></td>
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</tbody>
</table>
Challenges in Haemophilia 1953 and 2013

Triple „V“ der Hämophilie
- Verbluten
- Verkrüppeln
- Verarmen

R. Marx 1953

Question of Triple „A“
- Availability
- Access
- Allocation

2013
From Self-Sufficiency to Optimal Use of Blood and Blood Products in Europe – Initiatives from 1989 until 2009

1989
Self-Sufficiency in the EC

1994
EC Communication 1994:
Development and use of quality-assessment criteria and good practices regarding the collection, processing and transfusion of blood and blood products and patient follow-up procedures’ "encouragement of health professionals to make optimal use of blood and blood products’

1996
1996 Adare, Ireland:
Blood safety and self-sufficiency is influenced by "optimal use of these products by treating physicians taking fully into account the very special nature of their source".

1998
Vienna 1998:
The distribution and transfusion of blood components are among the final links in the blood transfusion chain. They are concerned with both the maintenance of the quality of blood components themselves and the quality of the service in delivering and using them.”

1999
1999 Wildbad Kreuth, Germany:: Rec. No 99
•...transfusion safety should be prioritised on the basis of achievable safety gains.
• Optimising blood transfusion practices ...in terms of health gain and cost benefit than additional testing strategies.

2007
The EU optimal use project 2007:
The aim of this project is to encourage the optimal use of blood components across Europe through sharing of information and best practice for the benefit of patients voluntary unpaid donation

2009
European Symposium on „Optimal Clinical Use of Blood Components”
April 24th – 25th 2009
Wildbad Kreuth, Germany
Discussion of future challenges

OPTIMAL USE IS TO AVOID\textsuperscript{1} ...

- Overuse
- Underuse
- Inappropriate use

OPTIMAL USE IN HAEMOPHILIA CARE REQUIRES\textsuperscript{2} ...

... administering the right quantity of the right blood product in the right way at the right time to the right patient, and appropriate documentation of both the process and the outcome.

\textsuperscript{1}Advisory Council on the Assessment of Developments in the Health Care System: Report Appropriateness and Efficiency 2000/2001, Addendum

\textsuperscript{2}Wildbad Kreuth Initiative: Conclusions and Recommendations No 71
Optimal Use of Blood and Blood Products in Europe Wildbad Kreuth Initiatives (WBK) 1999-2016

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>1999</td>
<td>Coagulation Factor Concentrates (FVIII and FIX)</td>
</tr>
<tr>
<td>2009</td>
<td>Red Blood Cells, Platelet Concentrates, Albumin, Fresh Frozen Plasma</td>
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<tr>
<td>2013</td>
<td>Immunoglobulines</td>
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<td>2016</td>
<td>Platelets</td>
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Recommendations
Publications
Recommendations

• To optimize the organization of haemophilia care nationally, it is recommended that a formal body be established in each country to include the relevant clinicians, national haemophilia patient organisation, health ministry, paying authority and (if appropriate) regulatory authorities.

• The minimum factor VIII consumption level in a country should be 3 I.U. per capita.

• Decisions on whether to adopt a new product should not be based solely on cost.

• Prophylaxis for children with severe haemophilia is already recognized as the optimum therapy. Ongoing prophylaxis for individual adults should also be provided when required based on clinical decision making by the clinician in consultation with the patient.

• Children with inhibitors who have failed, or who are not suitable for, immune tolerance therapy (ITI) should be offered prophylaxis with bypassing agents.

• Single factor concentrates should be used as therapy wherever possible in patients with rare bleeding disorders.

• Orphan drug designation for a factor concentrate should not be used to hinder the development, licencing and marketing of other products for the same condition which have demonstrably different protein modification or enhancement.
Principles

1. To optimise the organisation of haemophilia care, a system should be established in each member State to allow the implementation of a multidisciplinary approach for the treatment and care of patients (for example by setting up an advisory body including representatives of the relevant clinicians, national haemophilia bodies, patients’ organisations, the health ministry, the paying authority, blood establishments and the regulatory authorities or by setting up centres of excellence);

2. In each member State, the coagulation factor VIII utilisation level should be at least 3 International Units (I.U.) per capita;

3. Decisions on whether to use a new or an alternative product should be based on evidence of safety and effectiveness and not solely on cost;

4. The evidence of the effectiveness of different treatment regimes should be strengthened. Prophylaxis is currently recognised as the optimum therapy for children with severe haemophilia. Ongoing prophylaxis for adults should be provided, when required based on a clinical decision by the clinician in consultation with the patient;

5. Prophylactic treatment with bypassing agents should be offered to haemophiliac children who have developed inhibitors and in whom immune tolerance induction therapy has failed or was unsuitable;

6. Single coagulation factor concentrates should be used as therapy wherever possible in patients with rare bleeding disorders.
Rationale Kreuth IV: Open questions on the use of coagulation factor concentrates

- Translation of earlier WBK III?
- Best practices in Europe:
  - Prophylaxis in children & adults?
  - Treatment of elderly haemophilia patients?
  - Issues with ITI?
  - Surgery?
- New therapy approaches (e.g. patient tailored / pharmacokinetic, low dose prophylaxis, gene therapy)?
- Access to innovative factor concentrates?
  - Regulatory aspects/requirements
  - HTA aspects / requirements
- How to advance tools for therapy evaluation (e.g. registries)?
What is the rationale for a number IV WBK initiative with regard to Clotting Factors?

1. Clotting factors

- What are the clinical relevance and additional benefit of innovative coagulation factor concentrates?
- How can the results regarding the development of inhibitors with plasma-derived or recombinant clotting factors be seen in clinical practice?
- How is the progress in the implementation of the WBK III recommendations (resolution CM/Res (2015)3 on principles concerning haemophilia therapies)?
- What are relevant points from the patient perspective?
- How is the development of cost with clotting factors?
Haemophilia Care in Europe

Priority: Supply of factor concentrates - for all, not only in Europe – Best practice in haemophilia care

The socio-economic reality and haemophilia treatment varies in the EU & other countries of Europe.

Intervention
1. Treatment of Life Threatening Bleed
2. Treatment of Non-Life Threatening Bleed
3. Orthopedic Operations
4. Inhibitors Against Factor VIII/IX
5. Social Integration and Prophylactic Substitution
6. Life Style
**CHALLENGES:**

**YESTERDAY – TODAY – TOMORROW**

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Yesterday</th>
<th>Today</th>
<th>Tomorrow</th>
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<tr>
<td>Therapy options</td>
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<td>Risk of infection</td>
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<td>Development of inhibitors</td>
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<td>Other adverse events, innovative therapies</td>
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<tr>
<td>Prophylactic substitution - children</td>
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<tr>
<td>Prophylactic substitution - adults</td>
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<tr>
<td>Social integration</td>
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<td>Quality of life</td>
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<td></td>
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<td>Supply shortages</td>
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<td>Registries</td>
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<tr>
<td>Access to innovative therapies</td>
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<td>Compliance, adherence</td>
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<td>Benefit assessment, outcome measurement</td>
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<td>Financing</td>
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<tr>
<td>Specified methodological standards</td>
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*Karin Berger, Workstream „Outcomes“, GTH*
SURVEY BY THE BLUTERBETREUUNG BAYERN E.V. (BBB)
YOUR WISHES AS A PATIENT WITH HEMOPHILIA

- **Aim:** evaluation of unmet medical needs of patients with hemophilia (PWH) in Bavaria from a patient perspective

- **Questionnaire** of 45 items regarding
  1. Demographics
  2. Therapy, worries related to hemophilia, satisfaction with medical care
  3. Wishes related to extra service and information offers, suggestions how to improve hemophilia care

- **Response rate 51.4%**
### 6. Medical care

<table>
<thead>
<tr>
<th></th>
<th>that's right</th>
<th>that's rather right</th>
<th>that's rather not right</th>
<th>that's wrong</th>
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</thead>
<tbody>
<tr>
<td>1. I am satisfied with the quality of health care</td>
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<td>2. I have confidence in the physicians and the treatment</td>
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<td>3. I am satisfied with the availability of a physician in charge</td>
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<tr>
<td>4. Our problems with hemophilia are taken seriously</td>
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### 9. What would you like to be informed on

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<thead>
<tr>
<th></th>
<th>yes</th>
<th>no</th>
<th>perhaps</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. On general treatment methods / possibilities</td>
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<td>2. On the current state of science</td>
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<td>3. On topics with regard to social legislation like e.g. disadvantageous balancing</td>
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<tr>
<td>4. On practical everyday helps for the life with hemophilia</td>
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<tr>
<td>5. On activities for patients with hemophilia</td>
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</tbody>
</table>
OFFERS OF THE BBB FOR PSYCHOSOCIAL SUPPORT SEEM TO BE HELPFUL AND NEEDED IN ADDITION TO THE MEDICAL CARE

- **Results**
  - Substitution therapy was mostly uncomplicated
  - Satisfaction with medical care was high
  - „Chronic pain due to hemophilia“ increases in patients >24 years old
  - Overall, 80-100% of patients from all age groups were interested to be informed on the current state of science

- **Conclusions**
  - The survey confirmed the high level of German health care for PWH
  - Most patients wished more information by their treating physicians
  - Worries of elderly PWH and chronic pain should be addressed
  - Offers of the BBB seem to be helpful and needed in all age groups