Barriers to access in the developing (and developed) world

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Montreal – October 22-23, 2015
I will address these issues

• Realities of provision
• Problems of safety
• The burden of EBM in haemophilia
• The politics of containment
Barriers to Access for Haemophilia

- Money
- Money
- Money
- ...........

- HTCs
- CFCs – pd
- CFCs - recombinant
- General care
Average global factor VIII use per capita based on World Bank rankings
A question of Priorities

Global military expenditures as percentage of GDP, 2006

- Saudi Arabia – 8.5%
- Israel – 8%
- Syria – 5.1%
- Iran – 4.6%
- USA – 4%
- Russia* – 3.6%
- Pakistan – 3.2%
- Turkey – 2.0%
- India – 2.7%
- Egypt – 2.7%
- UK – 2.6%
- South Korea – 2.5%
- France – 2.4%
- China* – 2.1%
- Italy – 1.8%
- Germany – 1.3%
- Canada – 1.2%
- Venezuela – 1.2%
- Japan – 1%
Global distribution of total reported cases of haemophilia A
Per capita FVIII consumption and patient numbers in 2011
India as a case study

There are many others
Observed (calculated at 0.9 per 1,00,000) and estimated (calculated at 4 per 1,00,000 population) prevalence of haemophilia A for states and UT of India.
Blood collection in India
Problem 2 - Insufficiency

- Current collection 10 million units/year
- Aim to increase to 12.5 million units/year – 1% of population
- Is recovered plasma an option?
Some numbers

- India – Population 1.25 billion (2013)
- Estimated prevalence of haemophilia A 125,000
- FVIII to reach 2 IU/Capita (vastly inadequate) = 2.5 billion IU
- This will require extraction from 12,500,000 litres of plasma
- If a 90% whole blood separation is assumed, this will need ca 70 million blood donations
# The consequences – Inadequacy

**Treatment decisions and usage of clotting factor concentrate by a cohort of Indian haemophilia patients**

<table>
<thead>
<tr>
<th></th>
<th>Severe ((n = 18))</th>
<th>Moderate ((n = 6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of haemorrhagic episodes</td>
<td>113</td>
<td>92</td>
</tr>
<tr>
<td>Number of bleeds not treated</td>
<td>1 (0.8)</td>
<td>1</td>
</tr>
<tr>
<td>Number of bleeds treated with</td>
<td>7 (6.19)</td>
<td>7</td>
</tr>
<tr>
<td>pain killers only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of bleeds treated with</td>
<td>38 (34)</td>
<td>33</td>
</tr>
<tr>
<td>rest, ice, elevation and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>compression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of bleeds treated with</td>
<td>28 (25)</td>
<td>22</td>
</tr>
<tr>
<td>clotting factor concentrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated amount of clotting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>factor concentrate required to</td>
<td>84280</td>
<td>74970</td>
</tr>
<tr>
<td>treat all bleeds*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount of clotting factor</td>
<td>26 650 (32)</td>
<td>23400 (31.3)</td>
</tr>
<tr>
<td>concentrate used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of school days lost</td>
<td>127/2240 (5.66)</td>
<td>103/1820 (5.65)</td>
</tr>
<tr>
<td>Number of physician contacts</td>
<td>34</td>
<td>27</td>
</tr>
</tbody>
</table>
Solutions (?)
Recovery and Good Wishes
Kenya: Health Ministry Denies Firing 140 National Transfusion Workers

The Health Ministry on Wednesday dismissed reports that it laid off 140 Kenya National Blood Transfusion Service workers.

In a statement from Mulei Muia, Head of Public Communication, the Ministry denied a report published in the People Daily today alleging that the workers’ contracts had been unprocedurally terminated and that this may lead to the eventual shutdown of the agency.

“The true position is that 139 members of staff were hired under Presidential Emergency Fund for Aids Relief Project (PEPFAR II), some since the year 2008 with the latest contracts renewed for a period of eight months from September 25, 2014. Those contracts lapsed on the 31st March 2016,” Mula said.

Muia further said that the terms of engagement for the staff were that their contracts would be renewed depending on the availability of stuff. He said KNBTS) has so far not received any funds to support staff employment and therefore the contracts cannot be renewed.

"We, therefore, would like to correct the erroneous impression created by the story that the employees’ contracts were terminated. All the staff members accepted the terms of employment in writing and appended their signatures," he added.

Muia further said that all the 24 KNBTS centres across the country are in full operation saying that over 150 government staff are still on board.
REVIEW ARTICLE

Purchasing factor concentrates in the 21st century through competitive tendering

C. R. M. HAY†
†The UK National Haemophilia Database, Manchester, UK; and †Department of Haematology, Manchester University, Manchester, UK
Solutions

Global Biopharmaceutical Manufacturing
Bioreactor utilization globally

Utilization at Top 5 Product Companies ~50%

Utilization Pushes 75% for the Rest of the Industry

Includes Roche, J&J, Amgen, Pfizer, Sanofi-Aventis
Single use and disposable technology for biopharmaceuticals
Lentiviral Vector Platform for Production of Bioengineered Recombinant Coagulation Factor VIII

H Trent Spencer, Gabriela Denning, Richard E Gautney, Boro Dropulic, Andre J Roy, Lajos Baranyi, Bagirath Gangadharan, Ernest T Parker, Pete Lollar and Christopher B Doering

Herein, we describe the development of a bioengineered fVIII product using a novel lentiviral-driven recombinant protein manufacturing platform. The combined implementation of these technologies yielded production cell lines that biosynthesize in excess of 2.5 mg/l of recombinant fVIII at the rate of 9 pg/cell/day, which is the highest level of recombinant fVIII production reported to date.
Safety is related to availability
## TTDs in haemophilics from western India
### Problem 3 - Safety

<table>
<thead>
<tr>
<th>Type of transfusion</th>
<th>No. of samples</th>
<th>HIV positive</th>
<th>HBsAg positive</th>
<th>HCV positive*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood (WB)</td>
<td>29</td>
<td>-</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Factor concentrate (FC)</td>
<td>28</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Cryoprecipitate (CP)</td>
<td>102</td>
<td>8</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Fresh frozen plasma (FFP)</td>
<td>88</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>FC + FFP</td>
<td>51</td>
<td>-</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>WB + FC + FFP + CP</td>
<td>59</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Not known</td>
<td>35</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Not transfused</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

*188 patients tested
Risk (%) that a person with haemophilia in Venezuela or U.S.A. will be exposed to HIV-contaminated blood product based on years of treatment and risk of an HIV-infected donation.

<table>
<thead>
<tr>
<th>Years of Treatment</th>
<th>Venezuela Lower (1/25700)*</th>
<th>Venezuela Mid (1/21200)*</th>
<th>Venezuela Upper (1/17500)*</th>
<th>USA Mid (1/545100)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3.4</td>
<td>4.2</td>
<td>5.0</td>
<td>0.16</td>
</tr>
<tr>
<td>10</td>
<td>6.8</td>
<td>8.1</td>
<td>9.8</td>
<td>0.33</td>
</tr>
<tr>
<td>15</td>
<td>10.0</td>
<td>12.0</td>
<td>14.3</td>
<td>0.49</td>
</tr>
<tr>
<td>20</td>
<td>13.1</td>
<td>15.6</td>
<td>18.6</td>
<td>0.66</td>
</tr>
<tr>
<td>30</td>
<td>19.0</td>
<td>22.5</td>
<td>26.6</td>
<td>0.99</td>
</tr>
<tr>
<td>40</td>
<td>24.4</td>
<td>28.8</td>
<td>33.7</td>
<td>1.3</td>
</tr>
<tr>
<td>50</td>
<td>29.5</td>
<td>34.6</td>
<td>40.2</td>
<td>1.6</td>
</tr>
<tr>
<td>60</td>
<td>34.3</td>
<td>39.9</td>
<td>46.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

“Cryo is evil”

A minipool process for solvent–detergent treatment of cryoprecipitate at blood centres using a disposable bag system

T. Burnouf,1 H. A. Goubran,2 M. Radosевич,1 M. A. Sayed,3 G. Gorgy4 & M. El-Ekiaby4

1Human Plasma Product Services, Lille, France
2Faculty of Medicine, Cairo University, Egypt
3Fayoum University, Fayoum, Egypt
4Shabrawishi Hospital Blood Bank, Giza, Egypt
The burden of “EBM”
Selection criteria
Eligible trials included randomised or quasi-randomised clinical trials, including controlled clinical trials comparing gene therapy (with or without standard treatment) with standard treatment (factor replacement) or other ‘curative’ treatment such as stem cell transplantation individuals with haemophilia A or B of all ages who do not have inhibitors to factor VIII or IX.

Data collection and analysis
No trials of gene therapy for haemophilia were found.

Main results
No trials of gene therapy for haemophilia were identified.

Review content assessed as up-to-date: 5 November 2014.
Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

The politics of containment

How “EBM” is used to restrict access
Progression of joint arthropathy during intensive prophylaxis

Kramer 2013 reported by Oldenburg 2015

Shock!
Horror!
Primary vs Secondary prophylaxis in children with haemophilia A and B

Survival curve analysis of outcome

Time to treatment failure

% with no major bleeds

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

0 1 2 3 4 5 6 7 8 9 10 11

Time in years

Primary
Secondary

P = 0.0049
CUMULATIVE # OF HEMARTHROSES
JOINT FAILURE INDICATED BY MRI SCORE 7-10
(OSTEOCHONDRAL DEFECTS)

N = 346 Joints
r = .36
R² = 0.13

MRI Showed Modest Correlation with # of Hemarthroses

M Manco-Johnson WFH GF 2013
Routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART)

Mean bleeds/year

On demand 28
Prophylaxis 0

Journal of Thrombosis and Haemostasis Volume 11, Issue 6, pages 1119-1127, 3 JUL 2013
<table>
<thead>
<tr>
<th></th>
<th>On-demand treatment</th>
<th>Prophylactic treatment</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Months 1–6 ((n = 20))</td>
<td>Months 7–13 ((n = 19))</td>
<td></td>
</tr>
<tr>
<td>Joint bleeds</td>
<td>15.0 (11–26)</td>
<td>0 (0–3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All bleeds</td>
<td>20.5 (14–37)</td>
<td>0 (0–3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Spontaneous bleeds</td>
<td>13.5 (7–29)</td>
<td>0 (0–1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Trauma bleeds</td>
<td>2.5 (0–9)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
## The World according to IQWIG

### Evidence for benefit of PRO vs OD in adolescents and adults

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>State of health</th>
<th>Pain</th>
<th>Joint function</th>
<th>Severe Bleeding</th>
<th>Life-threatening Bleeding</th>
<th>Health-related quality of life</th>
<th>Serious adverse events</th>
<th>Treatment discontinuation due to adverse events</th>
<th>Inhibitor development (all titres)</th>
<th>Inhibitor development (high responders)</th>
<th>Infections at catheter insertion site</th>
<th>Thromboembolisms</th>
<th>Catheter-related thromboses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- a: Hint of an added benefit of the test intervention only for average pain over the past 4 weeks.
- b: No evaluable data reported for the present benefit assessment.
- $\uparrow$: Indication of an added benefit or indication of lesser harm of the test intervention.
- $\downarrow$: Hint of an added benefit or hint of lesser harm of the test intervention.
- $\Leftarrow$: No hint of an added benefit or lesser harm of the test intervention.
- -: No data reported.
## The World according to IQWIG

### Evidence for benefit of PRO vs OD in children

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>State of health</th>
<th>Pain</th>
<th>Joint function</th>
<th>Severe bleeding</th>
<th>Life-threatening bleeding</th>
<th>Health-related quality of life</th>
<th>Serious adverse events</th>
<th>Treatment discontinuation due to adverse events</th>
<th>Inhibitor development (all titres)</th>
<th>Inhibitor development (high responders)</th>
<th>Infections at the catheter insertion site</th>
<th>Thromboembolism</th>
<th>Catheter-related thromboses</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-</td>
<td>-</td>
<td>b</td>
<td>a</td>
<td>b</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Data reported not interpretable due to several aspects that indicate a high risk of bias overall.
- No evaluable data reported.

ʁ: Hint of an added benefit or hint of lesser harm of the test intervention.
⇔: No hint of an added benefit or lesser harm of the test intervention
⁻: No data reported.
Barriers to access - Everywhere

- For haemophilia to be treated, health care has to be a societal priority
- Access is mostly a function of economics
- Treatment possibilities in the large, underdeveloped countries hinge on the development of blood systems and biopharmaceutics
- Enhancing supply will enhance safety
- Paradigms such as EBM and HTA, applied to put on the brakes in the rich countries, threaten to stop the motor from starting in the poor world.
After every storm the sun will smile; for every problem there is a solution, and the soul's indefeasible duty is to be of good cheer.

William R Alger
THANK YOU