Plasma Quality: How does it matter?

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Blood as Source of Life-Saving Medicines

For state-of-the-art medicine performance, blood transfusion and plasma products are indispensable!
Blood as Source of Life-Saving Medicines

Blood for transfusion
- Whole blood collected into containers, anticoagulant to prevent clotting, cold chain
- Blood components, obtained from whole blood by separation (centrifuge or apheresis):
  - Red blood cells: Oxygen transport
  - Platelets: Hemostasis (preventing bleeding)
- **Plasma**: clotting factors, immunoglobulins etc.
- Cryoprecipitate

Plasma derivatives
- **Plasma „fractionation“,** further purification of plasma proteins, e.g.
  - Clotting factors, e.g. Factor VIII for treatment of hemophilia A
  - Immunoglobulins, proteins specialized to bind e.g. pathogens or toxins, rendering them innoxious
  - Albumin, involved in the regulation of body fluids, used for resuscitation

Blood-derived medicinal products for the treatment of haemophilia and immune diseases are included in the WHO Model List of Essential Medicines
Clotting Factors: Haemophilia

- Haemophilia is a severe, inherited bleeding disorder
- Haemophilia patients are condemned to pain, disablement and early death, unless they receive effective treatment
- With the availability of clotting factor products, severe bleeds and mutilating outcome (below pictures from the 1960ies) can be avoided.
**Immunoglobulins**

- **Normal human immunoglobulins**
  - Natural set of antibodies as found in a given plasma donor population; pattern depending on epidemiological situation
  - Main indications: inborn lack of immunoglobulins, certain types of acquired immunodeficiency or immune dysfunctions
  - Repeated or chronic application (i.v., i.m., or s.c.)

- **Specific immunoglobulins**
  - Anti-D immunoglobulin for prophylaxis in rhesus incompatible mothers
  - Specific immunoglobulins for passive immunization against infections (e.g. hepatitis), or toxins (e.g. Tetanus)
  - Single or short term application
Plasma for Fractionation

- Obtained by separation of plasma from blood cells
  - donated whole blood (centrifugation of blood bags); “recovered plasma”
  - using apheresis (blood flows through a machine, plasma is collected, blood cells flow back into the donor); “source plasma”

- Anticoagulation to preserve clotting factors

- Freezing
  - the faster deep temperature (e.g. -25°C) is reached, the better the preservation of proteins; marker coagulation factor VIII
  - store frozen (e.g. at -20 °C) until fractionation; uninterrupted cold chain, maintained also during shipment
The HIV shock

- Plasma derivatives became available in the second half of 20th century. In the early enthusiasm about fundamental improvements of life expectancy and quality of life, e.g. of hemophilia patients, little attention was paid to virus transmission.

- The massive transmission of HIV and other viruses by blood products in the early 1980ies was one of the worst disasters of modern medicine, and caused dramatic reactions of industry and regulators to increase safety.

- The lesson learned from this is that quality and safety of blood products need to be ensured by specific precautions, and reinforced by regulatory control.
Virus Safety: What is the problem?

- Certain dangerous viruses (e.g. HIV, hepatitis B and C virus) can circulate in the blood of a donor feeling healthy:
  - in the early phase (incubation period): the donor still feels healthy; “diagnostic window phase”
  - after mild, unnoticed disease: the donor feels healthy again; “chronic persistence”
- In case a donation of such a donor with undetected infection would be used, and no precautions were in place, the virus would contaminate blood products, and infect potentially many patients
Assuring Quality and Safety

- There are powerful measures to prevent the transmission of viruses
  - Establishing a healthy donor population
    - recruit informed, motivated, reliable donors
    - discourage high-risk population
  - Testing blood for virus markers
    - test the raw material (plasma donations and pools), not final products
  - Manufacture of plasma derivatives including steps for virus elimination

- All three above points are essential. For instance, virus elimination steps might fail, if highly contaminated plasma would be used as starting material
WHO Recommendations for the production, control and regulation of plasma for fractionation *

„Human plasma is a source of important medicinal products which are obtained by a combination of large-scale processing steps known as “fractionation”. It is important that these products have an appropriate quality and safety profile.

Recognizing the importance of the provision of safe blood, blood components and plasma derivatives, the 58th World Health Assembly in 2005 (WHA Resolution 58.13) expressed its support for “the full implementation of well-organized, nationally coordinated and sustainable blood programs with appropriate regulatory systems” and stressed the role of “voluntary, non-remunerated blood donors from low-risk populations”.

The quality and safety of biologicals depends on careful choice and control of raw materials, and manufacture following good practice (GMP). It is not possible to “test safety into the final products”.

The origin of donations and their testing history needs to be documented.

Transfusion of blood products is a process, spanning over the whole chain from donor to patient. An important requirement is traceability, to enable corrective measures:
- from every product batch to the involved donations, and vice versa
- from patient to used batches

The compliance needs to be reinforced by regulatory control, e.g. official inspections.
Guidance and Advice

- WHO guidance documents and fact sheets (*), e.g.
  - Recommendations for the production, control and regulation of plasma for fractionation;

- WHO Blood Regulators Network (BRN), established 2006
  - Consistent with recommendations of the ECBS, the WHO BRN will address issues related to advancing technical expertise in the areas of blood, blood products and associated drugs and medical devices including in vitro diagnostics (IVDs).
  - Its Objectives are to: (a) identify issues; (b) share expertise and information; (c) promote convergence of regulatory policy and (d) propose solutions to specific issues, especially emerging public health challenges

* [www.who.int/bloodproducts](http://www.who.int/bloodproducts)
Testing for Virus Markers

- "Serological" Tests, which detect antibodies formed against the virus, or antigens (proteins coded by the virus), e.g.
  - Hepatitis B surface antigen (HBsAg)
  - Antibodies against Hepatitis C Virus (Anti-HCV)
  - Antibodies against HIV (Anti-HIV 1+2)

State-of-the-art Serological tests are a powerful screening tool with high sensitivity and specificity

- In addition, a number of infected donors in the “diagnostic window” (time between infection and appearance of serological markers in the blood, can be identified by direct detection of virus genome by Nucleic Acid Amplification Tests (NAT), e.g. PCR
NAT reduces the diagnostic window period

Spontaneous reports of probable HCV transmissions by transfusions in the years 1990-2007*

The PEI mandated in Germany
NAT-testing of blood components for transfusion
for HCV (1 April 1999) and HIV (1 May 2004)

* ca. 4.5 million donations per year
Manufacturing plasma pools (1996, 2006)

11 different manufacturers, different geographic origins; analysed by Cobas S201 with TaqScreen; reactives resolved with AmpliScreen assays

<table>
<thead>
<tr>
<th>Year</th>
<th>HCV-RNA pos (%)</th>
<th>HIV-RNA pos (%)</th>
<th>HBV-DNA pos (%)</th>
<th>not-resolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>17.8% (155/873)</td>
<td>0.8% (7/873)</td>
<td>0.5% (4/873)</td>
<td>3% (26/873)</td>
</tr>
<tr>
<td>2006</td>
<td>0.3% (1/331)</td>
<td>0% (0/331)</td>
<td>0% (0/331)</td>
<td>3.6% (12/331)</td>
</tr>
</tbody>
</table>

HCV NAT in plasma pools became obligatory by revision of the PhEur Monograph “Human Plasma for Fractionation” 2001:0853
Regulation of Plasma Products in Europe

- Marketing authorisation of products
- Certification of Plasma Master Files (EMEA), as central documentation of starting plasma quality
- Continuous GMP surveillance, with official inspections covering the whole chain from plasma collection to final product
- Official Medicines Control Laboratory (OMCL) batch release for all medicinal products manufactured from pooled plasma
- Pharmacovigilance; corrective measures
- Careful observation of the state of the art; competence to impose mandatory requirements and precautions

Plasma Safety in the European Communities

- Commitment of health politicians, strong legislation, reinforcement and continuous surveillance by authorities
- Commitment of blood services and industry
- Advanced technology
  - Virus marker testing: serology, plus for plasma pools mandatory HCV NAT; NAT against further viruses (HIV, HBV, HTLV, HAV, B19) performed on a voluntary basis
  - State-of-the-art guidance (Council of Europe, EMEA)
  - State-of-the-art manufacture of plasma derivatives including virus elimination steps, with experimentally validated efficacy

→ No documented virus transmission by plasma products licensed within the European Community since > 10 years
What is the global situation?

- The global need for plasma products exceeds by far the available supply.
- Procurement of plasma in industrialized countries limited.
- Alternatives to plasma products are not sufficiently available, or even not existent.
  - Hemophilia: recombinant products are expensive; gene therapy still experimental.
  - Normal immunoglobulin should cover the wide range of antigens (e.g. pathogens) prevailing in a population; this can be achieved by pooling of domestic plasma.
  - Specific immunoglobulins can be sourced only in immunized populations.
What is the global situation?

- Science, powerful technology, as well as regulatory guidance make remarkably high plasma safety achievable.
- We have channels of international collaboration (e.g. WHO).
- However, achieving plasma of high quality and safety is very demanding.
  - commitment of all involved parties
  - human resources
  - financial expenditure
- The status of blood systems, and the degree of supply of the population with blood products of good quality and safety is apparently very different throughout the world.

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Total Population (millions)</th>
<th>HIV Prevalence (% ages 15-49 [range])</th>
<th>Health Expenditure per capita (US$)</th>
<th>Donation per 1000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>AMRO</td>
<td>38.4</td>
<td>0.6 [0.3–1.9]</td>
<td>1.067</td>
<td>19.57</td>
</tr>
<tr>
<td>Brazil</td>
<td>AMRO</td>
<td>183.9</td>
<td>0.5 [0.3–1.6]</td>
<td>597</td>
<td>16.56</td>
</tr>
<tr>
<td>USA</td>
<td>AMRO</td>
<td>295.4</td>
<td>0.6 [0.4–1.0]</td>
<td>5.711</td>
<td>47.19</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>AFRO</td>
<td>75.6</td>
<td>[0.9 – 3.5]</td>
<td>20</td>
<td>0.32</td>
</tr>
<tr>
<td>Kenya</td>
<td>AFRO</td>
<td>33.5</td>
<td>6.1 [5.2–7.0]</td>
<td>65</td>
<td>3.58</td>
</tr>
<tr>
<td>Lesotho</td>
<td>AFRO</td>
<td>1.8</td>
<td>23.2 [21.9–24.7]</td>
<td>106</td>
<td>1.67</td>
</tr>
<tr>
<td>Swaziland</td>
<td>AFRO</td>
<td>1</td>
<td>33.4 [21.2–45.3]</td>
<td>324</td>
<td>8.50</td>
</tr>
<tr>
<td>South Africa</td>
<td>AFRO</td>
<td>47.2</td>
<td>18.8 [16.8–20.7]</td>
<td>669</td>
<td>22.51</td>
</tr>
<tr>
<td>Netherlands</td>
<td>EURO</td>
<td>16.2</td>
<td>0.2 [0.1– 0.4]</td>
<td>2.987</td>
<td>39.22</td>
</tr>
<tr>
<td>Denmark</td>
<td>EURO</td>
<td>5.4</td>
<td>0.2</td>
<td>2.762</td>
<td>69.54</td>
</tr>
<tr>
<td>Egypt</td>
<td>EMRO</td>
<td>72.6</td>
<td>&lt;0.1</td>
<td>235</td>
<td>2.31</td>
</tr>
<tr>
<td>India</td>
<td>SEARO</td>
<td>1.087,10</td>
<td>0.9 [0.5 – 1.5]</td>
<td>82</td>
<td>4.07</td>
</tr>
<tr>
<td>Australia</td>
<td>WPRO</td>
<td>19.9</td>
<td>0.1</td>
<td>2.874</td>
<td>49.16</td>
</tr>
<tr>
<td>Japan</td>
<td>WPRO</td>
<td>127.9</td>
<td>&lt;0.1</td>
<td>2.244</td>
<td>29.42</td>
</tr>
</tbody>
</table>
Dilemma

Developing countries may face particular problems with establishing or enhancing their own national blood systems

- **Resources**
  - financial capacity
  - human resources: scientists, transfusion experts, regulators, trained operators
  - infrastructure

- **Donor epidemiology**
  - high prevalence of transmittable pathogens
  - new or emerging infections

⚠️ A strong and robust quality system has to be established, with limited resources
2.1 billion airline passengers are traveling each year.

- The battle against infections and the struggle for blood safety are closely interrelated!
- Infections are a global problem necessitating global collaboration!
National Blood Programs

- WHO supports the full implementation of well-organized, nationally coordinated and sustainable blood programs with appropriate regulatory systems (WHA Resolution 58.13)

- Of crucial importance is the political will of governments to build capacities and develop a blood system integrated in the country's health care, as well a financial concept including domestic and international sources

- Another key factor is the willingness of the population to donate blood or plasma, which needs information and motivation campaigns without undue inducements. WHO stressed the role of “voluntary, non-remunerated blood donors from low-risk populations” (WHA Resolution 58.13)
Essentials of a Plasma Program

- Institution (blood establishment)
  - stable management, medical supervision, trained staff
  - adequate premises and equipment: hygiene standards, technology for collection (whole blood separation, apheresis), freezing capacity
  - quality system; Good Manufacturing Practice (GMP)
  - regulatory control; inspections

- Healthy blood and/or plasma donors
  - recruitment avoiding undue inducements, motivation campaigns
  - adequate information of donors about criteria for donation
  - testing of the donors’ blood
    - safety of donors, fitness for donation (e.g. Hb, protein)
    - safety of product (infection markers)

- Strategy for use
  - e.g. building up domestic fractionation, contract fractionation
Important Considerations

- Consider the resources available
  - financial situation
  - scientific, organizational and regulatory structures
  - motivation to donate; epidemiology of infections
- Determine expected outcomes
  - prolong survival, prevent severe outcomes, maintain working capacity, improve quality of life
- Evaluate the most promising resource applications
  - screening strategy: identify relevant pathogens, choose robust serological tests, expand to NAT
In countries with a Gross National Product less than $2000, only a minority of hemophilia patients reaches an age >19 years. However, also in such countries, awareness and establishment of treatment centers improves the situation.

Example hemophilia: the resources you need depend on the outcome you would like to see; you can adopt a step-wise approach.

Interventions:
1. Treat life-threatening bleeds
2. Treat major bleeds
3. Orthopedic surgery
4. Treating inhibitors
5. Prophylactic treatment

W. Schramm, 2006; modified
Summary

- Blood can be processed into life-saving medicines
- Plasma is a precious starting material; its high quality is of crucial importance for the quality of the products manufactured thereof
- The risk of transmitting dangerous pathogens can be minimized by collecting blood or plasma from low-risk donors, testing for infection markers, and proper manufacture
- The collection of plasma for fractionation should be well organized, in adequately equipped establishments with competent supervision and trained staff, controlled by a functioning quality system and regulatory oversight
- WHO supports the full implementation of well-organized, nationally coordinated and sustainable blood programs with appropriate regulatory systems