EUROPEAN SYMPOSIUM
IV. Wildbad Kreuth Initiative - Optimal use of clotting factors and platelets
6-7 May 2016, Freising, Germany

Prof. Karl-Walter Jauch
Downtown:
1st. Hospital 1813: „Allgemeines Krankenhaus“
Between 1843 und 1929:
- Many Buildings and Institutes from the University

CAMPUS BIOMEDIZIN MARTINSRIED – GROßHADERN (AUSZÜGE)

Research Center for Molecular Biosystems
Zentrum für Neuropathologie und Prionforschung (LMU)
CSD - Centrum für Schlaganfall und Demenzforschung (KUM)
Klinikum der Universität München (KUM)

Innovation Center for Biotechnology (IZB)

Biomedical Center (LMU)
Bio Center (LMU)
Max Planck Institute of Neurobiology
Max Planck Institute of Biochemistry
KEY DATA

- 46 Clinical Departments, Institutes and Divisions
- ca. 8.000 full-time employees
- 144 Wards
- approx. 120 Professors in Medical Care
- 92 Mio. € Third-party funds

1066 Mio. € Total Revenue 2015

- 675 Mio. € Medical Care
- 205 Mio. € Public benefits
- 87 Mio. € other additional incomes

CLOTTING FACTOR CONCENTRATES, BLOOD PRODUCTS, BLOOD AND BLOOD COMPONENTS HAVE A MAJOR IMPACT ON COSTS

- Approximately 60 Mill Euro
- From 272 Mill Euro Med.Prod.
SAFETY IS AN ULTIMATE GOAL OF BLOOD PROVISION IN ROUTINE CARE

German Transfusion law regulates since 1998
- Transfusion commission
- Transfusion officer
- Transfusion representative
- Obligation of documentation

Impact on health care providers regarding organisational structure, liability, resources and costs.

COMPARED TO RED BLOOD CELLS AND FRESH FROZEN PLASMA THE ANNUAL PLATELET USAGE SEEMS TO BE ALMOST STABLE
Approx 6,500 apheresis platelets per year are produced inhouse

- Secures a stable donor pool
- Independence (costs, supply)
- High quality products: "from bench to bed"
BLOOD AND BLOOD COMPONENTS ARE ESSENTIEL FOR PATIENT CARE IN A TERTIARY HOSPITAL

Top 5 platelet users (2015)

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Haematology / Oncology</td>
<td>48</td>
</tr>
<tr>
<td>Surgery</td>
<td>11</td>
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<tr>
<td>Paediatric Clinic</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac Surgery</td>
<td>9</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>8</td>
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</tbody>
</table>

PLATELET TRANSFUSIONS IN ONCOLOGY HAEMATOLOGICAL PATIENTS

Platelet Transfusion in Routine Clinical Practice in Oncology/Hematology patients
A Prospective Non-Interventional Study

Karin Berger, Georg Wittmann, Christina Rieger, Helmut Ostermann
Medizinische Klinik and Poliklinik III, University Hospital of Munich, Germany
Department of Transfusion Medicine, Cell Therapeutics, Haemostaseology, University Hospital of Munich, Germany

- In 3 months 1,207 platelets were transfused in haem / onc patients.
- A small number of hematological patients received a substantial amount (75%) of all transfused platelet concentrates.
- Transfusion triggers in the group ≥30 platelet units transfused per patient varied widely.
OPTIMAL USE OF BLOOD AND BLOOD PRODUCTS IS NECESSARY FROM ETHICAL, MORAL AND SOCIAL ASPECTS

„Blood is an expensive, scarce resource. Unnecessary transfusion may cause a shortage of blood products for patients in real need“


VIELEN DANK FÜR IHRE AUFMERKSAMKEIT
Kreuth IV: Use of Clotting Factors and Platelets
6-7 May 2016, Freising, Germany

Welcome Address

Michael Wierer,
EDQM Council of Europe

Organising Institutions

• European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe
• Ludwig-Maximilian-University (LMU), Klinikum, Munich (Germany)
• Paul-Ehrlich-Institut (PEI), Langen (Germany)
The Council of Europe

Core values:
• human rights
• pluralist democracy
• rule of law

The EDQM
• Council of Europe Directorate
• Convention on the Elaboration of a European Pharmacopoeia (1964)
• Mission: to contribute to a basic human right: access to good quality medicines and healthcare

European Committee (Partial Agreement) on Blood transfusion (CD-P-TS)

• Main tasks according to Terms of Reference

• (i) examine questions related to human blood transfusion, notably as regards quality and safety standards and their implementation, including collection, preparation, testing, storage, distribution and appropriate use;
• (iii) propose ethical, safety and quality standards for professional practices and blood component specifications
• ...
## The Kreuth initiative

<table>
<thead>
<tr>
<th>Title</th>
<th>Topics addressed</th>
</tr>
</thead>
</table>
| **Kreuth I**  
1999 | Optimal Use of blood components and plasma derived medicinal products  
Red cells, platelets, FFP, albumin, clotting factor concentrates and haemophilia treatment |
| **Kreuth II**  
2009 | Optimal Use of blood components: quality and best practices in haemotherapy  
Red cells, platelets, FFP, albumin, clotting factor concentrates and haemophilia treatment |
| **Kreuth III**  
2014 | Optimal Use of Clotting Factors and Immunoglobulins  
Human normal immunoglobulins, clotting factors for treatment of haemophilia (VIII, IX, new) |

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## Kreuth III Proceedings

**Optimal use of clotting factors and immunoglobulins**  
The EDOM is a directive of the Council of Europe, an International organisation between legal states located in the norms of human rights. The Council of Europe pursues to create a stronger European and legal principles based on the European Convention on human rights and other human rights in the norms of human rights.
Follow-up activities to Kreuth III

- **Haemophilia treatment recommendations**
  - Research in haemophilia B – approaching the request for high evidence levels in a rare disease. Haemophilia (2015), 21, 4–20
  - Dedicated EHC meeting hosted by PEI on 16 April 2014

- **Immunodeficiencies treatment**

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Council of Europe Resolutions

Adopted by the Committee of Ministers on 15 April 2015 at the 1225th meeting of the Ministers’ Deputies

Resolution on principles concerning haemophilia therapies

Resolution on principles concerning human normal immunoglobulin therapies for immunodeficiency and other diseases
Scientific Programme Committee

<table>
<thead>
<tr>
<th>LMU</th>
<th>PEI</th>
<th>EDQM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. W. Schramm</td>
<td>Prof. R. Seitz</td>
<td>Dr. M.E. Behr-Gross</td>
</tr>
<tr>
<td>Dr. K. Berger</td>
<td>Dr. A. Hilger</td>
<td>Dr. K.H. Buchheit</td>
</tr>
<tr>
<td>PD Dr. Dorothea Stahl</td>
<td>Dr. M. Wierer</td>
<td></td>
</tr>
</tbody>
</table>

Technical Organisation

Mr. D. Stijelja-Jovanovic, Ms. E. Zachari, Mrs B. Hovanyecz (EDQM)

Kreuth IV:
Optimal Use of clotting factors and platelets

6-7 May 2016, Freising, Germany
Optimal use of blood components – rationale for Wildbad-Kreuth Initiative IV

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Blood is unique!
It is of crucial importance that the blood and blood products that are available in the European Community are used with the greatest of care and their full potential.

Available Evidence

Best practice

Quality Management

Economic Aspects

Optimal use

Blood Safety in the European Community:
WBK I (1999): recommendations/conclusions

OPTIMAL USE IS TO AVOID¹ ...

• Overuse
• Underuse
• Inappropriate use

OPTIMAL USE IN HAEMOPHILIA CARE REQUIRES² ...

... 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.

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

1999
2009
2013
2016

Coagulation Factor Concentrates (FVIII and FIX)
Red Blood Cells, Platelet Concentrates,
Albumin, Fresh Frozen Plasma
Immunoglobulines Platelets

Recommendations
Publications

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,
licensing and marketing of other products for the same condition which have demonstrably different
protein modification or enhancement.
Major health political consequence of WBK III

Resolution CM/RES(2015)3 on principles concerning haemophilia therapies

- Resolutions of the Council of the EU are used to invite a member state to take action on a specific issue for example in health.
- These types of documents only set up political commitments or positions.... *
- In each member State, the coagulation factor VIII utilisation level should be at least 3 International Units (I.U.) per capita;
- 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;
- The evidence of the effectiveness of different treatment regimes should be strengthened.
- 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; **

** [https://www.edqm.eu/sites/default/files/resolution_cm/res_2015_3_on_principles_concerning_haemophilia_therapies.pdf]

Coagulation Factor concentrates

Overall Objectives of the Workshop 2016

- Critical appraisal of status quo and identification of gaps in clinical and outcomes research in haemophilia
- Discussion of perspectives on “innovative products”
- Identification of best practice and future needs and in haemophilia care
Rationale WBK 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)?

How many coagulation factor concentrates are needed for optimal patient treatment?

Haemophilia A
- Licenced* pdFVIII 10
  rFVIII 10
- Under development** 5

Haemophilia B
- Licenced* pdVIII 9
  rFVIII 3
- Under development** 1

*Authorized products by the European Medicines Agency (EMA) plus all products available in Germany (listing of the DHG, German Haemophilia Society)
**Approximately, products to some extent already in negotiation with the EMA

Clinical relevance?
Benefits?
Cost-Effectiveness?

How to get access to optimal treatment?

Securing reimbursement for patient centered haemophilia care: major collaborative efforts are needed
Karín C. Berge; Brian M. Feldman; Joan Wasserstein; Wolfgang Schramm; Victor Blancher; and Kathlén Fülscher on behalf of the Outcome Measures Expert Working Group of the International Prophylaxis Study Group (PSG)

- Challenges for patient centred health care provision
  - HTA-Assessment
  - Comparative effectiveness research
  - Benefit assessment

- Unique challenges of haemophilia to payer’s expectations
  - Lack of evidence
  - Barriers to randomized trials
  - Endpoints in haemophilia

- Future needs
  - To combine data from different sources in the future.
  - To intensify national and international collaboration. Eventually data interoperability at a national and international level may be achieved by leveraging alliances and technical platforms for data sharing.
Uncertainties on the impact of pd vs rec factor usage on inhibitor incidence

Why „Platelets“ were readopted for WBK IV

- Since the first Wildbad Kreuth initiative only a limited number of publications refer on guideline updates, efficacy / effectiveness of platelet transfusion.
- Evidence on haemovigilance data and product differences is still low.
- Transparency on platelet usage in daily routine care is lacking
- Pathogeninactivation
- Demographic developments
Rationale WBK IV: Open questions on the use of platelets

- Variation in availability and clinical use of platelets throughout the European Community?
- How to identify patients actually needing platelets? Prophylactic platelet transfusion?
- Which platelet product is the right one for the individual patient from a clinical and economic perspective?
  - Donor profile
  - Pathogen inactivation
  - Pool vs apheresis platelet concentrates
- How do we define efficacy / effectiveness of platelet transfusions, and which methods and tools are suitable to assess the outcome?

The blood donor population and the aging patient population needing transfusions come off balance

How much blood is needed?


Van Sengvinseni (2011) 100, 10-21

Demographic Changes: The Impact for Safe Blood Supply

Andreas Greinacher*, Konstantin Ferstl*, Wolfgang Hofmann*

Transfus Med Hemother 2010;37:141-148
Contemporary representative real world data (epi data, blood usage) are required to predict future needs

Patients undergoing HSCT require a considerable amount of platelet transfusions.

2013 – 2014: increase of allogeneic HSCTs by 2.6%, autologous HSCT by 5.3%

What data is needed for comprehensive and valid projections?

What data is needed (examples)?

- Production
  - Where?
  - How much?

- Decay
  - Where?
  - How much?

- Use
  - Which patients (age, diagnosis)?
  - Which procedures?
  - How much?
  - What product

Do we have appropriate evidence so far?

- Data on production
  - Blood services

- Data on decay
  - Blood services
  - Hospitals

- Data on use
  - Patient-level data
    - Hospitals
    - Registries
Platelet production varies considerably in EU

<table>
<thead>
<tr>
<th>Country</th>
<th>Proportion of PPC / APC production number (percent)</th>
<th>Changes in total PC production</th>
<th>Changes in total PC production</th>
<th>Population-related PCs / 1 000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled PCs</td>
<td>Apheresis PCs</td>
<td>Percent</td>
<td>Percent</td>
</tr>
<tr>
<td>France</td>
<td>161 896 (53.0%)</td>
<td>143 568 (47.0%)</td>
<td>+ 1.8%</td>
<td>-0.3%</td>
</tr>
<tr>
<td>Germany</td>
<td>231 139 (39.7%)</td>
<td>351 728 (60.3%)</td>
<td>- 1.9%</td>
<td>+0.9%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>9 892 (28.0%)</td>
<td>25 436 (72.0%)</td>
<td>+ 1.4%</td>
<td>+ 1.7%</td>
</tr>
<tr>
<td>United Kingdom*</td>
<td>76 094 (26.6%)</td>
<td>210 256 (73.4%)</td>
<td>+ 2.6%</td>
<td>+ 0.4%</td>
</tr>
</tbody>
</table>

*For United Kingdom, data were from National Health Service Blood and Transplant (NHSBT) only (England and North Wales).

Table modified according to Berger K. et al. Blood product supply in Germany The impact of apheresis and pooled platelet concentrates 2016 Transfusion Medicine and Hemotherapy, accepted.

Planning of future supply and demand of blood components

The NHS Blood and Transplant projects the aims and controls the results

- Stabilization of cost
  - Reduce apheresis collection to 60% of overall platelet demand by the end of 2015/2016
  - Implement Platelet Additive Solution for whole blood pooled platelets in 2015, and for apheresis in 2017
  - Reduce apheresis donations towards 40% following a review of the current activity to reduce to 60%

- Improvement in experience for donors and an improved return rate
- Increase donations

http://www.nhsbt.nhs.uk/download/board_papers/july14/m14_74_Platelet_Supply_Project.pdf
Challenges: Spreading and Emerging Pathogens
Continuing the Kreuth Initiative:
Current controversies in clinical use of blood components

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GERMANY

Email: haematologie@pei.de
Homepage: http://www.pei.de

Achievements of the Kreuth Initiative

- Scientific Publications
- Council of Europe Resolutions
  - CM/Res(2015)3 on principles concerning haemophilia therapies
  - CM/Res(2015)2 on principles concerning human normal immunoglobulin therapies for immunodeficiency and other diseases

Still controversies in clinical use of blood components?

- This meeting addresses two main topics
  - Clinical use of clotting factors
  - Clinical use of platelets
- These two areas are different in several aspects
  - Clotting factors
    - Well defined indications, spectrum of authorized products, specialist treaters, informed and active patient community
    - Novel therapies to be evaluated and implemented
  - Platelets
    - Transfusion triggers debated, diverse producers and methods, no organised patient community
Controversies in clinical use of clotting factors?

• Haemophilia treatment has been subject of all the previous Kreuth symposia
• However, there are still questions
  – Were the previous Kreuth recommendations translated in clinical practice?
  – Was there progress in equitable access to products?
  – How to implement best practices and treatment modalities, e.g. individualised therapy, ITI?
  – How to evaluate efficacy and safety of new therapies in the pipeline with limited number of patients?

Designated Orphan MP for haemophilia A

<table>
<thead>
<tr>
<th>#</th>
<th>Product</th>
<th>Sponsor</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pegylated rh FVIIa</td>
<td>Novo Nordisk</td>
<td>4/6/2006</td>
</tr>
<tr>
<td>2</td>
<td>Liposomal rh FVIII</td>
<td>Bayer Pharma AG</td>
<td>24/7/2009 (withdrawn)</td>
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<tr>
<td>3</td>
<td>Sequence-modified rhFVIIa</td>
<td>Bayer Pharma AG</td>
<td>9 October 2009</td>
</tr>
<tr>
<td>4</td>
<td>Recombinant porcine factor VIII (B domain deleted)</td>
<td>Inspiration Biopharmaceuticals</td>
<td>20 September 2010</td>
</tr>
<tr>
<td>5</td>
<td>Recombinant fusion protein FVIII attached to Fc of IgG</td>
<td>Biogen IDEC</td>
<td>20 September 2010</td>
</tr>
<tr>
<td>6</td>
<td>Pegylated rh-SDO sequence-modified FVIII</td>
<td>Bayer Pharma AG</td>
<td>23 February 2011</td>
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<td>7</td>
<td>Recombinant fusion protein FVIII with albumin</td>
<td>CSL Behring</td>
<td>15 April 2011</td>
</tr>
<tr>
<td>8</td>
<td>Pegylated rh FVIII</td>
<td>Novo Nordisk</td>
<td>26 April 2012</td>
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<td>9</td>
<td>Vatropraoag alfa (activated)</td>
<td>Novo Nordisk</td>
<td>9 August 2012</td>
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<td>10</td>
<td>Hum. mAb TFP</td>
<td>Novo Nordisk</td>
<td>10 October 2012</td>
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<td>11</td>
<td>Hum. bispecific mAb targeting FIX, IXa, X and Xa</td>
<td>Chugai Pharma Europe Ltd</td>
<td>16 January 2014</td>
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<td>12</td>
<td>Synth. siRNA against antithrombin mRNA + ligand with 3 N-acetylgalactosamine</td>
<td>Arqium Ltd Limited</td>
<td>20 July 2014</td>
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<td>13</td>
<td>rh FVIII modified (repeats from β chain of human chorionic gonadotropin)</td>
<td>Richardson Associates Regulatory Affairs</td>
<td>22 August 2014</td>
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<td>14</td>
<td>A combination of peptides H-Lys-Lys-Gly-Pro-Arg…</td>
<td>Apitope International IV</td>
<td>19 November 2014</td>
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</tbody>
</table>
Revision of EMA clinical guidelines*:
adequate or overdone?

- Involvement of PDCO (responsible for paediatric aspects; requirement of PUP studies)
- Involvement of PRAC (responsible for post authorisation studies)

Controversies in clinical use of blood components for transfusion?

- Transfusion of blood components has been subject of the 1999 and 2009, but not 2013 Kreuth symposia
- Do we have still problems left or did new issues come up in the seven years since 2009?
Starting point of the Kreuth Initiative

• “Indications of overuse, underuse and inappropriate use... led..., to convene a meeting of experts to address issues related to the optimal use of blood.”
  from Proceedings 1999; Preface W. Schramm

• “The wide differences in blood product used for the same patient category were due to a variety of causes of which only some could be explained by the clinical factors taken into account.”

Where are we now?

• Improvement of surgical technique
• Transfusion guidelines available; implemented?
• Propagation of patient blood management
• Economic pressure
• Example Germany:
  – Red cells declining use
  – Platelets steadily high

Data PEI, supply data collected purs. § 21 Transfusion Act
Controversies in clinical use of red cells?

- Red cells are transfused in order to prevent or reverse tissue hypoxia; however, indication is usually based on haemoglobin levels
  - Ongoing debate on transfusion triggers: “liberal versus restrictive”
- There is concern about potential adverse effects of transfusion
  - Immunological impact; concern about potential immunosuppression (infection, cancer)

Concerns about potential adverse effects on long-term outcome of red cell transfusion have been addressed by clinical studies

- Potential impact of dose (“liberal versus restrictive”)
  - Impact may depend on underlying disorder (cardiac or CNS disorders)
  - Restrictive trigger probably safe
- Potential impact of duration of storage
  - Metaanalyses and clinical trials; for example, RECESS study shows no significant impact
Controversies in clinical use of platelets?

• “Incredibly, with six decades of PLT transfusion history behind us, we have no standards for judging the in vitro or clinical haemostatic efficacy of PLT transfusion.”
  Cap AP. Platelet storage: a license to chill. Transfusion 56:13-16;2016
• Availability and clinical use of platelets quite diverse across Europe
• There are various methods to collect and process platelets, the impact of which on platelet integrity and functionality is still incompletely assessed
• Infectious risk; particularly bacterial contamination

Current clinical use of platelets

• Platelets are transfused in order to prevent or stop haemorrhage
  – Impact of underlying patient condition
  – Extent and severity of bleeding not easy to assess
• According to current guidelines, trigger for transfusion and parameter for monitoring is platelet count (increment)
  – Routine measurement of haemostatic platelet functionality in vitro and ex vivo is challenging
  – Clinical study endpoint usually corrected count increment
Current preparation methods of platelets

- Methods of collection
  - Apheresis; various equipment
  - Preparation from pooled buffy coats
- Content of plasma; various additive solutions
- Storage conditions
  - 22°C versus 4°C; thermocycling
  - Agitation
- Bacterial testing; pathogen inactivation

Adverse reactions to platelets

- „Platelet concentrates account for near 10% of all labile blood components but are responsible for more than 25% of the reported adverse events.”
- Adverse events may in part be due to underlying disorders; however more research on platelet concentrate related causes is needed
  - Impact of type of concentrate?
  - Damage and/or pre-activation of platelets during collection, manufacture and storage?
Further potentially relevant aspects

- Storage duration before transfusion?
- AB0 (and other blood group) compatibility?
- Donor characteristics?
- Status and management of plasmatic coagulation?
- Interactions with concomitant medications?

Collecting clinical data?

- In order to enable broad and comprehensive evaluation of efficacy and safety of therapies, it would be desirable to collect continuously clinical data of complete patient collectives
  - In haemophilia, patient registries are available and need to be expanded and interrelated

- Clinical data collection of patients receiving platelets would also be valuable

Continuing the Kreuth initiative

• There are still controversies and open issues concerning both main topics of this symposium
• The objectives of this meeting are
  – To exchange information about current clinical practice in Europe
  – To foster discussions about best practices and their implementation
  – To identify issues requiring further evaluation and to stimulate research

Kreuth 1999: “This report is the result of the constructive work associated with that meeting and should be the basis for further discussions so that the initiative taken at Wildbad Kreuth will be continued.”
from Proceedings 1999; Preface W. Schramm

• We hope that there will be also some concrete and useful outcome of this meeting, and that the Kreuth initiative will be continued in the future and contribute to further improvements towards the optimal use of blood products
Quality Indicators for Monitoring the Clinical Use of Blood

EUROPEAN SYMPOSIUM
IV Wildbad Kreuth Initiative - Optimal use of clotting factors and platelets
6-7 May 2016, Freising, Germany

C. Politis, Greece

Introduction

• The importance of quality management system (QMS) in transfusion medicine is well established, however the development of appropriate quality indicators (QIs) as a tool for quality monitoring and improvement has only recently begun to receive attention in this field
**Agenda**

- **General information** on QIs in transfusion
  - *Definitions – Classification – Characteristics*

- **Council of Europe**, EDQM – CDPTS
  - ✓ QIs for monitoring the clinical use of blood in Europe
    - *Enquiry - Evaluation of 2012 data*
  - ✓ Use of blood components, 2013 data

- **IHN/ISTARE** data on clinical use of blood components, 2014

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**General Information I**

**Definition of QIs**

- QIs are measurable, objective indicators of the efficiency of the key segments of a system

  *Vuk T. Blood Transf. 2010:8(suppl.1)*

- QIs are one of the tools of a QMS used to monitor and control process functioning, whereby the data collected provide a basis for the implementation of corrective measures and continuous improvement

- **Conformity** with a set quality standards and goals has to be demonstrated by measurement

  *ISO 9001 Standard*
General Information II

Characteristics of QIs

• Measurability
• Importance and relevance
• Potential for use
• Reliability
  (each QI should have clean numerator and denominator)
• Validity
  (QI should be adequately related to the problem monitored)
• Uniformity of data collection
• Other attributes

General Information III

QIs classification

• **Internal** (defined by the Institution management to control their processes and to upgrade their quality)
• **External** (are global, therefore they should obviate differences from different practice in data collection and processing)

  The Donabedian quality model

  Structural
  Process
  Outcome
  Performance

  **Key strategic QIs**
  **Auxiliary process QIs**

• **Specific, Detailed QIs**
**General Information IV**

Implementation of QIs: Objectives

- One of the purposes of measurement is for monitoring
  - In the case of the clinical use of blood, monitoring is a key ingredient of a quality system, also essential for harmonizing transfusion practices within and between countries
  - Indicators may contribute towards providing a general picture of the factors that influence the use of blood components and alternatives
- They allow trend analysis of various aspects of clinical practice and benchmarking

*Finally, they may facilitate assessing the effectiveness of transfusion in terms of its outcomes, not only under optimal circumstances but also in emergencies and crises*

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**Council of Europe- EDQM project 2010-2014**

**Inquiry into QIs for monitoring the clinical use of blood**

Objectives

- To identify and develop a set of commonly accepted performance QIs for monitoring the clinical use of blood and blood components in Europe, in accordance with R (2002) 11 on the Hospital’s and clinician’s roles in the optimal use of blood and blood products;
- To use these indicators as a tool for benchmarking purposes and to improve consistency and uniformity in the reporting of annual data on the clinical use of blood at local, regional, national and international levels;
- To add a chapter to the Guide on “Monitoring the clinical use of blood with focus on efficacy versus outcome of transfusion: annual performance indicators”
The Chronicle

- Proposal to CD-P-TS November 2010
- Execution of the pilot study
  Establishing a Working Group
  Members: Vincenzo de Angelis (Italy), Alina Dobrota (Romania), Olivier Garraud (France), Tomislav Vuk (Croatia), Fatima Nascimento (Portugal), Jana Rososchova (Slovak R), Harald Schennach (Austria)
  Project leader: Constantina Politis (Greece)
- Collecting data from 8 countries (Austria, Croatia, France, Greece, Italy, Portugal, Romania, Slovakia) for year 2010 or 2009
- Analysis of data performed by Cl. Richardson, Pantion University, Greece

Enquiry into Quality Indicators for monitoring the clinical use of blood

Based on
- the Recommendation (2002) 11
- 1999 and 2009 Kreuth initiatives for optimal use of blood
- EU’s “Manual of Optimal Blood Use”
- other international work

Structure of the inquiry
- General information and National Policy for clinical use of blood
- Evaluation of use of blood at local (hospital) level
  - Benchmarking between institutions by selected pathologies
- Specific quality indicators of transfusion practice based on EU’s “Manual of Optimal Blood Use”
- Indicators of monitoring the efficacy versus outcome of the transfusion including economic parameters
Section A.
General information and National Policy for clinical use of blood

- Respondent Information – Country
- National Policy
  - structure,
  - national regulations,
  - guidelines
- Quality standards and maintenance of records
- Haemovigilance and inspections for the clinical use of blood
- Information on Quality Management Systems for monitoring clinical performance in hospitals

Section B.

- Evaluation of use of blood at national/regional level
  - No. of units transfused per 1000 inhabitants and per no. of beds
  - Total Blood components issued/transfused
  - Transfused FFP/RBCs
- Evaluation of use of blood at local (hospital) level
- Special blood components transfused
  - Recovered Platelets/Aphaeresis Platelets
  - Untreated FFP/Pathogen inactivated FFP
  - Untreated platelets/Pathogen inactivated platelets
  - Irradiated blood components/Total blood components
Section B.
Evaluation of use of blood at local (hospital) level

- Admitted patients/ Beds
- Total blood components transfused/ Distributed
- Total blood components transfused/prescribed
- Total blood components transfused/ Transfused patients
- Total blood components transfused per clinical department/
  No. of units of total blood components transfused in hospital
- Total blood components transfused per patient, by clinical department

Section B.
Benchmarking between institutions by selected pathologies

**Selected Pathologies**
- Total hip replacement
- TTP
- Coronary by-pass, with 2-3 grafts
- Massive blood loss

**Institutions**
- General hospital
- University hospital
- Specialised hospital

**Rates (examples)**
- Mean units of RBCs used per patient with total hip replacement at institutional level
- Mean units of FFP used per patient with TTP at institutional level
- Mean units of total blood components used per patient in coronary by-pass with 2-3 grafts at institutional level
- Mean units of total blood components used per patient with massive blood loss at institutional level
Section C.
Specific quality indicators of transfusion practice based on EU’s “Manual of Optimal Blood Use”

- Prescription
- Ordering and wastage
- Request forms
- Patient sampling
- Compatibility testing and traceability
- Other indicators

This section is designed for local use only

Section D.
Indicators of monitoring the efficacy versus outcome of the transfusion including economic parameters

National or hospital data including research findings, if available
Assessment of efficacy/outcomes of transfusion
Parameter of success
  - Laboratory parameters
  - Outcome in terms of morbidity
  - Outcomes in terms of mortality
  - Outcomes in terms of time
  - Outcomes in terms of disease groups

Cost-effectiveness, cost-benefit analysis, cost-recovery evaluation
Other indicators
RESULTS

National policy for clinical use of blood

Existence of a national policy for clinical transfusion medicine, guidelines and quality standards

Implementation of international guidelines for the optimal use of blood and blood components
Numbers of countries providing responses to each section of the questionnaire

- A1.2: General information
- A3.4: National policy for the clinical use of blood
- B1.2: Indicators of use of the blood and blood components (red cells, fresh frozen plasma, platelets): national level
- B3: Evaluation of the use of blood at local (hospital) level
- B4: Benchmarking between institutions by selected pathologies
- B5: Distribution from blood establishment to hospital blood bank
- C: Specific quality indicators based on the EU Manual of Optimal Blood Use
- D: Indicators for monitoring efficacy in terms of the outcome of transfusion

Mandatory maintenance of records of blood transfusion, system for monitoring optimal clinical use, existence of a Haemovigilance system, and performance of regular inspections for the clinical use of blood and blood components
Units (total, RBC, FFP and platelets) transfused per 1,000 population, by country

The Excel worksheet into which the data were entered calculates automatically certain rates from these data n= 10 countries

Units (total, RBC, FFP and platelets) transfused per hospital bed

n= 7 countries
Units transfused per transfused patient, separately for RBC, FFP and platelets, and in total

n= 7 countries

Units transfused per transfused patient, by clinical department

Total blood units transfused in onco-haematology and surgery, as proportion of total transfusions in the hospital
Conclusions I

• The EDQM CD-P-TS Pilot Study has demonstrated significant variation of QIs for monitoring the clinical use of blood between countries and within countries.

• Data on QIs requested on the management of hospital blood bank stock show a loss ranging as high as 20%.

• QIs for measuring the efficacy of transfusion in terms of outcome show that a stable cooperation of individuals hospitals is required.

• QIs on adverse effects of transfusion through haemovigilance should be considered.
Conclusions II

- The inquiry into QIs was promising.
- The response rate was not as high as had been hoped: one factor is the difficulty of collecting some of the quantitative data by approaching one or more hospitals separately.
- CD-P-TS has suggested that the building up of a network of contact points is required for regular collection of validated data on blood usage and future projections.

EDQM CD-P-TS, 2013 data
Use of Blood Components in 32 MS
(Median values)

RBC  35 units: 1000 inhabitants
      (range 4-64)

\[
\text{Ratio}_{\text{RBC}}: \frac{\text{FFP}}{\text{RBC}} = 0.4 \quad (\text{range } 0.03 - 1.5 \text{ median } 0.31) 1:3
\]

\[
\frac{\text{Whole Blood Derived Platelets}}{\text{Apheresis Platelets}} = \frac{64}{36} \% 1.8 (0.0-85\% \text{ median } 34\%)
\]
EDQM CD-P-TS, 2013 data
Medicinal products

• Plasma for fractionation (29 MS)
  Average yield 9.1 lt : 1000 inhabitants (range 0-54 L)
  71% recovered plasma (range 11-100% median 72%)

• Human albumin (17 MS)
  Average use = 5088 kg (range= 0.0 - 35,379 kg, median 1,139 kg)

• Manufactured albumin (13 MS)
  iv administration 75% (range 0.0-1005, median 87%)

• Factor VIII (17 MS)
  Average use =34 x106 IU (range= 0-249 IU, median 4.0)

• Polyvalent Immunoglobulins
  Average use = 3,295 kg (range 0.0-28,048, median 700kg)

Red cells
Variation of RBCs per 1000 inhabitants may reflect the results of insufficient blood supply or limited hospital care. Programmes for “optimal use of blood” has been recently installed in order to reduce unnecessary donor exposure to patient.

For the same blood safety reason the use of aphaeresis platelets in relation to recovered platelets is relatively high in some countries.

CD-P-TS is suggesting that a better benchmark maybe achieved by including the number of hospital beds linking to blood component use.
Comments II

• The Hospital transfusion Committee should adopt procedures for regular transfusion auditing. In the case of significant deviations from the guidelines, corrective actions should be put in place.

• Patient blood management (PBM) programmes should provide best clinical care. Blood services and all BEs stakeholders should be involved in PBM programmes

Thank you
HOW NOVEL DRUGS CHANGE TREATMENT IN HAEMOPHILIA

Flora Peyvandi
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico and University of Milan, Italy

Outline

• State of the art of hemophilia treatment: limitations
• Novel products:
  – Extended half-life and non-replacement products
• What has been achieved:
  – Efficacy
  – Safety
• Update of clinical trials
• Paradigm shift in hemophilia treatment?
Haemophilia Treatment

**Limitations**

- **Short half-life**
  - 8-12 hours for FVIII and 18-24 hours for FIX
- **Frequent intravenous injections** for prophylactic treatment
- **Immunogenicity**
  - 30% of severe hemophilia A PUPs developed Inhibitor in the first 15-20 EDs
- **Venous access**
  - concomitant risks: infection, sepsis, and thrombosis

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**Novel products**

**rFVIII extended half-life**

<table>
<thead>
<tr>
<th>Product</th>
<th>Technology</th>
<th>Half-life t&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Estimated time to 1% after 50IU/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAY94-9027</td>
<td>Site-directed PEGylation</td>
<td>1.4–1.6 fold</td>
<td>~5 days</td>
</tr>
<tr>
<td>N8-GP</td>
<td>Site-directed glycoPEGylation</td>
<td></td>
<td>6.5 days</td>
</tr>
<tr>
<td>BAX855 (Adynovate)</td>
<td>Controlled PEGylation</td>
<td></td>
<td>4 days</td>
</tr>
<tr>
<td>rFVIII-Fc (Eloctate, Elocta)</td>
<td>Fc-fusion</td>
<td></td>
<td>4.9 days</td>
</tr>
</tbody>
</table>
Impact of reduction of injections

- Extended half-life product infused once weekly presents a longer time spent below the normal critical level
- Time below 1 IU/dL associated with breakthrough bleeding

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose (IU/kg)</th>
<th>Treatment regimen</th>
<th>Median ABR, bleeds-patient⁻¹-year⁻¹</th>
<th>Patients with no bleeding episodes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting rFVIII Products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAY94-9027</td>
<td>45–60 IU/kg</td>
<td>every 5 days</td>
<td>1.9</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>60 IU/kg</td>
<td>every 7 days</td>
<td>3.9</td>
<td>37</td>
</tr>
<tr>
<td>rFVIII-Fc (Eloctate)</td>
<td>25–65 IU/kg</td>
<td>every 3 - 5 days</td>
<td>1.6</td>
<td>45.3</td>
</tr>
<tr>
<td>BAX 855 (Adynovate)</td>
<td>65 IU/kg</td>
<td>every 7 days</td>
<td>3.6</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td>45 IU/kg</td>
<td>2xweek</td>
<td>1.9</td>
<td>39.6</td>
</tr>
</tbody>
</table>

Patients treated with rFVIII longer acting on weekly prophylaxis experienced a high ABR in comparison to prophylaxis regimen every 3-5 days and this treatment regimen did not provide adequate prophylaxis.

Efficacy - rFVIII extended half-life

- The prolongation of rFVIII half-life reduces the frequency of infusions

- Standard products \(\rightarrow\) three infusions/week
- rFVIII extended half-life \(\rightarrow\) two infusions/week

- Reduction in injection frequency \(\rightarrow\) 30 - 35%
- Higher trough level

![Graph showing the difference in trough levels between standard and extended half-life products.]

Novel products
rFIX extended half-life

<table>
<thead>
<tr>
<th>Product</th>
<th>Technology</th>
<th>Half-life (t_{1/2})</th>
<th>Estimated time to 1% after 50IU/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9-GP</td>
<td>Site-directed glycoPEGylation</td>
<td>3-5 fold</td>
<td>22 days</td>
</tr>
<tr>
<td>rFIX-Fc (Alprolix)</td>
<td>Fc-fusion</td>
<td></td>
<td>10 days</td>
</tr>
<tr>
<td>rIX-FP (Idelvion)</td>
<td>Albumin-fusion</td>
<td></td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>
Efficacy - rFIX extended half-life

- A good performance of extended half-life rFIX products
- These novel drugs simplify the prophylactic regimens

- Standard products → two infusions/week
- rFIX Extended half-life → one infusion/week

Reduction in injection frequency → 50%

Status clinical trials of extended half-life

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Pediatric trials</th>
<th>PUPs trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rFVIII Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAY94-9027</td>
<td>Phase III completed</td>
<td>Ongoing</td>
<td>//</td>
</tr>
<tr>
<td>NB-GP</td>
<td>Phase III completed</td>
<td>Active, not recruiting</td>
<td>Ongoing</td>
</tr>
<tr>
<td>BAX855 (Adynovate)</td>
<td>Approved by FDA at 2015</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
<tr>
<td>rFVIIIFc (Eloctate)</td>
<td>Approved by FDA at 2014 Approved by EMA at 2015</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
<tr>
<td><strong>rFIX Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N9-GP</td>
<td>Phase III completed</td>
<td>Active, not recruiting</td>
<td>Ongoing</td>
</tr>
<tr>
<td>rFIXFc (Alprolix)</td>
<td>Approved by FDA at 2014</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
<tr>
<td>rIX-FP (Idelvion)</td>
<td>Approved by FDA at 2016</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Safety of extended half-life products

- One inhibitor case detected during phase 3 trial of N8-GP on PTPs
- No inhibitors detected in other clinical trials
- No data available from clinical trials on PUPs
- Long term safety of novel extended half-life products and an accurate post-registration surveillance is required

Novel rFVIIa products

<table>
<thead>
<tr>
<th>Fc-fusion</th>
<th>Albumin-fusion</th>
<th>CTP-fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion of the Fc domain of human IgG</td>
<td>Fusion of the human albumine</td>
<td>Fusion of the C terminus peptide of human chorionic gonadotropin (hCG)</td>
</tr>
<tr>
<td>rFVIIa-FC</td>
<td>rFVIIa-FP</td>
<td>Factor VIIa-CTP</td>
</tr>
</tbody>
</table>
Novel rFVIIa products

<table>
<thead>
<tr>
<th>Product</th>
<th>Half-life $t_{1/2}$</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIIa-Fc</td>
<td>5.5 fold (in mice)</td>
<td>Intravenous</td>
</tr>
<tr>
<td>rFVIIa-FP (CSL689)</td>
<td>3- to 4-fold</td>
<td>Intravenous</td>
</tr>
<tr>
<td>rFVIIa-CTP</td>
<td>3-fold</td>
<td>Intravenous and subcutaneous injection</td>
</tr>
</tbody>
</table>

Novel products
Non-replacement products

- Inhibition of TFPI
  - monoclonal antibody (anti-TFPI)

- Inhibition of antithrombin (AT)
  - small interference RNA (siRNA)
Bispecific antibody - ACE910 (Emicizumab)

- **ACE910** is a chimeric bi-specific humanized antibody directed against FIXa and FX.

- Mimics the cofactor function of FVIII, binds FIXa with one arm and FX with the other placing in spatially appropriate positions and promote FIXa-catalyzed FX activation.

![Diagram of ACE910 binding FIXa and FX](image)


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Non-replacement products

<table>
<thead>
<tr>
<th>Product</th>
<th>Technology</th>
<th>Half-life</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of natural anticoagulants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concizumab (NN7415)</td>
<td>anti-TFPI Antibody</td>
<td>once weekly</td>
<td>Intravenous and subcutaneous injections</td>
</tr>
<tr>
<td>ALN-AT3 (Fitusiran)</td>
<td>RNA interference (RNAi) against AT</td>
<td>once weekly or monthly</td>
<td>Subcutaneous injections</td>
</tr>
</tbody>
</table>

Promotion of thrombin generation by mimicking the cofactor activity of FVIII

<table>
<thead>
<tr>
<th>Product</th>
<th>Technology</th>
<th>Half-life</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE910 (Emicizumab)</td>
<td>Bispecific antibody to FIXa/FX</td>
<td>once weekly</td>
<td>Subcutaneous injections</td>
</tr>
</tbody>
</table>
Status clinical trials of non-replacement products

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concizumab</td>
<td>Phase I Ongoing (NCT02490787)</td>
<td>Hemophilia A and B</td>
</tr>
<tr>
<td>(NN7415)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALN-AT3</td>
<td>Phase I/II Ongoing (NCT02554773)</td>
<td>Hemophilia A and B, Hemophilia patients with inhibitor</td>
</tr>
<tr>
<td>(Fitusiran)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE910</td>
<td>Phase III Ongoing (NCT02622321)</td>
<td>Hemophilia A, Hemophilia patients with inhibitor</td>
</tr>
<tr>
<td>(Emicizumab)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Promotion of thrombin generation by mimicking the cofactor activity of FVIII

Safety – Non replacement products

- **Concizumab (NN7415):**
  - No serious AEs either healthy volunteers or hemophilia patients
  - No anti-concizumab antibodies

- **ALN-AT3 (Fitusiran):**
  - No thromboembolic events or clinically significant D-dimer increases
  - No instances of anti-drug antibody (ADA) formation

- **ACE910 (Emicizumab):**
  - no clinically relevant abnormal coagulability was indicated
  - Two of 48 (4.2%) subjects were anti-drug antibodies positive


(Uchida N et al Blood 2016; 127:1633-1641)
**Paradigm shift in hemophilia treatment?**

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**rFVIII extended half-life products**

- The use of smaller amounts of products with slightly less frequent infusions can probably attain increased trough levels, thus protecting patients from breakthrough bleeding
  - The benefits of such therapeutic strategy approach are yet to be evaluated
  - The annual cost of the treatment should remain affordable or unchanged

---

**Paradigm shift in hemophilia treatment?**

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**rFIX extended half-life products**

Could simplify the prophylactic regimens for haemophilia B patients:

- reducing the dosage frequency (~50%)
- extending the protection from bleeding
- improving adherence to treatment
- rendering this therapy less distressing to the patient
Non-replacement products

• Could make prophylactic regimens more straightforward:
  - reduce dosage frequency
  - extend protection from bleeding

• Moreover, subcutaneous administration would also simplify prophylaxis particularly in children with poor venous access

• Significant change in haemophilia patients with inhibitor
CURRENT CHALLENGES USING PLATELET CONCENTRATES

Professor Jean-Pierre Cazenave, MD, PhD
ARMESA
Strasbourg, France

Transfusion of platelet concentrates (PC):
a never ending challenge

• 1950's: platelet transfusions reduce mortality from hemorrhage in patients with acute leukemia
• Increase use: essential part of treatment of cancer, hematological malignancies, bone marrow failure, stem cell transplantation
• Problems: type of PC, risks for donors and patients, limited resources
• Introduction of new technologies: bacterial detection, pathogen inactivation
• Hemovigilance
• Consensus conferences and guidelines: safety and efficacy
• Regulatory approval by national agencies
• Costs
Pathogen inactivation (PI) of blood components
A change of paradigm
(Toronto Consensus Conference 2007*)

Active surveillance cannot foresee the risk of an emerging pathogen transmitted by transfusion. This type of risk needs a **proactive approach** according to the **principle of precaution**

1. PI implementation for **100% of blood components**
2. PI implementation **should not wait its availability for all 3 blood components** (platelets, plasma, RBC)
3. PI should be implemented when **safe methods of inactivation for large spectrum of pathogens** are available
4. Use of PI **should be universal** for all patients


---

Hemovigilance objectives relative to introduction of a new technology
(Toronto Consensus Conference 2007)

- Monitor safety of PC in routine use
- Monitor safety in broad patient populations
- Monitor safety in special populations
  - Pediatric patients
  - Infants and neonates
  - Rare congenital disorders
- Detect low frequency adverse events that cannot be studied in clinical trials
Intercept components have undergone rigorous review for regulatory approvals

Indications to transfuse PC: a complex decision

- Increasing use of PC: medicine, pediatrics and neonatology, surgery, obstetrics
- Many etiologies: thrombocytopenia (central or peripheral), thrombopathia
- Clinical bleeding is a therapeutic indication
- Prophylactic indication: risk factors modulate transfusion threshold
- Reduce risks to PC transfusion: infections, immune reactions (including refractoriness), TRALI
- Type of PC: single donor or pooled standard buffycoat, pathogen inactivated (amotosalen, riboflavin, UVC), donor profile
- Prescription: over- or under-use, availability, cost
What type of platelet concentrate are we talking about?

- **Donor profile**: male or female; HLA-, HPA-, HNA- matched; single or pooled
- **Processing methods to prepare PCs**: PRP (USA), buffycoat (Europe), apheresis
- **Modifications**: leucoreduction, additive solution, bacterial detection (1 or 2 tests), pathogen inactivation
- **Storage**: 3-5-7 days, temperature, agitation, transport
- **QC**: platelet concentration and content/PC, swirling, in vitro function
- **In vivo**: platelet recovery and survival, CCI, bleeding grade

Difficulties in assessing the clinical efficacy and safety of platelet concentrates

- **It might be good to remember the history of transfusion medicine**: progress by trial and errors, new technologies, clinical observation, clinical trials, evidence based medicine, hemovigilance
- **Are apheresis PC or buffycoat PC equivalent?**: apheresis machines different (microaggregates, swirling), anticoagulants, degree of leucoreduction, PAS
- **How to evaluate efficacy?**: surrogate markers and/or bleeding grade
- **Is safety for donors or patients equivalent for both types of PC?**
- **Clinical trials face complexity in transfusion medicine**: many evolutive diseases with various primary treatments (radiations, chemotherapy, antiplatelet agents...)
- **Evaluation of cost, a necessity but not an obsession**: albumine, delay in implementation
Safety and efficacy of platelet concentrates are difficult to evaluate in clinical trials due to uncontrolled factors

1. Indirect surrogate markers of therapeutic efficacy: relationship between CCI and bleeding unclear
2. Clinical scores to measure bleeding are uncertain: relationship with prevention of bleeding
3. Clinical trials in transfusion are small: 100 to 650 patients
4. Criteria to select inclusion of patients are poorly linked to clinical reality
5. No real historical comparison is possible with labile blood products empirically developped by trials and errors
6. Conception of new criteria for clinical trials in transfusion
7. Importance of active hemovigilance surveillance

Indications of PC in adult and pediatric patients with central thrombocytopenia are more frequent

- Increased frequency: hematological malignancies, solid tumors, aplasia, SCT, chemotherapy
- Usual posologies (France 2015): $0.5-0.7 \times 10^{11}/10 \text{ kg body weight}$
- Posology for neonates: $0.1-0.2 \times 10^{11}/\text{kg body weight (15-20mL/kg)}$
- Therapeutic transfusion of PC: when clinical bleeding
- Prophylactic transfusion of PC: when risks factors of bleeding
- Transfusion threshold: 10 G/L (stable patients), 20, 50 G/L

A MAJOR QUESTION:
PROPHYLAXIS OR PLATELETS ON DEMAND
### Relationship of CI, CCI to Grade 2 Bleeding and transfusion interval

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Dose</th>
<th>1 Hr CI</th>
<th>1 Hr CCI</th>
<th>Interval</th>
<th>Grade 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLADO-Low</td>
<td>417</td>
<td>2.0</td>
<td>10</td>
<td>10.0</td>
<td>1.1</td>
<td>58</td>
</tr>
<tr>
<td>PLADOMedium</td>
<td>423</td>
<td>4.0</td>
<td>19</td>
<td>10.0</td>
<td>1.9</td>
<td>59</td>
</tr>
<tr>
<td>PLADO-High</td>
<td>432</td>
<td>8.0</td>
<td>38</td>
<td>11.0</td>
<td>2.9</td>
<td>60</td>
</tr>
<tr>
<td>SPRINT-IA¹</td>
<td>318</td>
<td>3.7</td>
<td>21</td>
<td>11.1</td>
<td>1.9</td>
<td>59</td>
</tr>
<tr>
<td>SPRINT-C²</td>
<td>327</td>
<td>4.0</td>
<td>34</td>
<td>16.0</td>
<td>2.4</td>
<td>58</td>
</tr>
<tr>
<td>EUROSP-IA³</td>
<td>52</td>
<td>3.9</td>
<td>28</td>
<td>13.1</td>
<td>3.0</td>
<td>73³</td>
</tr>
<tr>
<td>EUROSP-C</td>
<td>51</td>
<td>4.3</td>
<td>35</td>
<td>14.9</td>
<td>3.4</td>
<td>69³</td>
</tr>
<tr>
<td>HOVON-IA¹</td>
<td>87</td>
<td>3.4</td>
<td>20</td>
<td>11.4</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>HOVON-C²</td>
<td>99</td>
<td>3.9</td>
<td>34</td>
<td>17.1</td>
<td>3.4</td>
<td>Group</td>
</tr>
</tbody>
</table>

¹Plasma inactivated amotosalen + UVA
²Plasma Control
³Grade 1 and 2 bleeding combined as mild bleeding

---

### The evolution of transfusion risks

- **HCV**
- **HBV**
- **HIV**

The origin of PI

Bacterial contamination risk of platelets

Next New Virus??

Updated by J. P AuBuchon from: NEJM 1999;341:126-7
Why inactivate pathogens in labile blood components?

1. Increase transfusion safety by a proactive rather than passive approach
2. Prevent sepsis due to bacterial contamination
3. Closing the window period, small copy numbers of viruses
4. Prevent transfusion-transmitted viral diseases
5. Prevent emerging pathogens from entering the blood supply
6. Prevent adverse events, save lives

Intercept Blood System
A broad spectrum of pathogen inactivation

<table>
<thead>
<tr>
<th>Enveloped viruses</th>
<th>Gram-negative bacteria</th>
<th>Spirochetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>Klebsiella pneumoniae</td>
<td>Treponema pallidum</td>
</tr>
<tr>
<td>HIV-2</td>
<td>Yersinia enterocolitica</td>
<td>Borrelia burgdorferi</td>
</tr>
<tr>
<td>HBV</td>
<td>Escherichia coli</td>
<td></td>
</tr>
<tr>
<td>DHBV</td>
<td>Pseudomonas aeruginosa</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>Salmonella choleraesuis</td>
<td></td>
</tr>
<tr>
<td>BVDV</td>
<td>Enterobacter cloacae</td>
<td></td>
</tr>
<tr>
<td>HTLV-I</td>
<td>Serratia marcescens</td>
<td></td>
</tr>
<tr>
<td>HTLV-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV/EBV/HHV-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WNV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chikungunya</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zika virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza virus (H1N1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avian flu virus (H5N1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XMRV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-enveloped viruses</th>
<th>Gram-positive bacteria</th>
<th>Protozoa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bluetongue virus 11</td>
<td>Staphylococcus epidermidis</td>
<td>Trypanosoma cruzi</td>
</tr>
<tr>
<td>Simian Adenovirus-15</td>
<td>Staphylococcus aureus</td>
<td></td>
</tr>
<tr>
<td>Feline calicivirus</td>
<td>Streptococcus pyogenes</td>
<td>Plasmodium falciparum</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Listeria monocytogenes</td>
<td>Leishmania mexicana</td>
</tr>
<tr>
<td>Human adenovirus 5</td>
<td>Corynebacterium minutissimum</td>
<td>Babesia microti</td>
</tr>
</tbody>
</table>

In general, 5 to 6 log reduction in infectious assays
In addition replaces gamma irradiation

- Residual leukocytes
- T lymphocytes, cytokines
- Bacterial spores resistant
- Prions resistant

Gram-negative bacteria
- Klebsiella pneumoniae
- Yersinia enterocolitica
- Escherichia coli
- Pseudomonas aeruginosa
- Salmonella choleraesuis
- Enterobacter cloacae
- Serratia marcescens

Gram-positive bacteria
- Staphylococcus epidermidis
- Staphylococcus aureus
- Streptococcus pyogenes
- Listeria monocytogenes
- Corynebacterium minutchissimum
- Bacillus cereus (vegetative)
- Lactobacillus sp.
- Bifidobacterium adolescentis
- Propionibacterium acnes
- Clostridium perfringens

Spirochetes
- Treponema pallidum
- Borrelia burgdorferi

Protozoa
- Trypanosoma cruzi
- Plasmodium falciparum
- Leishmania mexicana
- Babesia microti

Residual leukocytes
- T lymphocytes, cytokines

Bacterial spores resistant

Prions resistant
Clinical experience with Intercept platelets and plasma in Alsace 2006-2015

Bacterial detection in platelet concentrates has not been implemented in France

Quantitative aspects of pathogen inactivation in platelet concentrates and plasma transfused to patients in Alsace (2006-2014)

<table>
<thead>
<tr>
<th>Intercept components transfused in Alsace</th>
<th>Components (n)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC-IA</td>
<td>Total</td>
<td>140,990</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20,921</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 404 newborns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 823 children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 19,694 adults</td>
</tr>
<tr>
<td></td>
<td>BCPC-IA</td>
<td>89,954</td>
</tr>
<tr>
<td></td>
<td>APC-IA</td>
<td>51,036</td>
</tr>
<tr>
<td>FFP-IA</td>
<td>Total Units (200 mL/unit)</td>
<td>124,724</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17,960</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 658 newborns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 786 children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 16,516 adults</td>
</tr>
<tr>
<td></td>
<td>Pools for plasma exchange therapy</td>
<td>3,753</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(corresponding to 33,046 units of 200mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 9 children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 312 adults</td>
</tr>
</tbody>
</table>
Ten years of hemovigilance using PC inactivated by amotosalen + UVA

1. Increase transfusion safety and maintain hemostatic efficacy by a proactive rather than passive approach.
2. Prevent sepsis due bacterial contamination and avoid bacterial detection
3. Replace gamma irradiation for TA-GvHD
4. Avoid CMV serology for allogeneic transplants
5. Prevent transfusion-transmitted viral diseases (closing the window period, small copy numbers, mutants) and protect emerging pathogens (CHIKV, DENV, WNV, ZIKV) from entering the blood supply
6. Reduce acute adverse events (NHFTR), no toxic effects reported, no neo-antibodies
7. Hemostatic efficiency of Intercept PC does not require to transfuse more platelets (total dose) or more red cells. Efficient in surgery of Glanzmann thrombasthenia
8. Reduce outdates

<table>
<thead>
<tr>
<th>Year</th>
<th>PC (n)</th>
<th>TTBI (Grade 1-4)</th>
<th>TTBI (Grade 3)</th>
<th>TTBI (Grade 4 death)</th>
<th>TTBI/10,000 PC</th>
<th>PC (n)</th>
<th>TTBI (1-4) (death)</th>
<th>TTBI/10,000 PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>231,853</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0.17</td>
<td>6,420</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>232,708</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>0.39</td>
<td>15,393</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2008</td>
<td>239,349</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>0.25</td>
<td>15,544</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>241,634</td>
<td>9</td>
<td>7</td>
<td>0</td>
<td>0.37</td>
<td>21,767</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>253,147</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0.08</td>
<td>21,897</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>267,785</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0.11</td>
<td>23,179</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>275,986</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>0.25</td>
<td>24,849</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>285,288</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0.14</td>
<td>24,954</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2014</td>
<td>278,477</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0.07</td>
<td>24,881</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>2015</td>
<td>92,000</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.11</td>
<td>8,000</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Total*</td>
<td>2,398,227*</td>
<td>47*</td>
<td>28</td>
<td>9</td>
<td>0.20</td>
<td>186,884*</td>
<td>0 (0)*</td>
<td>0</td>
</tr>
</tbody>
</table>

*Fischer’s exact test, two-sided: p-value: 0.048; relative Risk = 7.3 with Confidence Interval lower bound = 0.7.
Emerging Chikungunya and dengue in France

1. Pathogen inactivation of PC and plasma by Intercept was introduced in 2006-2007 for all patients transfused in Ile de la Réunion, Martinique, Guadeloupe and Guyane during an epidemic of Chikungunya and dengue

2. Epidemic of Chikungunya in the French carribean islands starting in February 2014

3. Number of clinical cases June 15, 2014: Saint Martin (3430), Saint Barthélemy (620), Martinique (37600), Guadeloupe (40400), Guyane (390)

4. Hémovigilance at EFS-Martinique and Guadeloupe-Guyane: CHIKV NAT since February 24, 2014 in addition to 28 days of exclusion of previous CHIKV infection, 72 h quarantine for RBCC, pathogen inactivation by Intercept of all platelets (PC-IA) and plasma

5. Information post donation at EFS-Martinique and Guadeloupe-Guyane: 10 PC-IA (8 APC-IA an 2 BCPC-IA) coming from CHIV viremic donnors were transfused to 10 patients. No infection was detected in these patients

6. Surveillance of Chikungunya and dengue in metropolitan France (summer 2014): all the prerequisites for autochthonous transmission of Chikungunya are present: extension of Aedes albopictus in Southern France (up to Alsace), large number of travelers returning from French Carribean Islands (408 cases of CHIKV and 150 cases of DENV confirmed by laboratory)

7. 10/20/2014: 4 autochthonous cases of dengue fever in Southern France
   5 autochthonous cases of chikungunya in Montpellier/ Southern France

Zika virus epidemy, a public healh emergency of international concern (WHO, February 1st 2016)

- Areas with active Aedes mosquito-borne transmission of ZIKA virus: Africa (1951-1981), Thailand, French Polynesia (2013), Brazil-Mexico-French Carribean Islands-Puerto Rico (2015-2016) and many imported cases (France, USA…)
- 80% ZIKV infections remain asymptomatic
- Clinical symptoms: self-limiting, similar to flu-illness, chikungunya or dengue, severe complications: Guillain-Barré syndrome, microcephaly, long term complications
- Viremia may last up to 14 days and beyond
- Transmission: intrauterine, perinatal, sexual, transfusion blood component
- Reservoir of ZIKV: central nervous system, semen
- Recommendations for blood donation: deferral (4weeks), RT-PCR; women and pregnant women
- Pathogen inactivation: plasma (SD, amotosalen), platelets (amotosalen), red blood cells (IND authorization for S-303)

« WHAT IS THE NEXT NEW VIRUS? », THE STORY GOES ON!
Proactive or passive surveillance
Random-effects model (because of statistical heterogeneity): RR 1.08, 95% CI 0.91 to 1.30; P=0.37

"No evidence of a difference in mortality, “clinically significant” or “severe” bleeding, transfusion reactions or adverse events between pathogen-reduced and standard platelets."

"There is a need to complete further trials of effectiveness in order to understand the differences in bleeding outcomes, if any, between pathogen-reduced platelets and standard platelets"

The Cochrane Library, 2013
Conflict of interest disclosure of Jean-Pierre Cazenave

Cerus Corporation (The Netherlands)
  Co-Investigator of clinical trials
  Honoraria for presentations
  Research contracts
Outline

- A bit of history
- Scientific Advice
- The German system for deciding on reimbursement
- A way forward?
**Criteria for an marketing authorisation**

- Demonstration of efficacy
- Favourable benefit/risk balance

- Relative efficacy not necessarily required or evaluated (by law)
- Regardless of possible costs (by law)
Outline

- A bit of history
- Scientific Advice
- The German system for deciding on reimbursement
- A way forward?

National support for developers
Scientific Advice at PEI 2015

- National advice plays a major role, especially for early development and clinical trial authorisation
European support for developers

SAWP: Scientific Advice Working Party, PDCO: Paediatric Committee,
CAT: Committee for Advanced Therapies,
CHMP: Committee for Medicinal Products for Human Use,
PRAC: Pharmacovigilance Risk Assessment Committee
COMP: Committee for Orphan Medicinal Products

CHMP scientific advice

In the end one advice letter that is considered „morally“ binding!
Centralised Scientific Advice

Outline

- A bit of history
- Scientific Advice
- The German system for deciding on reimbursement
- A way forward?
Gemeinsamer Bundesausschuss (G-BA)
Federal Joint Committee

- Highest decision-making body of joint self-governance of physicians, dentists, psychotherapists, hospitals and statutory health insurance funds
- Decides what is covered within the benefit catalogue of the statutory healthy insurance
- Based on the law „Fünftes Sozialgesetzbuch (SGB V)"
- Supervised by German Ministry of Health, decisions and guidelines are audited by ministry
- Located in Berlin
- Impartial Chair: Prof. J. Hecken
Organisational Aspects

- G-BA, IQWiG and IQTIG are financed by levies for out-patient and in-patient care (currently 4.9 Cent per case out-patient, 1.63 Euro per case in-patient)

- Statutory health insurance: approx. 70 Millionen insured,
  - Spending 2014: 193,600,000,000 Euro (i.e. 2765 Euro/insured person)

Institute for Quality and Efficiency in Health Care (IQWiG)

- Independent scientific institute (foundation)
- Will take on work only by demand of G-BA or BMG
- Located in Köln
Evaluation of added benefit

- Patient relevant endpoints
  - Mortality (survival)
  - Morbidity (symptoms and complications)
  - Health related quality of life

- In comparison to available and approved treatments i.e. appropriate comparator therapy („zweckmäßige Vergleichstherapie“ ZVT)

- Using criteria of evidence based medicine EBM

- Publication: Allgemeine Methoden, IQWiG, Version 4.2

Evaluation of added benefit

- Evaluation of „quality“ of studies
  - Assessment of the risk of bias (blinding, randomisation, etc.)
  - Subgroups
  - Data consistency

- Number of studies, Direction of effect

- Conclusion on the evidence base/certainty of conclusion
  - Proof
  - Indication
  - Hint
Extent and grading of effect

- 6 categories:
  - Major added benefit
  - Considerable added benefit
  - Minor added benefit
  - Non-quantifiable added benefit
  - No added benefit proven
  - Less benefit

<table>
<thead>
<tr>
<th>Extent category</th>
<th>All-cause mortality</th>
<th>Serious (or severe) symptoms (or late complications) and adverse events</th>
<th>Health-related quality of life</th>
<th>Non-serious (or non-severe) symptoms (or late complications) and adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major or marked improvement in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy</td>
<td>Major increase in survival time</td>
<td>Major improvement</td>
<td>No applicable</td>
<td></td>
</tr>
<tr>
<td>Considerable or marked improvement in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy</td>
<td>Moderate increase in survival time</td>
<td>Improvement or relevant evidence</td>
<td>Important evidence</td>
<td>Important evidence</td>
</tr>
<tr>
<td>Minor or moderate and not fully marginal improvement in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy</td>
<td>Any increase in survival time</td>
<td>Any reduction</td>
<td>Relevant evidence</td>
<td>Relevant evidence</td>
</tr>
</tbody>
</table>

* Amendments to the ANV in italics.

ANV: Arzneimittel-Nutzungsbeurteilungsverfahren (System for Early Benefit Assessment of New Pharmaceuticals)
Recommendation of IQWiG

- Combining “quality” and “extent” will result in e.g.
  - "Indication of non-quantifiable added benefit"
  - “Proof of considerable added benefit"

- Basis for G-BA decision making
  - Orphan drugs handled slightly different: added benefit is regarded as demonstrated (by law)

- After G-BA decision basis for price negotiations
  - If no added benefit is demonstrated price of appropriate comparator forms the basis, if possible grouped with other approved products

Hurdles to access

- Pharmaceutical Quality
- Efficacy Favourable B/R
- Reimbursement Cost/Effectiveness
- Added benefit
A bit of history

Scientific Advice

The German system for deciding on reimbursement

A way forward?
European support for developers


Report of the pilot on parallel regulatory-health technology assessment scientific advice
G-BA, BfArM und PEI vereinbaren strukturierte Zusammenarbeit

Gemäß einer gemeinsamen Ausschreibung des Gemeinsamen Bundesausschusses (G-BA), Paul-Ehrlich-Institut (PEI) und Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
09 / 2015

Mit dem Ziel, möglichst frühzeitig ang und strukturiert bei gemeinsamen Fragestellungen hinsichtlich der Zulassung von Arzneimitteln und der frühen Nutzenbewertung von Arzneimitteln andererseits zusammenzuarbeiten, haben der Gemeinsame Bundesausschuss (G-BA), das Bundesinstitut für Arzneimittel undmedizinprodukte (BfArM) und das Paul-Ehrlich-Institut (PEI) eine Vereinbarung erarbeitet. Diese nennt die G-BA und die beiden Bundesbehörden ausdrücklich das Abschluss des Pharmazeutikums am Dienstag in Berlin mit. Im Hinblick darauf, im Rahmen der Durchführung von klinischen Arzneimittelstudien Qualität herauszustellen und für die Bearbeitung der kassenärztlichen Fragestellungen (Zulassung) als auch für die Bearbeitung der sozialversicherungsrechtlichen Fragestellungen (Früh-Nutzenbewertung) zu generieren.

Um dies zu erreichen, vereinbarten die Institutionen verschiedene Maßnahmen, unter anderem:

- die wöchentliche Beteiligung von Experten der jeweiligen Institutionen im Verkehr der klinischen Studien bei der Beratung der pharmazeutischen Unternehmen (Joint Scientific Advisor);
- die wöchentliche Kenntnisnahme von Protokollen durchgeführt im klinischen Verkehr;
- die Fortführung der jeweils wöchentlichen Verfahren im Rahmen der frühen Nutzenbewertung;
- regelmäßige wöchentliche Treffen von Mitarbeiterinnen und Mitarbeitern, um die jeweiligen aktuellen und wichtigen Fragestellungen in den Verfahren zu bearbeiten und zu koordinieren.
Contact me for any questions: Jan Mueller-Berghaus mueja@pei.de
Coagulation factor and platelet usage: Current challenges of benefit, effectiveness and risk assessment

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Email: Karin Berger@med.uni-muenchen.de

Agenda

• Why benefit / effectiveness and risk assessment?
• Challenges: benefit / risk assessment for clotting factor and platelet usage
• Open Questions & Outlook
Shortened Health Care Budgets

- Financial Crisis
  - Short-term effects
  - Long-term effects

- Trigger for Health Care Reform
- Lower tax payments
- Lower insurance income
- Budget cuts, personnel cuts, reimbursement restrictions etc.

Value for Money? Effectiveness / Benefits / risks

Cost constrained healthcare systems

Global Healthcare Spending Growth

- Asia
- Europe-Left Axis
- North America-Left Axis
Costs of Adverse Drug Reactions (ADR) in clinical routine care have a major economic impact

197,000 deaths due to ADR sum up to costs of € 79 billion*

* European Commission

ADRs related Hospital costs

- €636 million
- €400 million
- €706 million

The role of payers has become more prominent

Policy-makers, payers are increasingly mandating what doctors can prescribe

- Treatment protocols
- Cost sharing e.g. pay for performance
- Gate-keeper function

Value based informed decision making

- HTA assessments
- Comparative / relative effectiveness
- Risk Assessment
Payers have a strong focus on relative effectiveness

**Definition: relative effectiveness**

"...the extend to which an intervention does more good than harm compared to one or more alternative interventions under the usual circumstances of health care practice."

High level pharmaceutical forum

---

**Efficacy and Effectiveness Studies**

<table>
<thead>
<tr>
<th>Pre-Authorisation</th>
<th>Post-Authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market Authorization</td>
<td>Access</td>
</tr>
<tr>
<td><strong>How things work</strong></td>
<td><strong>Doing the right thing</strong></td>
</tr>
<tr>
<td><strong>Efficacy studies</strong></td>
<td><strong>Effectiveness studies</strong></td>
</tr>
<tr>
<td>– condition-specific endpoints</td>
<td>– comprehensive patient-relevant endpoints</td>
</tr>
<tr>
<td>– strong links to the mechanism of action</td>
<td>• Clinical</td>
</tr>
<tr>
<td>– short-term horizon</td>
<td>• PROs</td>
</tr>
<tr>
<td>– Small sample size</td>
<td>– relatively longer-term horizons</td>
</tr>
<tr>
<td></td>
<td>– Large sample size</td>
</tr>
</tbody>
</table>
Cooperation between EMA and EUnetHTA:

“The objective of the EMA-EUnetHTA collaboration is to identify and undertake specific steps to improve the efficiency of the processes and conditions for patients’ timely access to an effective medicine.”

(Report on the implementation of the EMA-EUnetHTA three-year work plan 2012-2015 S.3)

Patient-relevant endpoints and patient reported outcomes

Effectiveness
- mortality
- morbidity events
- adverse reactions
- symptoms
- function
- health-related quality of life
- participation and activity
- adherence and compliance

Available evidence may be incomplete, not consider the outcomes most relevant to patients, or not apply to certain patient populations. PCORI.
Relative effectiveness research: Endpoints

**Clotting Factor Concentr.**

<table>
<thead>
<tr>
<th>Patient relevant endpoints</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bleeds</td>
<td>- patient relevant endpoints</td>
</tr>
<tr>
<td>- Arthropathy</td>
<td>- Mortality</td>
</tr>
<tr>
<td>- Osteoporosis</td>
<td>- Haemorrhagic Diathesis</td>
</tr>
</tbody>
</table>

**Patient-reported endpoints**

- HRQoL
- Activity and Participation
- Patient Preferences
- Compliance and Adherence

**Risks**

- Inhibitor development
- Infections

**Patient-relevant endpoints**

- Mortality
- Haemorrhagic Diathesis

**Patient-reported endpoints**

- HRQoL
- Patient Preferences

**Risks**

- Immunologic reactions
- Non-immunologic reactions
- Infections

---

**Haemophilia-associated patient-relevant clinical outcomes**

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Parameter</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeds</td>
<td>frequency, localisation, severity</td>
<td>patient survey, patient diary</td>
</tr>
<tr>
<td>Target Joints</td>
<td>4 or more bleeds in one joint within 6 months*</td>
<td>patient survey, patient diary</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>mobility, function, joint replacement, arthrodesis</td>
<td>clinical joint status, Haemophilia Joint Health Score (HJHS), WFH Physical Examination Score (Gilbert Score), Arnold-Hilgartner System, Petterson Score, Magnetic Resonance Imaging (MRI) Score, ultrasound</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>fracture</td>
<td>patient survey, patient record</td>
</tr>
<tr>
<td>Therapy-related infectious diseases</td>
<td>hepatitis, HIV, clotting factor concentrates used</td>
<td>laboratory values, patient survey, patient record</td>
</tr>
<tr>
<td>Development of inhibitors</td>
<td>duration and intensity of treatment, gene mutations, clotting factor concentrates used</td>
<td>patient survey, patient record</td>
</tr>
<tr>
<td>Mortality</td>
<td>cause of death</td>
<td>death certificate, patient record</td>
</tr>
</tbody>
</table>

*Valentino L.A. Haemophilia (2009), 15 (Suppl. 1), 5-22.
Haemophilia-associated

**Patient Reported Outcomes (PROs)**

<table>
<thead>
<tr>
<th>Patient Reported Outcomes</th>
<th>Parameter</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-specific quality of life</td>
<td>Example: Haemophilia-Qol 36 items/9 Scales: physical health, daily activities, joint damage, pain, treatment satisfaction, treatment difficulties, emotional functioning, mental health, relationship and social activities(^1)</td>
<td>Haemophilia-Qol (adults and children), Haemo-Qol-A, Haem-A-Qol, Children Haemophilia Outcome (CHO)-Kids Assessment tool (KLAT)</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>Example: Euro-QoL-SD-questionnaire with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression(^2)</td>
<td>EQ-5D, SF-36, SF-12</td>
</tr>
<tr>
<td>Activity</td>
<td>FISH (8 activities: eating, dressing, chair transfer, squatting, walking, step climbing, running(^3)) or HAL (7 domains(^4))</td>
<td>Functional Independence Score (FISH), Haemophilia Activities List (HAL; PedHAL)</td>
</tr>
<tr>
<td>Social integration</td>
<td>education, work, days absent, hospital stays</td>
<td>patient survey</td>
</tr>
<tr>
<td>Adherence and compliance</td>
<td>continuous treatment according to therapeutic guidelines</td>
<td>patient survey, patient diary</td>
</tr>
</tbody>
</table>


Which outcomes are feasible to be determined in clinical routine care and meet access requirements?

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Measurement</th>
<th>Prioritization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>un-important</td>
<td>moderately important</td>
</tr>
<tr>
<td>Bleeds</td>
<td>patient survey, patient diary</td>
<td></td>
</tr>
<tr>
<td>Target Joints</td>
<td>patient survey, patient diary</td>
<td></td>
</tr>
<tr>
<td>Arthropathy</td>
<td>clinical joint status, Haemophilia Joint Health Score (KJHS), WFH Physical Examination Score (Gilbert Score)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>radiological joint status (Petterson Score)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Magnetic Resonance Imaging (MRI)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>ultrasound</td>
<td>2</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>patient survey, patient record</td>
<td>9</td>
</tr>
<tr>
<td>Therapy-related infectious diseases</td>
<td>laboratory values, patient survey, patient record</td>
<td>2</td>
</tr>
<tr>
<td>Development of inhibitors</td>
<td>patient survey, patient record</td>
<td>2</td>
</tr>
<tr>
<td>Mortality</td>
<td>death certificate, patient record</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^1\)Each of 14 physicians prioritized health outcomes taking into consideration the ability of their assessment in clinical routine care.
Challenges in assessing the outcomes

Consensus is needed on
• patient relevant endpoints to be measured for relative effectiveness research and cost-effectiveness evaluations
• on measurements used in routine care to assess patient relevant endpoints is needed
• how / where data that is accessible and appropriate for research purposes can be collected

Relative effectiveness research need Real Life Data

Real Life Data
"Everything that goes beyond what is normally collected in the Phase III clinical trials program in terms of efficacy” - Definitions ISPOR 2007

Sources:
1. Databases: cross-sectional and longitudinal databases
2. Patient and population surveys: epidemiological information.
3. Patient chart reviews: Used to reflect particular insights in patient management.
4. Observational data from cohort studies/ real life studies.
5. Pragmatic clinical trials: experimental trials, which raise questions regarding the extent to which they reflect what is happening in real life.
6. Registries: Involve registering and subsequently analyzing all patients treated at a particular centre for a particular condition on a continuous basis.
National Registries

- 27 European countries have a national registry
- Located at the Ministry of Health or are organized by large treatment centers or patient organizations
- Restricted access to most of the registries, therefore unclear what data is collected

Problem: There are European countries with less than 200 registered patients with severe HA

Haemophilia: European Registries

- **PedNet**: To facilitate research and healthcare development in children with haemophilia
- **ABIRISK**: (Anti-Biopharmaceutical Immunization: prediction and analysis of clinical relevance to minimize the RISK) to generate a comprehensive database concerning ADA formation in haemophilia and other diseases treated with biopharmaceuticals
- **EUHANET**: EUHANET is a project aimed at establishing a network of haemophilia centres to work together on a number of related projects to improve the care of European citizens with inherited bleeding disorders.
- **EUHASS**: European Haemophilia Safety Surveillance to monitor the safety of treatment for people with inherited bleeding disorders throughout Europe
Do these registries collect appropriate data for relative effectiveness research?

1. Step
Identification what Real World Data (RWD) is required for specific research questions

2. Step
Databasescreening and evaluation e.g.
- Accessibility of data?
- Granularity of data?
- Contemporary data?
- Representative data?
- Linkage?

---

Platelet-associated patient-relevant outcomes

**PubMed last 10yrs**
Effectiveness AND „platelet transfusion”

Mostly Surrogate parameters are used as endpoints
- Platelet increment
- Platelet recovery
- Time to next transfusion
- Number of transfusions

Only a very limited number of publications presents data on

- Patient-relevant clinical endpoints
  - Mortality
  - Bleeds
  - Transfusion reactions
- Patient – reported outcomes
  - Quality of life
  - Patient Preferences?
Platelet-associated patient-relevant outcomes

• What is needed?
  – Definition of appropriate endpoints for effectiveness research
  – Discussion on methodological approaches „How to measure patient relevant endpoints associated with platelet transfusion“
  – access to data required

SMART DATA

A chance for relative effectiveness research in coagulation factor and platelet usage?
Thank you for your attention!
Patient Organisation View

Brian O Mahony
President, EHC

EHC Survey on the ‘State of Haemophilia Care in Europe’

• Conducted in late 2015/early 2016
• 2014 data on Factor use
• 37 countries responded
• 31/35 who responded in 2012
• 6 new responses Estonia, Georgia, Israel, Kyrgyzstan, Montenegro, Norway
Organisation of Care

• No CCC in 2015 in:
  – Armenia, Estonia, Kyrgyzstan, Latvia, Macedonia, Montenegro, Spain and Ukraine

• Countries who developed CCC since 2011:
  – Albania, Bulgaria, Hungary, Lithuania, Portugal and Serbia

• Spain lost CCC status since 2011 for 64 HTCs

NHC or Co-Ordinating Group

• 18 countries have a National Co-ordinating group

• 19 countries do not have a National Co-ordinating group

• Azerbaijan, Macedonia, Romania developed a National Co-ordinating group since 2012

• Finland, Germany, Greece, Italy, Lithuania and Spain have lost their National Co-ordinating group since 2012
Access to home treatment (2015 survey)

Levels of access in %
- 76-100%
- 51-75%
- 10-50%
- <10%
- 0%
- Unanswered

Increase in access to prophylaxis

In children (in 6 countries)
- Azerbaijan, Bulgaria, Romania, Russia, Serbia and Ukraine

In adults (in 7 countries):
- Belgium, Czech Republic, Ireland, Lithuania, the Netherlands, Poland and Spain

In both children AND adults (in 6 countries)
- Austria, Italy, Latvia, Portugal, Slovenia and Turkey
Access to specialist services
2015 Survey

Most available specialist services:

• Paediatrics
  – always available in 33 countries
  – never or rarely available in 0 countries

• Emergency care
  – always available in 30 countries
  – never or rarely available in 0 countries

• Orthopaedics
  – always available in 29 countries
  – never or rarely available in 0 countries

Access to specialist services
2015 Survey

Least available specialist services:

• Social & psychosocial support
  – always available in 12 countries
  – never or rarely available in 10 countries

• Pain management
  – always available in 15 countries
  – never or rarely available in 9 countries

• Rheumatology
  – always available in 16 countries
  – never or rarely available in 6 countries
Access to specialist services: 2012-2015

• Improvement in access to:
  : Genetics – 5 countries
  : Physiotherapy – 4 countries
  : Pain Management – 3 countries
  : Infectious disease specialist – 3 countries
• Access to social and psychological support decreased in 2 countries

Ageing and Haemophilia

• 32/36 countries unaware of any specific clinical services for ageing PWH
• 28/36 do NOT have guidelines for managing cardiovascular risk in PWH
• 17/36 countries aware of educational programmes for clinicians or patients
• 22 countries – patient organisation have raised concerns about ageing and PWH
Status of the implementation of EDQM 2013 recommendations

<table>
<thead>
<tr>
<th></th>
<th>NHC Implemented in</th>
<th>Min 3 IU/capita FVIII</th>
<th>Prophylaxis in children</th>
<th>Prophylaxis for adults when required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implemented in</td>
<td>18 countries</td>
<td>18 countries</td>
<td>33 countries</td>
<td>31 countries</td>
</tr>
<tr>
<td>Not implemented in</td>
<td>19 countries</td>
<td>8 countries</td>
<td>4 countries</td>
<td>6 countries</td>
</tr>
<tr>
<td>No data for</td>
<td>8 countries</td>
<td>19 countries</td>
<td>8 countries</td>
<td>8 countries</td>
</tr>
</tbody>
</table>

Patient Priorities

- Continues to be inadequate use of factor concentrates: 7 countries < 3 and 10 < 4 IU/PC
- 50% countries do not have a national co-ordinating body
- ITI availability poor in many countries
- Access to hepatitis C treatment not prioritised
- Need for access to new EHL factors at sustainable cost and with individualisation of therapy
- Need for agreed protocols on ageing
Clinical Trials with Clotting Factors
-A Regulatory Perspective-

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Role of Regulators...
- Scientific Advice
- Approval of Clinical Trials
- Marketing authorisation
  - Quality
  - Efficacy
  - Safety
- Pharmacovigilance
- Surveillance
- Consequences/Measures

Interaction between NCA – Applicant/MAH
**European approach...**

- **Scientific Advice** (national/centralized)
- **Approval of Clinical Trials** (national/centralized)
- **Marketing authorisation** (national/centralized)
- **Pharmacovigilance** (centralized)
- **Surveillance** (national/centralized)
- **Consequences/Measures** (national/centralized)

**coordination/collaboration/communication**

---

<table>
<thead>
<tr>
<th><strong>Since 1996 GL requirements</strong></th>
<th><strong>Since 2012 GL requirements</strong></th>
<th><strong>Comment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>50 PTP &gt; 12y (incl. 12 PTP for PK and 5 PTP for surgery)</td>
<td>50 PTP &gt; 12y (incl. 12 PTP for PK and 5 PTP for surgery)</td>
<td>No change</td>
</tr>
<tr>
<td>20 children &lt; 6y, to be started before MA</td>
<td>50 children 0-12y</td>
<td>Paediatric Regulation / PIP</td>
</tr>
<tr>
<td>PUP CT not required</td>
<td>50 PUP for novel products 100 PUP follow up</td>
<td>Inhibitor review 2005 PIP</td>
</tr>
<tr>
<td>Post-authorisation: No specific requirements</td>
<td>200 patients to be followed for 100 ED-specific testing schedule</td>
<td>Inhibitor review 2005</td>
</tr>
</tbody>
</table>
Post-marketing-investigation FVIII

- **Inclusion Criteria**
  - PTP(>150ED); <1% FV III:C; immunocompetent (CD4 >200/µl) HIVneg or <200 particle/µl
- **Documentation Patients characteristics**
- **Enrolment:** 200 PTP FVIII
- **Testing schedule:**

![Testing Schedule Table]

Post-marketing study procedure

- **Before patient enrolment:** no suspected inhibitor, confirmed by lab testing
- **Documentation of**
  - treatment regimen (incl. surgery)
  - treatment outcome
  - all adverse events
- **Development of recruitment to be regularly reported**
- **Progress report 2y after MA, completion within 4y**
- **Protocol (incl. timelines) will be approved at MA**
European Pharmacovigilance Legislation

Regulation (EU) 1235/2010
Directive 2010/84/EU

- Pharmacovigilance Risk Assessment Committee (09/2012)
- Rationalising PSUR management (substance classes, no routine PSUR-reporting for low risk/established products)
- ADR reporting (individual direct reporting to NCA, EudraVigilance..)
- Risk Management Plans
- Strengthened basis for post-authorisation studies (safety and efficacy)

RMP for FVIII and FIX products

- Safety monitoring and risk minimisation activities:
  - Comprehensive Analysis of *de novo* and recurrent inhibitors (source of report, titre and type of inhibitor, incidence estimate, risk classification + patient background and follow up data)
  - Lack of drug effect
  - Hypersensitivity / anaphylactic reactions
- Post-marketing investigation
- Recommendation to include patients in registries
### GCP Trials in Haemophilia ....April 2016

Source: EU Clinical Trials Register (www.ClinicalTrialsRegister.eu)

<table>
<thead>
<tr>
<th></th>
<th>Total CT</th>
<th>Ongoing</th>
<th>OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Haemophilia</td>
<td>147</td>
<td>92</td>
<td>26</td>
</tr>
<tr>
<td>CT Haemophilia PUP</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Haemophilia PUP ongoing</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT HA PUP</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT HB PUP</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Haemophilia PTP</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Haemophilia PTP ongoing</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT HA PTP ongoing</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT HB PTP ongoing</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Pro’s and Con’s

**Clinical Trials**
- ☑️ mandatory for every new Product
- ☑️ same pre-defined evaluation criteria
- ☑️ consistent with regulatory requirements
- ☑️ high data quality
- ☑️ Regulators do have access to data
  - selected patients
  - unknown confounding
  - limited sample size and study period
  - open uncontrolled study design

**Registries**
- ☑️ same data parameter for all products
- ☑️ all patients (PTP and PUP) included
- ☑️ real life and long follow up data
- ☑️ large number of patients
- ☑️ comparison among products
  - voluntary
  - unknown confounding
  - no standardized dataset yet
  - Regulators do have no access to data
How to get the best capture of data?

- for regulatory purposes
- for scientific/clinical purposes
- for HTA purposes
- for the benefit of patients

Issues.....

- Plasma-derived vs. recombinant products
- Full-length vs. B-domain-deleted
- Brand-associated effects
- Inhibitor: prevention, treatment, eradication
- Emerging pathogens
- Modified donor selection criteria
- New products= new problems?
Options...

- Clinical trials (GL)
- Registries (harmonized/standardized)
- Pharmacovigilance
- Scientific research...

Regulatory Tools

- Pre- and postauthorisation CT concept
- Pharmacovigilance:
  - RMP
  - PSUR/PSUSA
  - Signal detection
- Consequences/measures: e.g. referrals
**Prospects....**

- **Pre- and postauthorisation CT concept**
  - critical review of GL (status quo/identification of gaps …e.g. outcomes/HTA/novel products)

- **Registries**
  - need for standardization/harmonisation clarification of data access/reporting pathways....

**Identification of best practice and needs in Haemophilia care**
Inhibitor development in PUPs
- SIPPET and previous studies -

F.R. Rosendaal
Leiden University Medical Center

IV Wildbad Kreuth Initiative
Optimal use of clotting factors and platelets
Freising, 6 May 2016

Disclosures

No conflicts of interest
Introduction inhibitors

- high cost treatment: € 400 000-1 000 000 per year
- increased burden
- increased mortality: no excess to more than doubling


Risk factors inhibitors

- F8 mutation
- family history of inhibitor
- immunomodulatory genetic variants
- intensity of initial treatment
- prophylaxis ($\downarrow$)
- type of FVIII product
- age at first treatment
- ethnicity

FVIII product and inhibitors

Previously untreated patients

cryoprecipitate 6.2%
early concentrates 9.0%
ultrapure concentrates >25%

Previously treated patients

FVIII CPS-SD 4.4/1000 py
FVIII CPS-P 20.1/1000 py


(Gouw, N Engl J Med 2013)
## Replication: four studies

<table>
<thead>
<tr>
<th>Design</th>
<th>Period</th>
<th>Countries</th>
<th>N</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RODIN</td>
<td>cohort</td>
<td>2000-2010</td>
<td>14</td>
<td>574 mutation, age, +</td>
</tr>
<tr>
<td>FCN</td>
<td>cohort</td>
<td>1993-2014</td>
<td>1</td>
<td>353 mutation, age, +</td>
</tr>
<tr>
<td>UKHCDO</td>
<td>cohort</td>
<td>2000-2011</td>
<td>1</td>
<td>407 mutation, age, +</td>
</tr>
<tr>
<td>EUHASS</td>
<td>case-series</td>
<td>2008-2012</td>
<td>26</td>
<td>417 none</td>
</tr>
</tbody>
</table>


## Four studies meta-analysed

- all inhibitors -

![Graph showing RR=1.42, CI95 1.13-1.80](image)

**Four studies**

- Adjustment for confounding -

<table>
<thead>
<tr>
<th></th>
<th>unadjusted</th>
<th>adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>RODIN</td>
<td>1.37</td>
<td>1.60</td>
</tr>
<tr>
<td>FCN</td>
<td>1.61</td>
<td>1.55</td>
</tr>
<tr>
<td>UKHCDO</td>
<td>1.60</td>
<td>1.64</td>
</tr>
<tr>
<td>EUHASS</td>
<td>0.99</td>
<td>n.d.</td>
</tr>
</tbody>
</table>


**Confounding**

- mutation type
- intensity
- family history
- .................

![Diagram](image)

Kogenate

association underestimated

inhibitor rate
Confounding

- the main problem of observational studies
  - mnemonic: grey hair and death risk
  - a main cause is the physician: confounding by indication

- when the physician cannot know any risk factor: no confounding
  - idiosyncratic side-effect of drugs
- when all risk factors known: adjustment
  - and reasoning over direction of effect

- when likelihood of subtle unknown or unmeasurable factors
  - confounding remains, unless influence physician removed
  - this is done by randomisation

Confounding

- mutation type
- intensity
- family history
- ..................

Kogenate

low risk

association correctly estimated

inhibitor rate
Overview of studies rFVIII vs pdFVIII

(Mannucci, Thromb Haemost 2015)

Meta-analyses rFVIII vs pdFVIII

- 24 studies, 2094 patients
  - all (42% severe) 27.4% 14.3%
  - prospective, severe haemophilia, high titre 19.4% 6.0%
  - attenuating effects of testing frequency

- individual patients data meta-analysis (IPD), 761 patients
  - all (86% severe) 40.2% 21.8%
  - Cox regression
    - univariate HR 2.2
    - multivariate HR 1.3
    - major interactions with intensity

(Iorio, J Thromb Haemost 2010; Marcucci, Thromb Haemost 2015)
Overall conclusions literature

- different immunogenicity of products has been observed before

- literature is unclear on immunogenicity of rFVIII vs pdFVIII
  - seems higher for rFVIII
  - confounding by indication likely

- really time to do a randomised trial and resolve this

Rationale for SIPPET

- relevant clinical question

- reasonable prior that risk increased with rFVIII

- high likelihood of residual confounding in observational studies
  - must do randomised study
Assumption SIPPET

- differential rate of inhibitors by product is a class effect
- due to presence of VWF in pdFVIII
- Note:
  - neither assumption necessary for the study

Design

- randomised
- international multicenter
- open label
- blocked (block size 1:1)
- severe haemophilia A
- previously untreated patients or minimally exposed
  - <5 with blood components (no concentrate)
  - < 6 yrs
  - negative for inhibitor at screening
- follow-up for 3 yrs, or 50ED, or inhibitor
- endpoint: >0.4 BU (Nijmegen Bethesda)
  - secondary: >5 BU
Contrast

- Per country only one brand of pdFVIII and rFVIII available
  - only licensed brands
- Per centre randomisation between pdFVIII and rFVIII
- Ties brand, treatment preferences and ethnicity to country
- Balances these factors optimally between rFVIII and pdFVIII
Analysis

- check if randomisation ‘worked’
  - no ‘confounding by chance’

- estimate risk of inhibitor over time (survival curves)

- quantify differences between arms (Cox)
  - adjust for ‘confounding by chance’

- quantify random error (confidence interval)

- repeat for high-titre inhibitors

Inclusion

303 Screened

264 Eligible and randomised

13 Excluded

251 Analyzed

39 Screening failure and drop out

216 completed study
35 early termination
Geographical distribution

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>pdFVIII</th>
<th>rFVIII</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=125</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n=126</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median age (mo.)</td>
<td>14.0</td>
<td>15.0</td>
</tr>
<tr>
<td>null mutation</td>
<td>86.3%</td>
<td>81.4%</td>
</tr>
<tr>
<td>family history haemophilia</td>
<td>47.6%</td>
<td>42.6%</td>
</tr>
<tr>
<td>family history inhibitor</td>
<td>11.5%</td>
<td>10.1%</td>
</tr>
<tr>
<td>previous treatment</td>
<td>44.8%</td>
<td>42.1%</td>
</tr>
<tr>
<td>treatment regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>on-demand</td>
<td>48.8%</td>
<td>44.4%</td>
</tr>
<tr>
<td>standard prophylaxis</td>
<td>16.8%</td>
<td>15.1%</td>
</tr>
<tr>
<td>modified prophylaxis</td>
<td>34.3%</td>
<td>40.5%</td>
</tr>
</tbody>
</table>
Inhibitor occurrence

<table>
<thead>
<tr>
<th></th>
<th>pdFVIII</th>
<th>rFVIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td>high-titre</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>persistent</td>
<td>74.4%</td>
<td>72.2%</td>
</tr>
<tr>
<td>peak titre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>peak (median)</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>range</td>
<td>0.8-1100</td>
<td>0.7-1850</td>
</tr>
</tbody>
</table>

Cumulative incidence by arm

A) all
- 44.5% (CI95 34.7-54.3)
- 26.8% (CI95 18.3-35.2)

B) high-titre
- 28.4% (CI95 19.6-37.2)
- 18.6% (CI95 11.1-26.9)
Cox regression

<table>
<thead>
<tr>
<th></th>
<th>hazard ratio</th>
<th>CI95</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>1.87</td>
<td>1.17-2.96</td>
</tr>
<tr>
<td>high titre</td>
<td>1.69</td>
<td>0.96-2.98</td>
</tr>
</tbody>
</table>

adjusted HRs similar to crude HRs

Sensitivity analysis

- country -

- one country
Conclusions

- higher rate of inhibitors with rFVIII than pdFVIII
  - for all and high titre inhibitors
- found in randomised comparison
- robust in adjusted and sensitivity analyses
- increase size 70-90%: substantial
Consequences
- scenarios -

- ignore
- ask for more studies
- treat all PUPs with pdFVIII
- treat first with pdFVIII, then switch to rFVIII
- differentiate
  - low risk rFVIII
  - high risk pdFVIII, or pdFVIII and then switch to rFVIII

High vs low-risk patients

<table>
<thead>
<tr>
<th></th>
<th>pdFVIII</th>
<th>rFVIII</th>
<th>Number needed to Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>26.8%</td>
<td>44.5%</td>
<td>5</td>
</tr>
<tr>
<td>high-risk**</td>
<td>30.7%</td>
<td>46.5%</td>
<td>6.3</td>
</tr>
<tr>
<td>low-risk</td>
<td>9.5%</td>
<td>38.2%</td>
<td>3.4</td>
</tr>
</tbody>
</table>

** presence of null mutation
Acknowledgments

- local investigators
- DMSB
- Syntesi Research
- Patients and parents

SPONSORS OF THE STUDY
- Grifols, Spain
- Kedrion Biopharma, Italy
- LFB, France

UNRESTRICTED GRANTS

Flora Peyvandi
Pier Mannucci
Inhibitors in Haemophilia
Prophylaxis – Immune Tolerance Induction

Pr Hervé Chambost
Haemophilia Reference Care Centre – Haematology Oncology Department University
Children Hospital La Timone – Marseille – France

Disclosure for Hervé CHAMBOST
(none related to this presentation)

<table>
<thead>
<tr>
<th>Shareholder</th>
<th>No relevant conflicts of interest to declare</th>
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</thead>
<tbody>
<tr>
<td>Grant / Research Support</td>
<td>CSL Behring, LFB, NovoNordisk</td>
</tr>
<tr>
<td>Consultant</td>
<td>Baxalta, Bayer Healthcare, CSL Behring, NovoNordisk</td>
</tr>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Paid Instructor</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Speaker bureau</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Clinical trials (PI)</td>
<td>Bayer Healthcare, Biogen, CSL Behring, NovoNordisk, Octapharma</td>
</tr>
</tbody>
</table>
Inhibitors in Haemophilia: which issues?

Inhibitor development represents the major residual treatment related complication, with consequences

- **for the patient**
  - possible decreased efficiency of treatments
  - no access to the gold standard treatment (long term prophylaxis)
  - arthropathy, physical disability, impaired quality of life, survival

- **for the society**
  - higher cost of treatments for bleedings (bypassing agents / on demand, prophylaxis) and for the inhibitor (ITI)
  - social cost

- **for the future**
  - impaired outcome for gene therapy and/or long-lasting factors?

Inhibitors in Haemophilia: which solutions?

A major challenge would be to prevent inhibitor development

How to deal with the inhibitor after its occurrence?

- To treat bleedings
- To treat the inhibitor
- To prevent bleedings
Prophylaxis – Immune Tolerance Induction

Practices in the real life at a country level
The experience in France

<table>
<thead>
<tr>
<th>Type / Severity</th>
<th>Patients (n)</th>
<th>Inh + (n)</th>
<th>(%)</th>
<th>High Response (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia A</td>
<td>5813</td>
<td>595</td>
<td>359</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1963</td>
<td>472</td>
<td>24.0</td>
<td>300 (64%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>831</td>
<td>60</td>
<td>7.2</td>
<td>27</td>
</tr>
<tr>
<td>Mild</td>
<td>3019</td>
<td>63</td>
<td>2.1</td>
<td>32</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>1299</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>403</td>
<td>14</td>
<td>3.5</td>
<td>11</td>
</tr>
<tr>
<td>Moderate</td>
<td>365</td>
<td>1</td>
<td>0.3</td>
<td>-</td>
</tr>
<tr>
<td>Mild</td>
<td>531</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

* Inhibitors confirmed by the specific working party

Inhibitors in the French Cohort

Inhibitor history recorded at the last follow-up in the whole cohort
The current Burden of Inhibitors in FranceCoag

Inhibitor history recorded at the last follow-up (≥11/03/2013)

103 patients with currently relevant inhibitor

- Inh > 0.6 UB (n=77)
- ITI (n=36)
- Bypassing agents (n=66)

Haemophilia A 549 162 Inh+ 29.5% 95 (59%) HR

Inhibitors in the PUPs’ HA Cohort

Inhibitor history recorded at the last follow-up (≥11/03/2013)

43 patients with currently relevant inhibitor

- Inh > 0.6 UB (n=33)
- ITI (n=25)
- Bypassing agent (n=25)

12 Prophylaxis
aPCC = 8 (4 ITI+)
rFVIIa = 4 (3 ITI+)
## Treatment of bleedings in haemophilia patient with inhibitor

<table>
<thead>
<tr>
<th>Low titers, low responding, transient inhibitors ...</th>
<th>High titers, high responding, anamnesis ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Treatment / FVIII concentrates (higher dose)</td>
<td>✓ Bypassing agents (BPA) = rFVIIa or aPCC*</td>
</tr>
<tr>
<td>✓ Prophylactic objectives are achievable</td>
<td>✓ Possible poor response, life-threatening bleedings</td>
</tr>
<tr>
<td></td>
<td>✓ Disability, impaired quality of life, absence at school, impaired academic achievement and productivity ...</td>
</tr>
</tbody>
</table>

* FENOC Study : Astermark et al, Blood 2007

---

**Immunotolerance Induction**
Treatment of inhibitor

Immunotolerance Induction: the rationale

Series with heterogeneous protocols in the literature

- Bonn regimen
- Malmö regimen
- van Creveld regimen

Large international Registries
Risk factors for response - 50 to 80% of tolerance

One randomized trial (International ITI)

---

**Plenary paper**

The principal results of the International Immune Tolerance Study: a randomized dose comparison

Charles R. M. Hey, and Donna M. Dimichelle, on behalf of the International Immune Tolerance Study

**Trial characteristics**

We found one randomised trial that compared high- and low-dose immune tolerance induction, which included 115 males with haemophilia A and inhibitors.

**Key results and conclusions**

The single included trial was too small to be certain that both doses of immune tolerance induction were equally successful at removing inhibitors. However, the high-dose treatment destroyed all inhibitors faster and with less bleeding events than the low-dose treatment. Since there was only one available trial, further trials are needed to establish the best immune tolerance induction regimen with respect to starting time, dosing intensity and frequency.
Prophylaxis with bypassing agents (BA)
Anti-Inhibitor Coagulant Complex Prophylaxis in Hemophilia with Inhibitors

Cindy Leissinger, M.D., Alessandro Gingeri, M.D., Bülent Arntzen, M.D., Erik Bernsop, M.D., Chiara Biasoli, M.D., Shannon Carpenter, M.D.


<table>
<thead>
<tr>
<th>Reference/study design</th>
<th>No. patients, age at start of prophylaxis, prophylactically bleeding frequency</th>
<th>SAP dose</th>
<th>Duration of SAP (range)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized crossover study of 10 pts of aPCC prophylaxis</td>
<td>26</td>
<td>2.5-8.12 y</td>
<td>3 10 unit/kg every other day</td>
<td>12 mo</td>
</tr>
<tr>
<td>aPCC 85 U/kg ≤ 15% on</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 nonconsecutive days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy or once every 2 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or twice a week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significantly fewer absences from school/work during prophylaxis.

Figure 2. bleeding episodes during the two treatment periods.

Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors


Haemophilia (2014), 20, 65–72

<table>
<thead>
<tr>
<th>Reference/study design</th>
<th>No. patients, age at start of prophylaxis, prophylactically bleeding frequency</th>
<th>SAP dose</th>
<th>Duration of SAP (range)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized control</td>
<td>56</td>
<td>7-56 y</td>
<td>aPCC 85 U/kg every other day</td>
<td>12 mo</td>
</tr>
<tr>
<td>Randomized crossover study of 10 pts of aPCC prophylaxis with 12 mo of on-demand therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. New target joints and associated bleeding episodes.
Conclusions of the clinical trials / bypassing agent prophylaxis

- BAP reduces bleedings and improves QoL*
- Most of the knowledge is based on relatively short courses in series of patients with joint damage: no strong evidence for arthropathy prevention
- 1 series of early and long term BAP (> 6y) with encouraging data
- Which choice criteria among the products?

* Pro-FeibaStudy: Gringeri A et al, Haemophilia 2013
* Ettingshausen C. et al, Haemophilia 2010

Prophylaxis and Immunotolerance in the real life of patients with inhibitor
**Case 1:** 35y, sHA, HR inhibitor, 32 UB at 3y
Challenged X times / FVIII
Treated on demand with aPCC
No ITI till 32y, severe bleeder phenotype
High dose aPCC prophylaxis (< 48h)
Additional infusions +++ of aPCC / bleeds

Severe arthropathy, target joints, disability and impaired quality of life despite hard constraints and highly costly treatment

Expertise by social insurance (3 times)

Overtreatment ? Unjustified TRT ?

---

**Case 1: ITI and outcome**

First course of ITI, high dose (100 UI/kg x 2/d – 200 UI/kg/d)
Opportunity of knee arthroplasty after years of aPCC prophylaxis, using continuous infusion with Factor VIII to start a previously negotiated ITI

Moderate anamnestic response, rapidly favourable outcome
ITI declared as a success after 24 months (no inhibitor, N recovery, half life > 8h) - Efficient FVIII Prophylaxis each other day
Rare bleedings, positive psychological effect, cost reduction +++

*Never too late ?*
**Case 2 : 6y, sHA, HR inhibitor**

8 BU at 1y, discovered after 7 CED, elbow haemarthrosis with poor response to FVIII

Treatment / rFVIIa on demand

Immediate start of ITI : peak 410 BU at 10 days

Poor compliance, poor peripheral venous access

Several complications: infections and mechanical dysfunction of the Central Venous Devices

Frequent hematomas and hospitalisations

Intermittent prophylaxis (rFVIIa)

Partial response : stop ITI after 6 months (40 BU)

*Not prepared and too early ITI ?*

---

**Case 2 :**

1st course ITI stopped after 6 months (18 m old)
Inhibitor < 5 / 1 / 0 UB 10 / 16 / 21 months later

Treatment / rFVIIa on demand

Recurrence of elbow hemarthroses, target joint

A new Port a cath for rFVIIa prophylaxis 1 year later

Good observance and feasability of venous access

3y old, project of school, 2nd course of high dose ITI and FEIBA prophylaxis (Bonn regimen):

Inhibitor = 0 / 320 / 1500 BU at D0/, D3, D10

Clinical response at 6 months (stop FEIBA)

Complete response 14 m later (FVIII prophylaxis eod)

*The right treatment at the right moment ?*
Conclusion (1)

Treatment of bleeds / bypassing agents is well known but not optimal for many patients with inhibitor

ITI should be undertaken at least once in each patient in good conditions but the optimal characteristics and the criteria of failure remain to define

Indications of By-Passing Agent Prophylaxis remains debated and even a controversial subject with reimbursement organisms

Conclusion (2)

ITI and BA Prophylaxis represent challenging treatments, with key issues for the patient, his family and the society. All potential difficulties, such as venous access or other practical conditions have to be addressed before starting these treatments to optimize the adherence: education and multidisciplinary support are critical.

Indications of ITI and BA Prophylaxis represent rare situations in a rare disease: clinical trial and registries are complementary tools to be encouraged to complete the knowledge in this field.
Thank you

Back Up
High-dose ITI - the Bonn Protocol

**Original Bonn Protocol**
LR: 50-100 IU FVIII/kg body weight/d, every other day or 3 times per week
HR: 100 IU FVIII/kg bw i.v. twice daily and FEIBA 50 IU /kg bw i.v. twice daily

**Modified Bonn Protocol**
HR: 100-150 IU FVIII/kg bw every 12 hours; according to the bleeding tendency concomitant treatment with FEIBA 50-100 IU/kg bw once or twice daily

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-ITI titer [BU]</th>
<th>Time to BU &lt;1 [mo]</th>
<th>Time to complete success [mo]</th>
<th>Success rate in HR [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kreuz et al., Haemophilia 1995</td>
<td>42 (0.8-1052)</td>
<td>2.5</td>
<td>4 (0.5-42)</td>
<td>14/16 (87%)</td>
</tr>
<tr>
<td>Brackmann et al, Vox Sang 1996</td>
<td>89 (0.8-520)</td>
<td>7 (0.7-15)</td>
<td>14.5 (4.1-25.4)</td>
<td>21/22 (95%)</td>
</tr>
</tbody>
</table>

Low dose ITI – Van-Creveld-Protocol

25-50 IU FVIII/kg bw every other day*

*FVIII dosage is decreased each time the absolute FVIII recovery was > 30% until prophylactic dose (10-15 IU/kg bw) is reached

Probability of the presence of a clinically relevant inhibitor level under low dose ITI

Mauser-Bunschoten et al, Blood 1995

- Success rate 86%
- Success rate associated with pre-ITI titre and maximum BU < 40
- Time to success predicted by maximum BU < 40
- Low dose ITI beneficial for inhibitor patients with maximum BU < 40

Ter Avest et al, Haemophilia 2010
**Malmö Protocol**

- Extracorporeal immune adsorption with Protein-A-columns on two consecutive days
- Cyclophosphamid (12-15 mg/kg bw i.v. for two days after start of ITI followed by 2-3 mg/kg bw for 5 days)
- Intravenous gammaglobulins (400 mg/kg bw for 5 days)
- Administration of FVIII concentrate at 8-12 hour intervals to maintain FVIII:C 40-100%

- Success rate 62.5% (10/16 pts)
- Duration of treatment 9-37 days

**ITI Protocols**

<table>
<thead>
<tr>
<th>Bonn protocol</th>
<th>Malmo protocol</th>
<th>van Creveld</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII 100 U/kg BID</td>
<td>Immunoadsorption using protein A column if inhibitor titer &gt;10 BU/mL</td>
<td>FVIII 25-50 IU/kg BID for 1-2 weeks then 25 IU/kg every other day</td>
</tr>
<tr>
<td>FEIBA 100 U/kg BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cyclophosphamid 12-15 mg/kg IV daily x 2 days then 2-3 mg/kg PO daily x 8-10 days

FVIII is given to achieve a 40%-100% FVIII level followed by FVIII infusion every 8-12 hours to achieve 30%-80% level

IVIG 2.5-5 g IV immediately after the first FVIII infusion followed by 0.4 g/kg daily days 4-8
How I treat bypassing therapy for prophylaxis in patients with hemophilia A and inhibitors

Cindy A. Leissinger, Tammuella Singleton, and Rebecca Kruso-James

1Louisiana Center for Bleeding and Clotting Disorders, Tulane University Medical Center, New Orleans, LA; and 2Washington Center for Bleeding Disorders, Bloodworks Northwest, Seattle, WA

(Blood. 2015;126(2):153-159)

Table 1. Prospective, randomized clinical trials of BAP in patients with hemophilia

<table>
<thead>
<tr>
<th>Study design</th>
<th>No. patients, age at start of prophylaxis (years)</th>
<th>BAP dose (µg/kg/day)</th>
<th>Duration of BAP (days)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sit: Prospective study</td>
<td>22</td>
<td>rt VIIa 900 µg/kg/day</td>
<td>3 mo</td>
<td>45% reduction in bleeding events treated with 90 µg/kg per day</td>
</tr>
<tr>
<td>(1) randomized, double-blind study</td>
<td></td>
<td>rt VIIa 270 µg/kg/day</td>
<td></td>
<td>55% reduction in bleeding events treated with 270 µg/kg per day (not statistically significant compared with placebo)</td>
</tr>
<tr>
<td>(2) randomized, crossover study</td>
<td></td>
<td></td>
<td></td>
<td>Significantly fewer hospital admissions and absences from schoolwork during prophylaxis</td>
</tr>
<tr>
<td>Study of 6 mo of APC at enrollment</td>
<td></td>
<td></td>
<td></td>
<td>62% reduction in all bleeding events</td>
</tr>
<tr>
<td>Study of 114 patients</td>
<td></td>
<td></td>
<td></td>
<td>61% reduction in major joint bleeds</td>
</tr>
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<td></td>
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<table>
<thead>
<tr>
<th>No. patients, age at start of prophylaxis (years)</th>
<th>BAP dose (µg/kg/day)</th>
<th>Duration of BAP (days)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of 114 patients</td>
<td>60</td>
<td>APC:Cq &gt; 15 U/kg every 3 mo</td>
<td>72.5% reduction in annual bleeding rate</td>
</tr>
</tbody>
</table>
Access: supply, procurement & tenders

Dr Paul Giangrande
Chairman, Medical Advisory Group
&
Brian O Mahony
President,
European Haemophilia Consortium

Recommendations from previous “Kreuth” meetings:

- A network of comprehensive care centres should be established in each country (1999)
- National database is desirable (1999)
- Advocate establishment of formal system in each country to ensure best practice (2009)
- Foster equitable access to treatment in EU (2009)
- The minimum factor VIII consumption level in a country should be 3 iu/capita (2013)
- Decisions on whether to adopt new product should not be based solely on cost (2013)
EHC Survey:

- Survey carried out in late 2014: sent to all 45 patient National Haemophilia Organisations
- 38 completed surveys received:
  - 20 by patient organisations (NMOs)
  - 7 by clinicians
  - 11 by both patient organisations/clinicians
- Clarifications received from doctors nominated by EAHAD from 5 countries
Procurement method:

**Tender (19)**
- Albania
- Azerbaijan
- Belarus
- Bosnia & Herzegovina
- Czech Republic
- Denmark
- Hungary
- Ireland
- Moldova
- Montenegro

**Alternative (17)**
- Poland
- Portugal
- Romania
- Russia
- Serbia
- Slovak Republic
- Slovenia
- Ukraine
- United Kingdom

**Both (2)**
- Austria
- Belgium
- Croatia
- Estonia
- Finland
- France
- Germany
- Greece
- Italy
- Kyrgyzstan
- Latvia
- Netherlands
- Norway
- Spain
- Sweden
- Switzerland
- Turkey

COUNTRIES: Albania, Azerbaijan, Austria, Belarus, Belgium, Bosnia & Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom.
Products tendered for:

• 18/19 tendered for plasma derived FVIII
• 13 tendered for plasma derived FVIII/VWF
• 16 tendered for recombinant FVIII
• 17 tendered for plasma derived FIX
• 8 tendered for recombinant FIX
• 11 tendered for bypassing agents
• 11 tendered for PCC’s
• 7 tendered for products for rare bleeding disorders

Selection criteria:

**Tender (19)**
- Price 18
- Safety 14
- Quality 12
- Efficacy 12
- Supply 10
- Convenience 8

**Alternative/ Combined (19)**
- Price 12
- Safety 9
- Quality 8
- Efficacy 10
- Supply 6
- Convenience 3
Clinician involvement in tender process:

19 Countries
• All have a legal framework for tender
• 16 have a tender board
• Clinicians involved in 16/19 countries
  - Formally involved in all aspects in 5 countries
  - Scientific and technical aspects only in 6
  - Informally involvement/observers in 5
  - Not involved at all in 2
  - No response from 1

Involvement in alternative /combined process:

19 Countries
• 14 have a legal framework for tender
• 8 have a procurement board
• Clinicians involved in 12/19 countries
  - Scientific and technical aspects in 3
  - Informally involved in 9
  - Not involved in 7
Patient involvement in procurement:

- **Patient organisation involved in 15/19 countries which hold tenders:**
  - Formally involved in all aspects in just 2 countries
  - Scientific and technical aspects only in 3
  - Informally involved/observer in 5
  - Not involved at all in 9

- **Patient organisation involved in 6/19 countries which organise alternative procurement processes:**
  - Formally involved in 1
  - Informally involved in 5
  - Not involved in 13

### Main representatives on tender boards:

<table>
<thead>
<tr>
<th>Health Insurance funds</th>
<th>Medicines agencies or pharmacies</th>
<th>Hospitals or blood centres</th>
<th>Ministries of Health</th>
<th>Clinicians or Haemophilia Centres</th>
<th>Patient Organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosnia&amp;Herzegovina</td>
<td>Denmark</td>
<td>Albania</td>
<td>Albania</td>
<td>Ireland</td>
<td>Ireland</td>
</tr>
<tr>
<td>Hungary</td>
<td>United Kingdom</td>
<td>Czech Republic</td>
<td>Azerbaijan</td>
<td>Denmark</td>
<td>Serbia</td>
</tr>
<tr>
<td>Montenegro, Serbia</td>
<td>Azerbaijan</td>
<td>Ireland</td>
<td>Belarus</td>
<td>Montenegro</td>
<td>Serbia</td>
</tr>
<tr>
<td>Slovak Rep.</td>
<td>Romania</td>
<td>Portugal</td>
<td>Ireland</td>
<td>Serbia</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

**Involved in all aspects of the process**

- Romania
- Portugal
- Bosnia & Herzegovina
- Moldova

**Involved only in scientific and technical aspects of the process**

- Portugal
- Slovenia
- United Kingdom
Main representatives on procurement boards:

<table>
<thead>
<tr>
<th>Health Insurance funds</th>
<th>Medicines agencies or pharmacies</th>
<th>Procurement Agencies</th>
<th>Ministries of Health or Local authorities</th>
<th>Clinicians or Haemophilia Centres</th>
<th>Patient Organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyrgyzstan</td>
<td>France</td>
<td>Kyrgyzstan</td>
<td>Kyrgyzstan</td>
<td>Italy</td>
<td>Kyrgyzstan</td>
</tr>
<tr>
<td></td>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>Kyrgyzstan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Involved in all aspects of the Process

Involved only in Scientific and Technical aspects of the process

<table>
<thead>
<tr>
<th>Tender /Procurement Boards: duration of terms of office and contracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term of office of the committee</td>
</tr>
<tr>
<td>Tender: 9 2.3</td>
</tr>
<tr>
<td>Alternative: 3 1.5</td>
</tr>
<tr>
<td>Typical duration of the contract awarded</td>
</tr>
<tr>
<td>Tender: 18 1.4</td>
</tr>
<tr>
<td>Alternative: 7 1.9</td>
</tr>
</tbody>
</table>
Outcomes:

Lower prices obtained for most products when using tender system compared to alternative procurement process:

- Recombinant FVIII: 0.56 vs. 0.69 €/unit (19%↓)
- Plasma derived FVIII: 0.4 vs. 0.64€/unit (37%↓)
- Plasma derived FIX 0.4 vs. 0.54 €/unit (26%↓)

No difference in case of recombinant factor IX, where monopoly exists (0.73 vs. 0.72 €/unit)

<table>
<thead>
<tr>
<th></th>
<th>Tender</th>
<th>Alternative Process</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (€)</td>
</tr>
<tr>
<td>Recombinant FVIII*</td>
<td>12</td>
<td>0.56</td>
</tr>
<tr>
<td>Plasma-Derived FVIII</td>
<td>15</td>
<td>0.40</td>
</tr>
<tr>
<td>Recombinant FIX</td>
<td>6</td>
<td>0.73</td>
</tr>
<tr>
<td>Plasma-Derived FIX*</td>
<td>15</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Clinician involvement:

- Significant reduction also noted in price of by-passing agents when clinicians were involved

Patient involvement:
Conclusions of EHC survey:

- Tenders promote real competition and result in lower prices
- Cost savings not as significant where there is a product monopoly
- Involvement of both clinicians and patient organisation in tender process helps to deliver best outcomes
- Registries can be vital to predict demand

Fig. 1. Annual UK factor VIII usage per calendar year, 1989–2011, inclusive. This shows a greater than fourfold increase in factor VIII consumption over two decades. The dip in usage in 2001 corresponded to the interruption in supply of Kogenate and Helixate, which halved the UK supply of rFVIII for 18 months, highlighting the importance of security of supply.

UK tender process:


- Individual centres negotiated contracts before 2004: great variability in price
- Policy of recombinant for all launched in 1996 but took until 2005 to be fully adopted
- Four national procurement exercises:
  - 2004-2006
  - 2007-2010
  - 2010-2014
  - 2014-2017

Objectives:


1. Establish a national framework contract for the whole UK (except Scotland) to run for 2 years with an option to extend for a further year.
2. Induce the manufacturers to behave in a truly competitive way to achieve maximum reduction in unit price.
3. Maintain plurality in the marketplace, retaining all of the suppliers.
4. Maintain some degree of prescribing freedom.
UK national procurement:

• Price of products has fallen significantly:
  – Savings of GB£ ≈260 M
  – “We probably have the lowest recombinant factor VIII prices in Europe, if not the world” UKHCDO Annual Report, 2010
  – Price now lower than plasma-derived factor VIII products
• No resistance to switching from patients
• No increase in incidence of inhibitors

UK national procurement:

• Process has evolved over the years
• Sealed bids have replaced e-auction
• Process links price to volume:
  – >200 M IU; 100-200 M IU; <100 M IU
• No product has been excluded from UK
• Further savings by introducing home delivery
  – (20% VAT payable on products used in hospitals but NOT if supplied to patient at home)
Current procurement system:

- Process led by Commercial Medicines Unit (CMU) of Department of Health
- 3 or 4 doctors nominated by UKHCDO to participate in process (alongside 2 commissioners and patient representative)
- Doctors advise on product selection criteria and volume bands
- Doctors not involved in any face-to-face meetings with companies
- Doctors not present when bids are opened

Provide feedback on service:

- Feedback sought by Commercial Medicines Unit of Department of Health from all haemophilia centres in May 2015
- Covers ten areas of supplier performance
- Possible ratings: excellent/good/average/poor/very poor
- Views on performance of home delivery companies also sought
Provide feedback on service:

- Customer service
- Local company representative
- Accuracy of deliveries
- Timeliness of deliveries
- Order fulfilment
- Invoicing process
- Value added services offered by supplier
- Handling of complaints
- Overall satisfaction

<table>
<thead>
<tr>
<th>QUESTIONS</th>
<th>Excellent</th>
<th>Good</th>
<th>Average</th>
<th>Poor</th>
<th>Very Poor</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  How would you rate the Customer Service provided by the supplier?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2  How would you rate the handling of complaints by the supplier?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3  How would you rate your local representative?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4  How would you rate the support you receive from your local representative?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>5  How would you rate timeliness of deliveries?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6  How would you rate the accuracy of the deliveries?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>7  How would you rate order fulfillment?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>8  How would you rate the invoicing process?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9  How would you rate the value added services offered by the supplier?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>10 How would you rate the supplier’s overall performance?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADDITIONAL QUESTION</th>
<th>Excellent</th>
<th>Good</th>
<th>Average</th>
<th>Poor</th>
<th>Very Poor</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 How would you rate your homecare delivery supplier?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Principal conclusions:

- Tenders can deliver significant cost savings:
  - Greater volume can be bought with allocated budget
  - Savings can be ploughed back into service development
  - Savings not as significant where there is a monopoly
- National system with formal involvement from clinicians and patient organisation delivers the best results
- Process requires training and preparation
- Important that cost does not become the only criterion taken into account during tender process
- Registries help to predict demand for products
“This way, health of people with haemophilia has become dependent on cheaper products and not necessarily the most effective and safe products. On the other hand, medical experts in haemophilia who should be the very important voice in the scientific and medical choice of these products have been relegated to a completely secondary role in the choice of therapies that will be administered to their patients.”

HEMOPHILIA CARE IN EUROPE AND THE USA
CURRENT DATA AND FUTURE TRENDS

Patrick Robert
The Marketing Research Bureau, Inc.

CLINICAL USE OF CLOTTING FACTORS & PLATELETS
KREUTH IV
May 6-7, 2016
Freising, Germany

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- Current Market: Europe
- Current Market: United States
- Future trends
From 1996 to 2014, the consumption of plasma-derived and recombinant factor VIII went up at an annual rate of 7.7%.

From 2008 onward, the annual growth rates of both plasma-derived and recombinant factor VIII declined because the number of new patients going on prophylaxis shrank year after year.

During the period 1996 – 2014, the factor VIII consumption grew faster than the population because of newly diagnosed patients, prophylaxis, higher doses prescribed on demand, more elective surgeries, weight gain and generally easier access to products, whose supply grew rapidly with the increasing production of recombinant products.
THE PLASMA PROTEINS MARKET IN EUROPE - 2014

CHANGE IN FACTOR VIII CONSUMPTION BETWEEN 2011 AND 2014
(Recombinant & Plasma-derived Factor VIII)

- Netherlands: -7.4%
- Greece: 0.6%
- Austria: 1.7%
- Russia: 2.5%
- Czech Republic: 4.3%
- Portugal: 1.4%
- Croatia: 3.5%
- Greece: 3.3%
- Baltic States: 2.9%
- Macedonia: 7.8%
- Serbia: 3.4%
- Bosnia: 7.6%
- Kosovo: 0.8%
- Montenegro: 2.0%
- Bulgaria: 1.8%
- Romania: 1.0%
- Ukraine: 0.9%
- Albania: 0.4%
- Sweden: 17.6%
- Germany: 17.1%
- Slovakia: 15.5%
- France: 15.4%
- Ireland: 15.4%
- Bulgaria: 13.7%
- Hungary: 12.6%
- United Kingdom: 11.7%
- Spain: 11.3%
- Denmark: 10.0%
- Belgium: 3.7%
- Baltic States: 2.9%
- Russia: 2.5%
- Austria: 1.7%
- Greece: 0.6%
- Netherlands: 17.4%

All Countries: 17.6%

2014 vs 2011: 0-98.6%
From 1996 to 2014, the consumption of plasma-derived and recombinant factor IX went up at an annual rate of 6.7%. Recombinant FIX growth rate was higher than rFVIII (14.6% vs. 12.5%).

From 2008 onward, the annual growth rates of recombinant factor IX declined because the number of new patients going on prophylaxis shrank year after year.

During the period 1996 – 2014, the factor IX consumption grew faster than the population because of newly diagnosed patients, prophylaxis, higher doses prescribed on demand, more elective surgeries, weight gain and generally easier access to products, whose supply grew rapidly with the increasing production of recombinant products.
Recombinant factor VIII was adopted faster in the United States than in Europe
MARKET PENETRATION OF RECOMBINANT FACTOR VIII 2005 - 2015
(Percent of Patients in the Sample)

MARKET SHARE CHANGE BETWEEN Q1/13 AND Q4/14 - FACTOR VIII CONCENTRATES
(Percentage of Patients in the Sample)
Recombinant factor IX was adopted quickly in the United States than in Europe because of plasma-derived FIX shortage in 1999.
In the United States the adoption of prophylaxis has accelerated: from 20% of hemophilia A and B patients in 2002 to almost 50% in 2012.

In 2014, 63% of the severe and moderate hemophilia A patients were on prophylaxis, and 24% of the hemophilia B patients.

In 2015, the introduction of the extended half-life recombinant products in the US did not elicit many conversions of new patients to prophylaxis, if any – particularly Eloctate. This may change in the future with CSL Behring’s Idelvion and with the introduction of monoclonal antibodies (Roche’s ACE 90, and Alnylam’s Fitusiran)

Percentage of Hemophilia Patients on Prophylaxis - 2002 to 2012 - United States

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent</td>
<td>16.6%</td>
<td>15.8%</td>
<td>17.3%</td>
<td>17.3%</td>
<td>15.9%</td>
<td>16.4%</td>
<td>13.2%</td>
<td>14.6%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Temporary</td>
<td>83.4%</td>
<td>84.2%</td>
<td>82.7%</td>
<td>82.7%</td>
<td>84.1%</td>
<td>86.6%</td>
<td>86.8%</td>
<td>86.4%</td>
<td>86.9%</td>
</tr>
<tr>
<td>Total</td>
<td>49.7%</td>
<td>48.7%</td>
<td>51.0%</td>
<td>51.0%</td>
<td>49.3%</td>
<td>51.5%</td>
<td>50.8%</td>
<td>50.8%</td>
<td>50.4%</td>
</tr>
</tbody>
</table>

From 2002 to 2013, the percentage of hemophilia A patients on immune tolerance almost doubled in the US.

Approximately two thirds of the patients were prescribed a recombinant factor VIII, one quarter, Grifols Alphanate.

Due to its small sample, the survey did not indicate that patients on plasma-derived factor VIII had lower inhibitor development than those on recombinant factor VIII.

Table of Contents

- Current Market: Europe
- Current Market: United States
- Future trends
The gradual market penetration of the extended half-life (EHL) recombinant factors VIII and IX products are expected to have the following consequences:

- The number of international units sold will stabilize and possibly go down in Europe and the US.

- On the global market, the consumption of standard rFVIII and rFIX, as well as of plasma-derived factor products will continue to grow.

- Expenditure will continue to go up because the price per unit of the EHL recombinant factors will be higher than the price of the standard recombinant factors.
CONCLUSIONS

- In the 1990s, the recombinant factor products improved the safety of hemophilia care,

- The extended half-life recombinant factors are now enhancing treatment comfort, enabling patients to enjoy a quasi normal life,

- Inhibitor development may be attenuated or eradicated with the novel treatments (gene therapy, monoclonal antibodies),

- Cost and global access to factor therapy will remain major issues in the years to come.

Thank you!

www.marketingresearchbureau.com
Current practice in platelet transfusion

Gregor Bein
Institute for Clinical Immunology and Transfusion Medicine
Justus-Liebig-University Giessen

Center for Transfusion Medicine and Hemotherapy
German Center for feto-maternal Incompatibility
Universities of Giessen & Marburg Hospital, Germany

Current practice in platelet transfusion

• Hematology and Oncology patients
• Surgical patients
• ICU patients
• ABO and Rh D compatibility
  • Assessment of clinical efficacy (Lozano)
  • Pathogen reduced PCs (McLennan, Cazenave)
  • Pool vs Apheresis PCs (Garraud)
  • Platelet refractoriness (Garraud)
Current practice in platelet transfusion

Platelet transfusion
  Treatment of bleeding
  Prevention of bleeding

How to assess efficacy and safety?

Observational studies in transfusion medicine

• Question: Association of blood (platelet) transfusion and survival?

  e.g. Coronary artery bypass graft (CABG) surgery

• Answer: Transfusion is associated with decreased survival
Observational studies in transfusion medicine

Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes

![Graph showing the comparison of patients with and without platelet transfusions post-CABG (Primary and Reoperation CABG) for stroke and death.](image)

Spiess BD et al., Transfusion 44:1143 (2004)

Observational studies in transfusion medicine

Full adjustment for confounding variables:

Platelet transfusion at the time of CABG is not associated with adverse outcomes

Observational studies in transfusion medicine

Confounding by Indication

Guidelines

German Medical Association
Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives

Hematology and Oncology patients

Prophylactic platelet transfusion - threshold

Fecal blood loss in thrombocytopenic patients

Hematology and Oncology patients
Prophylactic platelet transfusion - threshold

**Patients with impaired platelet production (chemotherapy)**

<table>
<thead>
<tr>
<th>Prophylactic platelet transfusion: PLT count ≤ 10 x 10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional risk factors* for bleeding: PLT count ≤ 20 x 10⁹/L</td>
</tr>
</tbody>
</table>

*Infections, complications (GVHD), evidence of hemorrhage, fever above 38°C, leucocytosis, coagulation disorders, sharp decline in platelet count, pre-existing necrotic areas

---


255 adult AML patients receiving induction chemotherapy

1. Standard arm: platelets given if count < 20 x 10⁹/L
2. Low threshold arm: platelets given if counts < 10 x 10⁹/L with a temperature of < 38°C, 10-20 x 10⁹/L with temperature > 38°C, or if bleeding
### Hematology and Oncology patients

**Prophylactic platelet transfusion - threshold**

**Cochrane review 3 RCTs**
- Diedrich B et al., Transfusion 45:1064 (2005)

#### Outcomes up to 30 days

<table>
<thead>
<tr>
<th>Outcomes up to 30 days</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect</th>
<th>Participants</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher trigger 20 / 30 x 10⁹/L</td>
<td>Lower trigger 10 x 10⁹/L</td>
<td>RR</td>
<td>Participants</td>
</tr>
<tr>
<td>Patients with bleedings</td>
<td>177 per 1000 (168 to 336)</td>
<td>239 per 1000</td>
<td>RR 1.35 (0.95 to 1.9)</td>
<td>499 (3 studies)</td>
</tr>
<tr>
<td>Patients with bleedings grade 3 or 4</td>
<td>82 per 1000 (43 to 154)</td>
<td>81 per 1000</td>
<td>RR 0.99 (0.52 to 1.88)</td>
<td>421 (2 studies)</td>
</tr>
<tr>
<td>No of platelet transfusions</td>
<td>2.09 lower (3.2 to 0.99)</td>
<td></td>
<td></td>
<td>333 (2 studies)</td>
</tr>
<tr>
<td>Mortality</td>
<td>75 per 1000 (62 to 286)</td>
<td>134 per 1000</td>
<td>RR 1.78 (0.83 to 3.81)</td>
<td>255 (1 study)</td>
</tr>
</tbody>
</table>

Conclusion
Standard trigger (10 x 10^9/L) compared to a higher trigger
– No increase in the risk of bleeding (low-quality evidence)

Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion

Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematologic malignancies: an open-label, multicentre, randomised study


Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion

### Hematology and Oncology patients

#### Therapeutic-only vs prophylactic platelet transfusion

**Crighton GL et al., Cochrane Database Syst Rev 9:CD010981 (2015)**

<table>
<thead>
<tr>
<th>Outcomes up to 30 days</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Participants (studies)</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days with bleeding</td>
<td>0.5 higher (0.1 to 0.9)</td>
<td>RR 4.91 (0.86 to 28.12)</td>
<td>599 (1 study)</td>
<td>moderate</td>
</tr>
<tr>
<td>Patients with bleedings grade 3 or 4</td>
<td>3 per 1000 to 10 per 1000 (3 to 71)</td>
<td>RR 4.91 (0.86 to 28.12)</td>
<td>801 (2 studies)</td>
<td>low</td>
</tr>
<tr>
<td>No of platelet transfusions</td>
<td>0.5 lower (0.63 to 0.37)</td>
<td>RR 4.91 (0.86 to 28.12)</td>
<td>801 (2 studies)</td>
<td>moderate</td>
</tr>
</tbody>
</table>

**TABLE**

**Bleeding in two randomized controlled studies**

<table>
<thead>
<tr>
<th>WHO Bleeding Scale*</th>
<th>Wandt et al. (12)</th>
<th>p-value</th>
<th>Stanworth et al. (13, 22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>prophylactic</td>
<td>therapeutic</td>
<td>prophylactic</td>
<td>therapeutic</td>
</tr>
<tr>
<td>All patients</td>
<td>65 / 343 (19)%</td>
<td>4 (1)</td>
<td>12 / 299 (43)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (1)</td>
<td></td>
<td>12 / 301 (42)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>4 (1)</td>
<td></td>
<td>13 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Autologous HSCT</td>
<td>0 (0)</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0 (0)</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0)</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>5 / 20 (24)</td>
<td></td>
<td>9 / 158 (51)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (1)</td>
<td></td>
<td>3 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>4 (2)</td>
<td></td>
<td>13 (7)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*WHO Grade 2: mild bleeding (more than isolated petechiae); no enzythrocyte transfusion required; WHO Grade 3: bleeding requiring red cell transfusion; WHO Grade 4: symptomatic retinal or CNS bleeding, any life-threatening or fatal bleeding

**Wandt et al., Dtsch Arztebl Int 111:809 (2014)**
Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion

Conclusion
Prophylactic platelet transfusion
- Reduces bleeding episodes (primarily WHO grade 2)
- Insufficient evidence: WHO grade 3 or 4 bleeding, mortality
- 33% more platelet transfusions required


Hematology and Oncology patients
Different doses of prophylactic platelet transfusion

Cochrane review 7 RCTs

Conclusion
Low dose platelet transfusion
- requires more transfusions
- no increase in the risk of bleeding

High dose platelet transfusion
- does not decrease the number of transfusions
- no decreased risk of bleeding
- increase of adverse events?

Platelet transfusion for patients with hypoproliferative Thrombocytopenia - Summary

- Prophylactic platelet transfusions should be given (autologous HSCT?)
- Threshold: $\leq 10 \times 10^9$/L
- The standard dose of platelet concentrates is appropriate
Platelet transfusion thresholds prior to insertion of central lines

Cochrane review: No RCT

Surgical patients
## Platelet transfusion trigger in surgical patients

- **Minor surgery** \( \leq 20 \times 10^9/L \)
- **Major surgery** \( \leq 50 \times 10^9/L \)
- **Neuraxial surgery** \( \leq 70 - 100 \times 10^9/L \)
- **Massive bleeding** \( \leq 100 \times 10^9/L \)

Weak recommendations

low- to very-low-quality evidence

Throbocytopenia in the ICU patient
- PLT count within the first 24 hours of septic shock -

Figure 1. Kaplan-Meier survival estimates depending on the platelet count (EPodemology of Septic Shock Study, 2009–2013). p value from the log-rank test: less than 0.0001 for platelet count of more than 150,000/mm³ versus less than or equal to 50,000/mm³, p = 0.0025 versus 50–100,000/mm³ and p = 0.0421 versus 100–150,000/mm³.

Thiery-Antier N et al., Crit Care Med 44:754 (2016)

Conclusion
- High-quality data to support or refute the need for prophylactic platelet transfusion in the ICU are lacking

ABO-incompatible platelet (plasma) transfusion

25 publications report hemolytic transfusion reactions

In all cases but one, the implicated titer of anti-A or anti-B was
> 100 (saline) or
> 400 (antiglobulin)

Conclusion

– A low titer of anti-A/B will minimize the risk of hemolytic transfusion reaction
Further research is required

Rh D-incompatible platelet transfusion

Conclusion
- Rh Immune Globulin prophylaxis, if Rh D-mismatched platelet concentrates prepared from whole blood are transfused to Rh D negative females of childbearing potential

Pai M et al., Transfusion 56:550 (2016)

Conclusion

- Development of international standards for assessment and documentation of bleeding across transfusion trials
- Hypoproliferative thrombocytopenia and a no-prophylactic platelet transfusion strategy: patients perspective? Quality of life?
- Evidence based guidelines for platelet transfusion: Adherence to these guidelines?
How do we assess clinical efficacy of platelet transfusion?

Miguel Lozano, MD, PhD
Department of Hemotherapy and Hemostasis
University Clinic Hospital
Barcelona, Spain

Clinical Efficacy of Platelet Transfusion

- Prophylactic transfusion:
  - Increase patient’s platelet count
  - Prevent bleeding from occurring

- Therapeutic transfusion:
  - Stop bleeding
Assess Clinical Efficacy

• In clinical studies
• In routine practice

Platelet concentrates evaluation

• *In vitro* studies
• *In vitro* studies under flow conditions
• *In vivo* studies with radiolabeled platelets
• Clinical studies
• Postmarketing surveillance
Clinical Studies

- Postransfusion corrected count increment:
  - 1 hour
  - 24 hour
- % of successful platelet transfusion
- Interval between consecutive platelet transfusions
- Bleeding score

Corrected count increment calculation:

\[
CCI = \frac{(\text{Post} \cdot \text{transf. plt count} - \text{Pre} \cdot \text{transf. plt count}, \times 10^9/L) \times \text{body surface area, m}^2}{\text{Platelets transfused, } \times 10^{11}}
\]

\[
24 \cdot \text{hours } CCI = \frac{(25 - 5) \times 1.5}{3.5} = \frac{20 \times 1.5}{3.5} = 8.5
\]
The value of 10-minute posttransfusion platelet counts

B. O’CONNELL, E. J. LEE, AND C. A. SCHIFFER

Monitoring of platelet counts 1 hour after transfusion has become standard practice in most centers. In this study, platelet counts obtained 10 and 60 minutes after 48 platelet transfusions were compared. There was a close linear relationship (r = 0.98) between these values over a wide range of posttransfusion counts, indicating rapid equilibration of transfused platelets. Ten-minute posttransfusion samples are easier to obtain and are convenient for both patients and medical staff. TRANSFUSION 1988;28:66–67.

Definition of Successful Platelet Transfusion

• Corrected count increment:
  - 1 hour: > 7.5
  - 24 hour: > 4.5

Clinical Studies

- Postransfusion corrected count increment:
  - 1 hour
  - 24 hour
- % of successful platelet transfusion
- Interval between consecutive platelet transfusions
- Bleeding score

A randomized noninferiority crossover trial of corrected count increments and bleeding in thrombocytopenic hematology patients receiving 2- to 5- versus 6- or 7-day–stored platelets

_Sheila MacLevan,1 Kay Harding,2 Charlotte Llewelyn,2 Louise Choo,1 Lekha Bukrania,3 Edwin Massey,2,4 Simon Stanworth,5 Kate Pendry,2,6 and Lorna M. Williamson2_

BACKGROUND: Bacterial screening offers the possibility of extending platelet (PLT) storage to Day 7. We conducted a noninferiority, crossover trial comparing PLTs stored for 6 or 7 days versus 2 to 5 days.

STUDY DESIGN AND METHODS: Stable hematology patients were allocated to receive blocks of 2- to 5- and 6- or 7-day PLTs in random order. The primary outcome was the proportion of successful transfusions during the first block, defined as a corrected count increment (CCI) of more than 4.5 at 8 to 24 hours posttransfusion.
Clinical Studies

- Postransfusion corrected count increment:
  - 1 hour
  - 24 hour
- % of successful platelet transfusion
- Interval between consecutive platelet transfusions
- Bleeding score

Time To Next Transfusion After The Study Transfusion

<table>
<thead>
<tr>
<th>Survival Distribution Function</th>
<th>Intercept (n=105)</th>
<th>Reference (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to next platelet transfusion (days)</td>
<td>2.2</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Log-rank Test,  \( p = 0.717 \)

Clinical Studies

- *Postransfusion corrected count increment:*
  - 1 hour
  - 24 hour
- *Interval between consecutive platelet transfusions*
- *Bleeding score expressed as % of patients or % of days with bleeding*
% of Patients with Grade 2 or greater

<table>
<thead>
<tr>
<th>Study</th>
<th>Grade ≥2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRINT control¹</td>
<td>63.6 %</td>
<td>WHO</td>
</tr>
<tr>
<td>SPRINT amotosalen¹</td>
<td>62.6 %</td>
<td>WHO</td>
</tr>
<tr>
<td>SToP low dose²</td>
<td>51.7 %</td>
<td>WHO</td>
</tr>
<tr>
<td>SToP standard dose²</td>
<td>49.2 %</td>
<td>WHO</td>
</tr>
<tr>
<td>PLADO low dose³</td>
<td>70.0 %</td>
<td>WHO</td>
</tr>
<tr>
<td>PLADO medium dose³</td>
<td>68.0 %</td>
<td>WHO</td>
</tr>
<tr>
<td>PLADO high dose³</td>
<td>70.0 %</td>
<td>WHO</td>
</tr>
<tr>
<td>HOVON control⁴</td>
<td>19.0 %</td>
<td>CTCAE</td>
</tr>
<tr>
<td>HOVON PAS⁴</td>
<td>15.0 %</td>
<td>CTCAE</td>
</tr>
<tr>
<td>HOVON amotosalen⁶</td>
<td>32.0 %</td>
<td>CTCAE</td>
</tr>
<tr>
<td>IPTAS Intercept⁵</td>
<td>23.0 %</td>
<td>WHO</td>
</tr>
<tr>
<td>IPTAS Intercept control⁵</td>
<td>16.5 %</td>
<td>WHO</td>
</tr>
</tbody>
</table>


Asses Clinical Efficacy

- In clinical studies
- In routine practice
Survey of current practice for monitoring and management of platelet refractoriness in Italy

Anna Quaglietta, Antonio Nicolucci, Patrizia Accorsi, Alessandra Pompa, Luca Pierelli, Antonio Lacome

Out of 122 centers identified, 64 participated in the survey (response rate 52%). Response rate was 43.5% in northern Italy, 57.1% in central Italy, and 51.8% in southern Italy. Among respondents, 37.5% were from blood banks with a small volume of activity (i.e., <500 platelet transfusions/year), 14.1% from blood banks with an intermediate volume (500–1000 transfusions/year), and 48.4% from blood banks with a large volume of activity (>1000 transfusions/year). In northern and central Italy, the majority of centers had a large volume of activity (53.8% and 56.3%, respectively), while in southern Italy 47.6% of the centers had a small volume of activity.

As for patient characteristics, in the vast majority of the centers (95.23%), platelet transfusions were performed in both oncological patients and thrombocytophenic patients undergoing surgical procedures, representing 70% and 30% of transfused patients, respectively. In 47.7% of the centers, only oncological patients were transfused.

Time of evaluation of post-transfusion platelet values in hospitalized patients

Time of evaluation of post-transfusion platelet values in outpatients


Response to Platelet Transfusion

Response to Platelet Transfusion

Failed 1-h CCI

- **Product:**
  - Poor quality

- **Patient**
  - Immune destruction of platelets due to antibodies against HLA or HPA
  - Massive splenomegaly
  - Active bleeding

Conclusions

• Several tools to evaluate the clinical efficacy of a platelet transfusion
• In recently performed clinical trials, the most used tool has been the % of patients with bleeding rate ≥ 2 during the study period
• In routine, the most used is the CCI, although 1h-CCI, the most dependent on the transfused product, is only measured in a reduced percentage of hospitals
Platelets: infectious risk, testing strategies, pathogen inactivation

Sheila MacLennan
NHS Blood and Transplant, UK

Transfusion-transmitted infections in UK 1996 – 2014 (SHOT)

• Viruses (none fatal)
  – HBV – 11 (13 recipients)
  – HCV – 2 (2)
  – HIV – 2 (4)
  – HAV – 3 (3)
  – HTLV – 2 (2)(pre-testing)
  – HEV – 2 (6)
  • Malaria – 2 (2,1 fatal)
  • vCJD – 3 (4, all fatal)

• Bacteria
  – 40 (43 recipients)
    – 33 platelets
    – 7 red cells
    – 9 deaths from platelet contamination
Calculated viral risk from blood transfusion in the UK

<table>
<thead>
<tr>
<th>Virus</th>
<th>1 in x million donations released</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>6.47</td>
</tr>
<tr>
<td>HBV</td>
<td>1.32</td>
</tr>
<tr>
<td>HCV</td>
<td>28.0</td>
</tr>
<tr>
<td>HTLV</td>
<td>17.74</td>
</tr>
</tbody>
</table>


Bacterial transmissions reported to SHOT 1996-2014

- Diversion pouch: 2003
- Bacterial screening: 2011
- Changes to arm cleansing
Bacterial contamination of platelets (2008/9)

- 6 cases in 2008, 2 fatal
  - Both fatal cases from same apheresis donation
  - Another apheresis donation caused 2 cases
  - 2 pools
- 2009, 2 cases from same donation (discovered only due to pH testing at outdate)
  - Adult transfused with 1 pack
  - Baby transfused with 3 packs from a 4-part split of the other pack

Bacterial TTIs by species (most common) and age of platelets at transfusion, 1995-2009

<table>
<thead>
<tr>
<th>Age of platelets (days)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>NK</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>11</td>
<td>12</td>
<td>4</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td><em>Staph. epidermidis</em></td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td></td>
<td>4</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Group B Streptococcus</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Group G Streptococcus</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><em>Staph. aureus</em></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Strategies to minimise bacterial risk of platelets

• Better arm cleansing - DONE
• Diversion of first aliquot of blood – DONE
• Bacterial screening
  – Implemented NHSBT 2011
  – 1.35m screened (75% apheresis, 25% pools)
  – 458 confirmed pos (Feb 2011 – Feb 2016)
    – Apheresis platelets 224 (0.02%)
    – Pooled platelets 234 (0.07%)
  – One demonstrated bacterial TTI – 3 ‘near misses’

Bacterial screening strategies

• Variability in procedure for screening
  – Sampling of ‘mother pack’ only or ‘daughter packs’
  – Time of sampling
  – Volume and number of samples
  – Platform used - sensitivity
  – Quarantine period
  – Release as ‘negative to date’ or one-off result
  – Recall of initial reactive components
NHSBT process

• Sample ‘daughter packs’
• Minimum time pre-sample 36 hours
• Volume 2 x 8 mL (aerobic and anaerobic)
• BacTAlert
• 6 hour quarantine post-loading of samples
• Release as ‘negative to date’ with culture to beyond end of shelf life of component (7 days)
• Recall index component and associated packs if initial reactive result for further investigation

Pathogen inactivation (PI) for platelets

• Exploit the fact pathogens need nucleic acid to replicate but not necessary for platelet, plasma or red cells to function
• Act at the nucleic acid level
• Those in use are based on photodynamic methods: addition of photosensitising chemical followed by exposure to UV light
  – Intercept (UVA + Amotosalen)
  – Mirasol (UV + Riboflavin)
  – Both CE marked, both in routine use in some EU countries
• Theraflex (UVC light alone)
  – CE marked, not yet in use - Phase 3 study being planned
  – Low toxicity, cell and protein function thought to be preserved
• Need to balance sufficient dose to kill pathogens and limit the effect on component
Mechanism of action Intercept

- Amotosalen (5-59)
- Intercalation
- Crosslinking
- UVA Illumination

Helical region of single- or double-stranded DNA or RNA
strand separation and thus replication and transcription blocked

INTERCEPT Blood System for platelets & plasma

The INTERCEPT Blood System for Platelets

Step 1
Amotosalen

Step 2
Illumination

Step 3
CAD

Process Complete
Storage

Can treat a single or double-dose in one go
(double dose apheresis or pool of 7BC+)
The Mirasol system inactivates disease-causing agents by altering their nucleic acids in two primary ways:

1. **UV light only: reversible inactivation**
   - UV light alone breaks chemical bonds in the nucleic acids of pathogens

2. **UV light + riboflavin: irreversible inactivation**
   - Riboflavin molecules form complexes with nucleic acids
   - Oxygen independent electron transfer process leading to modification of guanine bases making pathogens unable to replicate

---

**Mirasol Process for Platelets**

- Connect and transfer product to illumination bag
- Add riboflavin solution
- Illuminate 4 to 10 minutes
- Transfuse or store for up to 7 days

Can treat a single or double-dose in one go (double dose apheresis or pool of 7BC+)
**Agents inactivated by Amotosalen/UVA**

**ENVELOPED VIRUSES**
- HIV-1
- HIV-2
- HBV
- HCV
- HTLV-I
- HTLV-II

**NON-ENVELOPED VIRUSES**
- Bluetongue virus, type 11
- Simian Adenovirus-15
- Feline caliciivirus
- Parvovirus B19
- Human adenovirus 5

**GRAM-NEGATIVE BACTERIA**
- Klebsiella pneumoniae
- Yersinia enterocolitica
- Escherichia coli
- Pseudomonas aeruginosa
- Salmonella choleraesuis
- Enterobacter cloacae
- Serratia marcescens
- Anaplasma phagocytophilia
- Orientia tsutsugamushi

**GRAM-POSITIVE BACTERIA**
- Staphylococcus epidermidis
- Staphylococcus aureus
- Streptococcus pyogenes
- Listeria monocytogenes
- Corynebacterium minutissimum
- Bacillus cereus (vegetative)
- Lactobacillus sp.
- Bifidobacterium adolescentis
- Propionibacterium acnes
- Clostridium perfringens

**PROTOZOA**
- Trypanosoma cruzi
- Plasmodium falciparum
- Leishmania sp.
- Babesia microti

**LEUKOCYTES**
- T-cells

---

**Mirasol System – Broadly Effective Against Clinically Relevant Pathogens**

Effectiveness Demonstrated Against Broad Range of Pathogens

<table>
<thead>
<tr>
<th>Pathogen type</th>
<th>Typical Performance</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong> (enveloped, non-enveloped; intracellular, extracellular)</td>
<td>~2–6 log (99.0–99.9999%)</td>
<td>Ruane et al. 2004; Goodrich et al. 2006a; Goodrich et al. 2006b</td>
</tr>
<tr>
<td><strong>Parasites</strong> (Malaria, Chagas, Babesiosis, Leishmaniasis...)</td>
<td>≥ 3.0 to &gt; 5.0 (&gt;99.9% to &gt;99.999%)</td>
<td>Cardo et al. 2006; Sullivan et al. 2008; Cardo et al. 2007; Tonnetti et al. 2007; Rentas et al. 2007</td>
</tr>
<tr>
<td><strong>Bacteria</strong> (Gram +, Gram -)</td>
<td>~2–5 log (99.0-99.999%)</td>
<td>Ruane et al. 2004; Goodrich et al. 2006b,</td>
</tr>
</tbody>
</table>

- Mirasol has been shown to be more effective than bacterial culture methods (96% vs. 50-70%) in preventing transfusion of contaminated platelet units at clinically relevant contamination levels (<20 CFU / product) Goodrich et al. 2009
**Bacterial screening**

**Pros**
- Simple to perform
- Recognised technology
- Reduces risk
- Can extend shelf life (but if false negative result then risk to patient increased)

**Cons**
- Different options for screening protocol
- False negatives (up to 50%)
- Need to recall initial reactives
- Reduces risk from bacteria only

**Pathogen Inactivation**

**Pros**
- 2 systems licensed and in use
- One treatment then no further manipulation
- Reduces risk from viruses, bacteria, protozoa
- Inactivates leucocytes
- Can extend shelf life
- Can stop CMV screening, relax donor exclusions e.g. travel
- May be especially important for emerging pathogens

**Cons**
- Long term toxicity not yet determined
- Loss of efficacy of treated component
- Errors in an increasingly complex process
- Cost
- No system available for red cells
- High viral load may exceed capacity of the system
## Platelet claims for CE Mark in Europe

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Mirasol</th>
<th>Theraflex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory classification</strong></td>
<td>Class III</td>
<td>Class IIb</td>
<td>Class IIa for bag, Class IIb for device</td>
</tr>
<tr>
<td><strong>Pathogen reduction</strong></td>
<td>Broad spectrum</td>
<td>Broad spectrum</td>
<td>Broad spectrum</td>
</tr>
<tr>
<td><strong>Shelf-life</strong></td>
<td>Up to 7 days in PAS and plasma</td>
<td>Up to 7 days in PAS</td>
<td>Up to 5 days</td>
</tr>
<tr>
<td><strong>Patient populations</strong></td>
<td>No exclusions*</td>
<td>No exclusions</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Inactivation of leucocytes</strong></td>
<td>Can replace gamma or x-irradiation</td>
<td>Can replace gamma or x-irradiation</td>
<td>Can replace gamma or x-irradiation</td>
</tr>
<tr>
<td><strong>Inactivation of CMV</strong></td>
<td>Can replace CMV sero-negative serology</td>
<td>Can replace CMV sero-negative serology</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

* contra-indicated in patients with allergy to photosensitiser

---

## PI platelets clinical considerations

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Mirasol</th>
<th>Theraflex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recovery and survival</strong></td>
<td>Reduced by 16-20% d5 plasma</td>
<td>Reduced by 25-27% d5 plasma</td>
<td>Reduced by 26-29% d5 SSP+</td>
</tr>
<tr>
<td><strong>Clinical studies</strong></td>
<td>Eurosprite d5 CI, SPRINT d5 bleeding, HOVON d7 CI, TESSI d6-7 CI</td>
<td>MIRACLE d5 CI</td>
<td>None</td>
</tr>
<tr>
<td><strong>Allergic reactions</strong></td>
<td>¿Due to PAS?</td>
<td>?</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>HV data</strong></td>
<td>Published, no issues raised</td>
<td>Limited</td>
<td>Not in use</td>
</tr>
</tbody>
</table>
Summary

• Infectious risk from platelet transfusion, primarily from bacteria, warrants risk reduction measures

• Depending on process used, screening and PI can be considered of equivalent efficacy with pros and cons of both

• Increasing use of PI in Europe

• Questions remain re toxicity and cost-effectiveness of PI (¿ more donor exposure)

• No methods licensed for red cell PI as yet

Acknowledgements

Thanks for slides and advice:

• Dr Rebecca Cardigan
• Dr Paula Bolton-Maggs
• Dr Su Brailsford
• Cerus
• Terumo BCT
Platelet transfusion and allo-immunization: Whole Blood (Buffy Coat) versus Apheresis Platelet Components

Olivier Garraud MD PhD, Prof.
Institut National de la Transfusion Sanguine, Paris, France
Faculty of Medicine of Saint-Etienne, University of Lyon, France

Links of Interest

• Invitations received from
  – Cerus Europe, Amersfoot, NL
  – TerumoBCT Europe, Brussels, BE
  – MacoPharma, Mouveaux, FR
Outline of the Presentation

1. Platelet Components (PCs): Buffy-Coats (BC-PCs) vs Single Donor [Apheresis] PCs (SDA-PCs): Recommendations
2. Allo-immunization: Hemovigilance records
3. Mechanisms of Immunization and main hypotheses
4. Published works
5. Conclusive remarks: Can we move forward?

Foreword_1

- Platelet Component (PC) processing undergoes statistic Quality Control (QC)
  - Residual leukocytes (LKs) after leukoreduction/leukodepletion (LKD) must be < 10⁶ per PC
    - In France, mean efficiency is ~ 1.5 – 2.5 10⁵
  - Residual Red Blood Cells (RBCs) are not specified in QC norms
    - Pathogen Reduction Technology with Amotosalen mandates that RBCs are minimal (colorimetric appreciation)
- It is usually recommended to prevent anti-RH:1 (D) immunization in at risk RH:-1 Recipients transfused with PCs processed from blood offered by RH:1 individuals (RBCs) (no RH proteins on platelets)
Antigens expressed on platelets

- A, B (ABO/ABH system)
- HLA class I – intense polymorphism
- HPA – near 30 antigens
- Occasionally polymorphisms on other surface molecules subject to genetic polymorphism

1_Recommendations (BC-PCs vs SDA-PCs) → France (55%—45%)

Apart in situations where Recipients present with (allo) anti-HLA/HPA antibodies (Abs), there is no specific preference of SDA-PCs over BC-PCs

BC-PCs and SDA-PCs are considered equivalent
Improving platelet transfusion safety: biomedical and technical considerations

Olivier Garraud1,2, Fabrice Cognasse2,3, Jean-Daniel Tissot4, Patricia Chavarin1, Syria Laperche1, Pascal Morel1, Jean-Jacques Lefrère1,6, Bruno Pozzetto2, Miguel Lozano7, Neil Blumberg8, Jean-Claude Osselaer4

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(Official) Representatives from France – Switzerland – Spain (Catalonia) – USA – Belgium

→ Preference for BC-PCs over routine SDA-PCs

Neither consensual nor universal: In certain countries (Blood Establishments [BEs]) – such as in the Netherlands – BC-PCs are the most common PCs (SDA-PCs for immunization situations only, < 10%) while in other countries (such as Germany), there still is a preference of SDP-PCs vs pooled PCs. In the US, pools come essentially from Platelet Rich Plasma [PRP], but voices start to raise in favour of BCs (M Yazer and others).

2_Hemovigilance reports on allo-immunization

It is however difficult to ascribe immunization to one component only as patients receiving PCs usually also receive RBCCs.

Meanwhile, allo-immunization is from far #1 Adverse Event (AE) in Transfusion
RBCCs PCs

PCs (BC- and SDA-PCs) lead to near as many allo-immunizations than RBCCs, respective to the number of issued BCs.

Table 12: Répartition des allo-immunisations isolées déclarées d'imputabilité 2 à 3, selon le type de PSL et la gravité, 2014

<table>
<thead>
<tr>
<th>Gravité</th>
<th>Famille de PSL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CGR</td>
<td>Plaquettes</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>129</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>2 134</td>
<td>231</td>
</tr>
</tbody>
</table>

Taux pour 100 000 unités cédées 87,8 76 0,8 73,9

RBCCs PCs

Table 13: Répartition des allo-immunisations isolées déclarées d'imputabilité 2 à 3, selon l’anticorps saisi, 2014

<table>
<thead>
<tr>
<th>Type d’anticorps</th>
<th>Effectif</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-erythrocytaire</td>
<td>2 341</td>
<td>98,96 %</td>
</tr>
<tr>
<td>Anti-Dort érythrocytaire – ABO</td>
<td>2</td>
<td>0,08 %</td>
</tr>
<tr>
<td>Anti-Dort érythrocytaire – non ABO</td>
<td>2 344</td>
<td>98,99 %</td>
</tr>
<tr>
<td>Anti-Dort érythrocytaire non précisé ou non listé</td>
<td>5</td>
<td>0,21 %</td>
</tr>
</tbody>
</table>

Anti-HLA

- anti-HLA/HPA infrequent as opposed to RBC Ags
- anti-class I can originate from either Platelets or residual LKs

Table 16: Répartition des anticorps anti-érythrocytaire non ABO dans l’allo-immunisation isolée déclarée d’imputabilité 2 à 3, 2014

<table>
<thead>
<tr>
<th>Anticorps anti-érythrocytaire non ABO</th>
<th>Effectif</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-HLA/HPA</td>
<td>24</td>
<td>0,51 %</td>
</tr>
<tr>
<td>anti-class I</td>
<td>9</td>
<td>0,04 %</td>
</tr>
<tr>
<td>non listées</td>
<td>2</td>
<td>0,04 %</td>
</tr>
<tr>
<td>Total</td>
<td>2 368</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Classical distribution of Abs to RBC AgH:1 prevention policy in force
### 3_Mechanisms for allo-immunization and main hypotheses

<table>
<thead>
<tr>
<th>Step</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>Introduction of foreign cells harbouring foreign antigens</td>
</tr>
<tr>
<td>2)</td>
<td>Detection of danger by the recipient’s innate immune system</td>
</tr>
<tr>
<td>3)</td>
<td>Innate defense (inflammation)</td>
</tr>
<tr>
<td>4)</td>
<td>Epitope uptake by HLA molecules in antigen presenting cells and export to the surface (preference for class II presentation)</td>
</tr>
<tr>
<td>5)</td>
<td>Recognition by a T-lymphocyte (CD4+) selected within the repertoire</td>
</tr>
<tr>
<td>6)</td>
<td>T-cell help to antigen reactive B-lymphocytes or direct pick up by B-cells if recall stimulation</td>
</tr>
<tr>
<td>7)</td>
<td>B-cell differentiation and maturation of some B-cells in Antibody secreting plasma cells</td>
</tr>
<tr>
<td>8)</td>
<td>Memory initiation (T-B-cell)</td>
</tr>
</tbody>
</table>

**The bases in immunology**

<table>
<thead>
<tr>
<th>Step</th>
<th>Process</th>
</tr>
</thead>
<tbody>
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<td>8)</td>
<td>Memory initiation (T-B-cell)</td>
</tr>
</tbody>
</table>

1) Transfusion, pregnancy
2) Functional innate immune system
3) Capacity in mounting an inflammatory response
4) Dendritic cells or memory B-cells present (residual leukocytes); “good” presenters (HLA class II selected)
5) *Selection in the T-cell repertoire*
6) Functional T-cell adaptive immunity
7) Functional B-cell adaptive immunity
8) *Same as 5,6,7*
1) Introduction of foreign cells harbouring foreign antigens
2) Detection of danger by the recipient’s innate immune system
3) Innate defense (inflammation)
4) Epitope uptake by HLA molecules in antigen presenting cells and export to the surface (preference for class II presentation)
5) Recognition by a T-lymphocyte (CD4+ selected within the repertoire)
6) T-cell help to antigen reactive B-lymphocytes or direct pick up by B-cells if recall stimulation
7) B-cell differentiation and maturation of some B-cells in antibody secreting plasma cells
8) Memory initiation (T, B-cell)

1) Transfusion, pregnancy
2) Functional innate immune system
3) Capacity in mounting an inflammatory response
4) Dendritic cells or memory B-cells present (residual leukocytes); “good” presenters (HLA class II selected)
5) Selection in the T-cell repertoire
6) Functional T-cell adaptive immunity
7) Functional B-cell adaptive immunity
8) Same as 5, 6, 7

## Table 1: Transfusion versus PE, specific chronologies up to reduced endogenous antigens

<table>
<thead>
<tr>
<th>RBCs:</th>
<th>MP-Combinations</th>
<th>Associated ESA</th>
<th>Population</th>
<th>Delayed Ngal expression</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>DRB3*01:01</td>
<td>Carried</td>
<td>yes</td>
<td>Gurley et al. 1991   [96]</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>DRB3*01:01</td>
<td>Carried</td>
<td>yes</td>
<td>Daha et al. 1993   [97]</td>
<td></td>
</tr>
<tr>
<td>B+</td>
<td>DRB3*01:01</td>
<td>Carried</td>
<td>yes</td>
<td>Wachter-Stoecklin et al. 1995 [98]</td>
<td></td>
</tr>
<tr>
<td>B+ light chain</td>
<td>DRB5*01:01</td>
<td>Carried</td>
<td>yes</td>
<td>Heilig et al. 1995   [99]</td>
<td></td>
</tr>
<tr>
<td>B+ light chain</td>
<td>DRB5*01:01</td>
<td>Carried</td>
<td>yes</td>
<td>Verheyen et al. 1996 [100]</td>
<td></td>
</tr>
<tr>
<td>B+ light chain</td>
<td>DRB5*01:01</td>
<td>Carried</td>
<td>yes</td>
<td>Bonten et al. 1996 [101]</td>
<td></td>
</tr>
<tr>
<td>B+ light chain</td>
<td>DRB5*01:01</td>
<td>Carried</td>
<td>no</td>
<td>Primary et al. 1997 [102]</td>
<td></td>
</tr>
<tr>
<td>B+ light chain</td>
<td>DRB5*01:01</td>
<td>Carried</td>
<td>no</td>
<td>Sander et al. 1997 [103]</td>
<td></td>
</tr>
<tr>
<td>B+ light chain</td>
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<td>Carried</td>
<td>no</td>
<td>Oba et al. 1997 [105]</td>
<td></td>
</tr>
</tbody>
</table>

## Platelets

**Genotypes**
- DRB3*01:01 & DRB4*01:011 shown to favour anti-HPA1a allo-immunization of HPA1b/1b pregnant women

**Table 2: Sibling donors for platelets**

<table>
<thead>
<tr>
<th>Donor Group</th>
<th>MP-Combinations</th>
<th>Associated ESA</th>
<th>Population</th>
<th>Delayed NK killing</th>
<th>References</th>
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<tr>
<td>A</td>
<td>DRB3*01:01</td>
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<td>yes</td>
<td>Gurley et al. 1991   [96]</td>
<td></td>
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<tr>
<td>B</td>
<td>DRB3*01:01</td>
<td>Carried</td>
<td>yes</td>
<td>Daha et al. 1993   [97]</td>
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</tbody>
</table>
A couple of recent reviews—among several—on the benefits of LKD, with focus on allo-immunization

Leucoreduction of blood components: an effective way to increase blood safety?

Maria Bianchi1,2, Stefania Vaglio1,2, Simonetta Pupella1, Giuseppe Marano1, Giuseppina Facco1,4, Giancarlo M. Llumbruno1, Giuliano Grazzini1

1Italian National Blood Centre, National Institute of Health, Rome; 2Blood Transfusion Service, "A. Gemelli" University Polyclinic, "Sacro Cuore" Catholic University, Rome; 3Faculty of Medicine and Psychology, "Sapienza" University of Rome, Rome; 4Immunohaematology and Transfusion Medicine Unit, "Città della Salute e della Scienza" Hospital, Turin, Italy

BACKGROUND:
OBJECTIVES:
SEARCH METHODS:
SELECTION CRITERIA:
DATA COLLECTION AND ANALYSIS:
MAIN RESULTS:
AUTHORS’ CONCLUSIONS:


Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion.

Abstract
A blood transfusion is an acute intervention, implemented to solve life and health-threatening conditions on a short-term basis. However, blood transfusions have adverse events, some of them potentially related to immune modulation or to a direct transmission of infectious agents (e.g. cytomegalovirus). Leukoreduction is a process in which the white blood cells are intentionally reduced in packed red blood cells (PRBCs) in order to reduce the risk of adverse reactions. The potential benefits of leukoreduced PRBCs in all types of transfused patients for decreasing infection and non-infectious complications remain unclear.

To determine the clinical effectiveness of leukoreduction of packed red blood cells (PRBCs) for preventing adverse reactions following allogeneic blood transfusion.

We ran the most recent search on 10th November 2015. We searched the Cochrane Injuries Group’s Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE (OvidSP), Embase(OvidSP), CINAHL Plus (EBSCO), LILACS (BIREME), and clinical trials registers. In addition, we checked the reference lists of all relevant trials and reviews identified in the literature searches.

Randomised clinical trials including patients of all ages requiring PRBC allogeneic transfusion. Any study was eligible for inclusion, regardless of the length of participant follow-up or country where the study was performed. The primary outcome was transfusion-related acute lung injury (TRALI). Secondary outcomes were death from any cause, infection from any cause, non-infectious complications and any other adverse event.

At least two review authors independently performed study selection, ‘Risk of bias’ assessments and data extraction. We estimated pooled relative risk for dichotomous outcomes, and we measured statistical heterogeneity using I² statistic. The random-effects model was used to synthesise results. We conducted a trial sequential analysis to assess the risk of random errors in cumulative meta-analyses.

Thirteen studies, most including adult patients, met the eligibility criteria. We found no clear evidence of an effect of leukoreduced PRBC versus non-leukoreduced PRBC in patients that were randomised to receive transfusion for the following outcomes: TRALI: RR 0.96, 95% CI 0.67 to 1.36, P = 0.80 from one trial reporting data on 1864 trauma patients. The accrued information of 1864 participants constituted only 28.5% of the diversity-adjusted required information size (DARIS) of 6548 participants. The quality of evidence was low. Death from any cause: RR 0.81, 95% CI 0.58 to 1.12, I² statistic = 63%, P = 0.20 from nine trials reporting data on 6485 cardiovascular surgical patients, gastro-oncology surgical patients, trauma patients and HIV infected patients. The accrued information of 6485 participants constituted only 55.3% of the DARIS of 11,735 participants. The quality of evidence was very low. Infection from any cause: RR 0.80, 95% CI 0.62 to 1.03, I² statistic = 84%, P = 0.08 from 10 trials reporting data on 6709 cardiovascular surgical patients, gastro-oncology surgical patients, trauma patients and HIV infected patients. The accrued information of 6709 participants constituted only 60.6% of the DARIS of 11,062 participants. The quality of evidence was very low. Adverse events: The only adverse event reported as an adverse event was fever (RR 0.81, 95% CI 0.64 to 1.02; I² statistic= 0%, P = 0.07). Fever was reported in two trials on 634 cardiovascular surgical and gastro-oncology surgical patients. The accrued information of 634 participants constituted only 84.4% of the DARIS of 751 participants. The quality of evidence was low. Incidence of other non-infectious complications: This outcome was not assessed in any included trial.

There is no clear evidence for supporting or rejecting the routine use of leukoreduction in all patients requiring PRBC transfusion for preventing TRALI, death, infection, non-infectious complications and other adverse events. As the quality of evidence is very low to low, more evidence is needed before a definitive conclusion can be drawn.

PMID: 26633306 [PubMed - in process]

Author information

Recent Cochrane meta-analysis: Not so strong? ???
Homologous transfused Platelets and allo-immunization

- Acknowledged or supposed intervention of:
  - CD8+ T-cell suppression
  - Regulatory T- and B-cells and likely tolerance
  - Soluble HLA antigens
  - Pre-storage and cytokines (and the like)
  - Transfusion Related Immuno Modulation or TRIM
  - Direct versus indirect allo-recognition of foreign antigens
  - Frequent transfusion: Generation of anti-idiotyp antibodies that are tolerogenic

Figure 2 Models of direct and indirect allorecognition that can lead to platelet alloimmunization (23–27). Direct allorecognition occurs when the T-cell receptor (TcR) of recipient CD4+ T cells directly interact with major histocompatibility complex (MHC) class II molecules on donor antigen presenting cells (APC). This leads to T-cell activation and help for B cell differentiation into plasma cells and production of anti-HLA class I antibodies. Leukoreduction of platelet concentrates removes this pathway. Indirect allorecognition is the default pathway for platelet MHC class I molecules. It occurs when donor platelet-derived MHC class I alloantigens are taken up by recipient APC and processed and presented by MHC class II molecules on the recipient APC. This leads to the generation of T cell help and alloantibody production.

Pavenski et al. Tissue Antigens, 2012
Platelet transfusion refractoriness

- Recognized more than 5 decades ago
- Clearly associated with leukocytes
- Boosted after previous transfusions, pregnancies, transplantations
- Much less PC refractoriness and immunizations when LKD became routine

Experimental (mouse) data

- Leukoreduction decreases experimental allo-immunization
- Extreme leukoreduction favours allo-immunization
  - Loss of the TRIM effect
  - Loss of the CD8⁺ (T_{reg}?) suppression (tolerance)
- Pre-storage (>24 h vs < 4h) decreases both expression of MHC I molecules on platelets and allo-immunization
- Soluble MHC antigens freed by stored platelets are weakly immunogenic
- (Works from J Semple et al., J Zimring et al.)
REVIEW ARTICLE

HLA alloimmunization against platelet transfusions: pathophysiology, significance, prevention and management

Katerina Pavenski1,2, John Freedman3,4,5 & J. W. Semple1,2,6,7,8
1 Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Ontario, Canada
2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
3 The Toronto-Patient Immunochemistry Group, Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Ontario, Canada
4 Department of Medicine, University of Toronto, Toronto, Ontario, Canada
5 Department of Pathobiology, University of Toronto, Toronto, Ontario, Canada
6 Research and Development, Canadian Blood Services, Toronto, Ontario, Canada
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Figure 1. Etiology of refractoriness to platelet transfusions.

Table 2. Summary of results of the TRAP study.

<table>
<thead>
<tr>
<th>Non Leukoreduced</th>
<th>Controls: untreated</th>
<th>Leukoreduced pooled</th>
<th>Leukoreduced single-donor apheresis platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>131</td>
<td>137</td>
<td>132</td>
</tr>
<tr>
<td>Alloimmunization</td>
<td>45%</td>
<td>18% (P &lt; 0.001)*</td>
<td>17% (P &lt; 0.001)*</td>
</tr>
<tr>
<td>Refractoriness</td>
<td>16%</td>
<td>7% (P = 0.03)*</td>
<td>8% (P = 0.06)*</td>
</tr>
<tr>
<td>Alloimmunization and refractoriness</td>
<td>13%</td>
<td>3% (P = 0.004)*</td>
<td>4% (P = 0.01)*</td>
</tr>
</tbody>
</table>

Adapted from reference 40.
*as compared to control group.

BC-PCs immunize significantly less than SDA-PCs regarding HPA, HLA antigenic specificities

Hypothesis: Pre-storage??

- SDA-PCs are sometimes LKD “in process” by the cell separator \(\rightarrow\) no need to re-filter the component, not with the TRIMA\textsuperscript{TM} system largely used in our observations (see further).
- BCs are made of overnight stored Whole Blood collections; LKD occurs in general after a 15-16 h pre-storage after collection

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Number of adverse reactions</th>
<th>Rate/10\textsuperscript{6}</th>
<th>Number of adverse reactions</th>
<th>Rate/10\textsuperscript{6}</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall reported</td>
<td>2983</td>
<td>6244</td>
<td>773</td>
<td>2469</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severity grade:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>2774</td>
<td>5806</td>
<td>692</td>
<td>2210</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 2</td>
<td>209</td>
<td>437</td>
<td>81</td>
<td>259</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>115</td>
<td>261</td>
<td>41</td>
<td>131</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4 (death)</td>
<td>7</td>
<td>15</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Imputability level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible (1)</td>
<td>1958</td>
<td>2217</td>
<td>397</td>
<td>1201</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probable (2) or (3)</td>
<td>1504</td>
<td>4027</td>
<td>310</td>
<td>3127</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allergic transfusion reaction</td>
<td>1917</td>
<td>4013</td>
<td>310</td>
<td>990</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FNHTR</td>
<td>452</td>
<td>296</td>
<td>247</td>
<td>225</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfusion reaction with anti-HLA or HPA</td>
<td>236</td>
<td>481</td>
<td>119</td>
<td>261</td>
<td>0.001</td>
</tr>
<tr>
<td>PLT transfusion reaction</td>
<td>80</td>
<td>167</td>
<td>29</td>
<td>93</td>
<td>0.006</td>
</tr>
<tr>
<td>TACO</td>
<td>34</td>
<td>33</td>
<td>13</td>
<td>6</td>
<td>0.16</td>
</tr>
<tr>
<td>TRALI</td>
<td>25</td>
<td>52</td>
<td>9</td>
<td>29</td>
<td>0.16</td>
</tr>
<tr>
<td>Transfusion-related</td>
<td>13</td>
<td>27</td>
<td>9</td>
<td>26</td>
<td>0.99</td>
</tr>
<tr>
<td>Hypersensitive</td>
<td>7</td>
<td>15</td>
<td>10</td>
<td>32</td>
<td>0.14</td>
</tr>
<tr>
<td>Posttransfusion p</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0.76</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>20</td>
<td>461</td>
<td>77</td>
<td>246</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BC-PCs lead to less adverse events than SDA-PCs in general

\(\text{Hypothesis: Pre-storage??}\)

- SDA-PCs are sometimes LKD “in process” by the cell separator \(\rightarrow\) no need to re-filter the component, not with the TRIMA\textsuperscript{TM} system largely used in our observations (see further).
- BCs are made of overnight stored Whole Blood collections; LKD occurs in general after a 15-16 h pre-storage after collection
Low frequency of anti-D alloimmunization following D+ platelet transfusion: the Anti-D Alloimmunization after D-incompatible Platelet Transfusions (ADAPT) study

Joan Cid,1,2 Miguel Lorenzo,1 Alyssa Ziman,3 Kamille A. West,2 Kerri L. O'Brien,4 Michael F. Murphy,5 Silvano Wendel,6 Alejandro Vázquez,7 Xavier Ortí,8 Tor A. Hervig,9 Meghan Delaney,10 Mike A. Fliegel2 and Mark H. Yazer11 on behalf of the Biomedical Excellence for Safe Transfusion collaboration

1Department of Haemotherapy and Haemostasis, Hospital Clínic, IDIBAPS, UB, Barcelona, Spain, 2Clinical Center, Department of Transfusion Medicine National Institutes of Health, Bethesda MD, 3UCLA Division of Transfusion Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 4Department of Haematology, National Darmstadt Medical Center, Bad Nauheim, Germany, 5Oxford University Hospitals and NHS Blood & Transplant, Oxford, UK, 6Hospital Sirio Libanês Blood Bank, São Paulo, Brazil, 7Department of Blood Transfusion, Hospital Universitario Puerta de Hierro, Majadahonda, 8Department of Haematology, Hospital Verge de la Cinta, Tortosa, Spain, 9Department of Clinical Science, Immunology University Hospital, University of Bergen, Bergen, Norway, 10Puget Sound Blood Center, Department of Laboratory Medicine, University of Washington, Seattle, WA, and 11Department of Pathology, Institute for Transfusion Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Summary

The reported frequency of D alloimmunization in D- recipients after transfusion of D+ platelets varies. This study was designed to determine the frequency of D alloimmunization, previously reported to be an average of 5 ± 2%. A primary anti-D immune response was defined as the detection of anti-D ≥ 28 days following the first D+ platelet transfusion. Data were collected on 485 D- recipients of D+ platelets in 11 centres between 2010 and 2012. Their median age was 60 (range 2–100) years. Diagnoses included haematological (203/485, 42%), oncological (64/485, 13%) and other diseases (218/485, 45%). Only 7/485 (1.44%; 95% CI 0.58–2.97%) recipients had a primary anti-D response after a median serological follow-up of 77 days (range: 28–2111). There were no statistically significant differences between the primary anti-D formers and the other patients, in terms of gender, age, receipt of immunosuppressive therapy, proportion of patients with haematological/oncological diseases, transfusion of whole blood-derived or apheresis platelets or both, and total number of transfused platelet products. This is the largest study with the longest follow-up of D alloimmunization following D+ platelet transfusion. The low frequency of D alloimmunization should be considered when deciding whether to administer Rh Immune Globulin to D- males and D- females without childbearing potential after transfusion of D+ platelets.

Keywords: platelet transfusion, D compatibility, anti-D alloantibodies, alloimmunization, RHDS.
Table III. Demographic and clinical information of the primary alloimmunized recipients versus all other recipients in this study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary anti-D recipients</th>
<th>All other recipients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of recipients (%)</td>
<td>7 (1.4)</td>
<td>478 (98.6)</td>
<td>NC</td>
</tr>
<tr>
<td>Gender</td>
<td>Male/Female</td>
<td>M/F</td>
<td>0.2</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>68 (50-100)</td>
<td>65 (59-65)</td>
<td>0.2</td>
</tr>
<tr>
<td>ABO group</td>
<td>O/A/AB/0</td>
<td>286/212/49/17</td>
<td>0.9</td>
</tr>
<tr>
<td>Maternal diagnosis</td>
<td>3/1</td>
<td>244/214</td>
<td>0.5</td>
</tr>
<tr>
<td>Interventions</td>
<td>3/3/1</td>
<td>197/177/104</td>
<td>0.9</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of pregnancy (yes)*</td>
<td>2/0</td>
<td>35/12</td>
<td>0.5</td>
</tr>
<tr>
<td>Patient location</td>
<td>European/American</td>
<td>322/256</td>
<td>0.6</td>
</tr>
<tr>
<td>Previous RBC transfusion</td>
<td>0/1</td>
<td>217/261</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous PC</td>
<td>2/3</td>
<td>549/68</td>
<td>0.9</td>
</tr>
<tr>
<td>Transfused PCs</td>
<td>2/4/1</td>
<td>179/288/71</td>
<td>0.8</td>
</tr>
<tr>
<td>Median length of nephrologist follow-up (range), days</td>
<td>214 (50-644)</td>
<td>75 (28-1111)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*For those whose pregnancy history was known.

Table IV. Type and quantity of the platelets transfused to the 405 recipients in this study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary anti-D recipients</th>
<th>All other recipients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmatic product type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole blood-derived platelets</td>
<td>1180</td>
<td>1650</td>
<td>2885</td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td>1970</td>
<td>696</td>
<td>2246</td>
</tr>
<tr>
<td>Total number</td>
<td>3150</td>
<td>2199</td>
<td>5349</td>
</tr>
</tbody>
</table>

Table V. Number of platelet concentrate units administered to those who produced a primary anti-D and those who did not. Data are presented as median (range) unless otherwise specified.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary anti-D recipients</th>
<th>All other recipients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients, n (% of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+ PC</td>
<td>2 (1-11)</td>
<td>2 (1-11)</td>
<td>0.9</td>
</tr>
<tr>
<td>D- PC</td>
<td>0 (0-16)</td>
<td>0 (0-17)</td>
<td>0.5</td>
</tr>
<tr>
<td>Total PC</td>
<td>2 (1-17)</td>
<td>3 (1-17)</td>
<td>0.5</td>
</tr>
<tr>
<td>PC, platelet concentrate, NC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC, platelet concentrate, NC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table I. Risque d’allo-immunisation plaquettaire anti-D et l’absence de prophylaxie selon le terrain et la durée de suivi. La durée de suivi correspond au temps écoulé entre la première exposition transfusionnelle à des plaquettes Rh+ et le dernier dépistage négatif à la recherche d’anticorps anti-RhD.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of anti-D</th>
<th>Terrain, éematique</th>
<th>x semaines de suivi</th>
<th>Médiane (extrêmes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg et al., 1971 [23]</td>
<td>8/102 (7.8)</td>
<td>Traitement immuno-suppressif</td>
<td>36 (2-174)</td>
<td></td>
</tr>
<tr>
<td>Balfour et al., 1986 [34]</td>
<td>8/109 (18.4)</td>
<td>Immunodépression, oncologie</td>
<td>27 (2-182)</td>
<td></td>
</tr>
<tr>
<td>McLeod et al., 1990 [16]</td>
<td>3/18 (18.7)</td>
<td>Immuno-inhibleur</td>
<td>3 (2-12)</td>
<td></td>
</tr>
<tr>
<td>Heinz et al., 1992 [30]</td>
<td>0/37 (0)</td>
<td>Immunodépression</td>
<td>27 (4-104)</td>
<td></td>
</tr>
<tr>
<td>Akinyel et al., 2000 [15]</td>
<td>0/74 (13.6)</td>
<td>Hématologie</td>
<td>5 (0-76)</td>
<td></td>
</tr>
<tr>
<td>Miller et al., 2002 [19]</td>
<td>0/35 (0)</td>
<td>Métabolisme hémodynamique</td>
<td>58 (2-133)</td>
<td></td>
</tr>
<tr>
<td>:</td>
<td>0/79 (0)</td>
<td>Oncotoxicologie pédiatrique hors greffe</td>
<td>27 (2-235)</td>
<td></td>
</tr>
<tr>
<td>:</td>
<td>0/79 (0)</td>
<td>Greffe de CSF pédiatriche</td>
<td>8 (6-11)</td>
<td></td>
</tr>
<tr>
<td>Cid et al., 2002 [21]</td>
<td>0/79 (0)</td>
<td>Hématologie (chloméphylubie ++++)</td>
<td>8 (1-17)</td>
<td></td>
</tr>
<tr>
<td>Cid et al., 2011 [17]</td>
<td>6/177 (5.4)</td>
<td>Hématologie</td>
<td>34 (4-351)</td>
<td></td>
</tr>
<tr>
<td>O’Brien et al., 2014 [25]</td>
<td>3/177 (11.9)</td>
<td>Oncologie</td>
<td>54 (4-375)</td>
<td></td>
</tr>
<tr>
<td>:</td>
<td>2/107 (1.9)</td>
<td>Pas d’immuno-dépression</td>
<td>59 (4-718)</td>
<td></td>
</tr>
<tr>
<td>:</td>
<td>0/62 (0)</td>
<td>Immuno-dépression</td>
<td>74 (4-9)</td>
<td></td>
</tr>
<tr>
<td>:</td>
<td>0/68 (0)</td>
<td>Pas d’immuno-dépression</td>
<td>74 (4-9)</td>
<td></td>
</tr>
</tbody>
</table>

CSF : cellules souches hémopoïétiques.
* Dans cette étude, les patients ont reçu des immuno-globulines anti-Rh.
Red blood cell alloimmunisation after platelet transfusion: a 5-year study

Pierre Moncharmont, Gregory Barday, Francis Meyer

Department of Haemovigilance, Rhône-Alpes French Blood Service, Gerland, Lyon, France

Table I - Number and type of PLT concentrates released and type of products involved in the post-transfusion RBC alloimmunisations observed during the study.

<table>
<thead>
<tr>
<th>Year</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products released:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of apheresis PC</td>
<td>15,135</td>
<td>14,906</td>
<td>15,666</td>
<td>14,762</td>
<td>13,506</td>
</tr>
<tr>
<td>(%)</td>
<td>(84.0)</td>
<td>(82.0)</td>
<td>(79.8)</td>
<td>(70.6)</td>
<td>(59.4)</td>
</tr>
<tr>
<td>Number of pooled PC</td>
<td>2,892</td>
<td>3,259</td>
<td>3,692</td>
<td>6,159</td>
<td>9,247</td>
</tr>
<tr>
<td>(%)</td>
<td>(16.0)</td>
<td>(18.0)</td>
<td>(20.2)</td>
<td>(29.4)</td>
<td>(40.6)</td>
</tr>
<tr>
<td>Type and number of products involved in the notified cases of RBC alloimmunisation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apheresis PC</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Pooled PC</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

PC: platelet concentrate; RBC: red blood cell.

1.3% allo-immunization to RBC Antigens

Anti-red blood cell antigen alloimmunization after platelet component transfusion: comparison of platelet sources

Considering this conflicting data, we thus aimed at revisiting the situation and we reviewed all PC transfusion episodes in a regional setting over the past five years. A total of 54,202 PCs were delivered to 17,135 patients from 2010 to 2014: 27,199 WBPCs and 27,003 APCs. The number of APCs that were collected in these regional facilities were 24,320 over those past years. Over this period, three types of separators were used: 20,750 by TRIMA (TerumoBCT) [0.8532%], 2,300 by AMICUS (Fenwall/Fresenius-Kabi, Lake Zurich, IL) [0.0945%], and 1,270 by MCS+ (Haemonetics, Braintree, MA) [0.0522%]. Hemovigilance surveys were operated by medical officers in hospitals and reported electronically to the national regulatory authority. The hemovigilance policy was regional and, based on that characteristics and on the homogeneity of the PC production by only one serving center, it can be assumed that intergroup comparisons in our study is valid.

Olivier CARRAUD1, Abdelallah BENAMARA1, Vincent BOST1, Pascale OBIOL1, Christiane MOUNIERS1, Sophie ACQUIAT2

1 EA3064 Faculty of Medicine of Saint-Étienne, University of Lyon, 42023 Saint-Étienne, France
Over 5 years, we recorded 25 and 10 RBC antigen alloimmunizations after WBPC and APC transfusions, respectively (p=0.015, by means of a corrected Khi² test; Odds ratio: 2.49). Details are given in Table 1. While being an exceptional event, alloimmunization to RBC antigens was more frequent after WBPCs compared to APCs. This study could not assess a bias in PC allocation in patients, pertaining that some patients may have more chances of getting immunized than others; however, there was no protocol in force in this region to assign BCs other than on parameters such as availability, ABO match and—eventually—age of the products. Thus, no patient category has received for example APCs in preference to WBBCs or vice-versa.

### Table 1: Reports of anti-red blood cell antigens allo-immunizations imputable to Platelet concentrate transfusion in a five-year regional survey in France: effect of platelet component processing

<table>
<thead>
<tr>
<th>BC-PC</th>
<th>Whole Blood Buffy Coat-derived Platelet Component</th>
<th>Single Donor Apheresis Platelet Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of PC issued</td>
<td># of anti-erythrophagocyte allo-immunizations recorded</td>
</tr>
<tr>
<td>2010</td>
<td>5494</td>
<td>BE1 (x2), BE1 (x2)</td>
</tr>
<tr>
<td>2011</td>
<td>4793</td>
<td>BE1 (x8), MO5 (x3)</td>
</tr>
<tr>
<td>2012</td>
<td>5551</td>
<td>BE1 (x6), BE1 (x2), BE1 (x2), KEL (x2), LE-1</td>
</tr>
<tr>
<td>2013</td>
<td>6237</td>
<td>BE1, BE2, BE2, KEL (x2), KEL (x2)</td>
</tr>
<tr>
<td>2014</td>
<td>6210</td>
<td>BE1, BE2, BE2, BE2, KEL (x2), KEL (x2)</td>
</tr>
<tr>
<td>Total</td>
<td>27,195</td>
<td>27,093</td>
</tr>
</tbody>
</table>

* TRIMA® was the only one cell separator used in 2012
** >90% of APCs were collected with TRIMA separators in 2013 (and none with AMICUS)
*** >90% of APCs were collected with TRIMA separators in 2013 (and none with AMICUS)
• Hypothesis
  – SDA-PC RBC contamination: ≤0.5x 10^6 residual RBCs
  – BC-PCs: estimated at below or equal 10^6 residual RBCs
  – PRT Amotosalen: must be below 4x 10^6 residual RBCs (visual estimation)

• However,
  – This doesn’t match with the pre-storage hypothesis (in process LKD)

• Is there a role for Microparticles? (experimentally more immunogenic than intact erythrocytes)??

• ??
5_Concluding remarks and paths for improvement?

• Allo-immunization linked to platelet transfusion is not frequent occurrence
  – Allo-immunization to HLA or HPA
  – Allo-immunization to RBC antigens
• BC- and SDA-PC seem equivalent regarding this risk
  – The ADAPT study
  – This can be mitigated if one considers anti-HLA immunization (BC-PC seem better)
  – ...if one considers anti-RBC Ag immunization (SDA-PC seem better)
  – Further studies needed to confirm

• What about storage?
  – Pre-storage → applied to the LKD process
    • It seems to experimentally reduce the allo-immunization
    • It reduces +++ the LK-derived cytokines/chemokines and the like (Biological Response Modifiers [BRMs])
  – Storage → applied to the inventory
    • Increases +++ the secretion/release of platelet-originating BRMs
      – Increasing FNHTRs
      – Increasing Allergic-Type reactions
    • Thus, it favours pre-inflammation
    • As inflammation is a requisite for adaptive immunity and allo-immunization, what about the actual effect of storage on allo-immunization??
• What about PRT implementation?
  – The TRAP study: taught that pre-storage LKD or irradiation or UBV illumination prevented further allo-immunization in recipients
  – What about actual reduction of allo-immunization in patients receiving PRT PCs (difficult to ascertain as those events are quite infrequent)
    • But?

Any question?

ogarraud@ints.fr
Availability of platelet concentrates in Europe

What is the kind of data we currently have?
What is the information these data transport?
What do we need for decision making on the optimal use of platelet concentrates?

Priv.-Doz. Dr. med. Dorothea Stahl, MBA
Section Head Transfusion Medicine
IV Wildbad Kreuth Initiative - Freising, 06.05.2016

What is a platelet concentrate?
- EDQM Guide Blood Components – Platelet component monographs - 12 (!) monographs

Available data sources – Available data
- Data from market analyses
  - Kalorama Information 2008, Blood Markets
  - Creative Ceutical Report 2015, An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients
- EDQM, Richardson C, Quality indicators for monitoring the clinical use of blood in Europe, data 2014
- AABB Blood survey report 2013
- National data, e.g. German data according to Transfusion Law §21

Collecting data for decision making: Information content derived from available data?
- Identification of knowledge gaps

Which kind of data / of data analysis would enhance the information needed?
- Clinical studies and “Real world data” / registry data
- Linking data with a broader scientific context – systems biology approach, systems medicine approach
- Linking data with infrastructural data of healthcare provision (micro- / macroenvironment) – health analytics
## EDQM Guide Blood Components – Platelet component monographs

### 12 (!) monographs
- Platelet, recovered, single unit
- Platelets, recovered, pooled
- Platelets, recovered, pooled, leucocyte-depleted
- Platelets, recovered, pooled, in additive solution
- Platelets, recovered, pooled, leucocyte-depleted, in additive solution
- Platelets, pooled, pathogen-reduced
- Platelets, apheresis
- Platelets, apheresis, leucocyte-depleted
- Platelets, apheresis, in additive solution
- Platelets, apheresis, leucocyte-depleted, in additive solution
- Platelets, apheresis, pathogen-reduced
- Platelets, cryopreserved

## Available data sources – Available data
Data from market analyses - Kalorama Information 2008, Blood Markets

<table>
<thead>
<tr>
<th>Region</th>
<th>Units of RBCs (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>15</td>
</tr>
<tr>
<td>Europe</td>
<td>22</td>
</tr>
<tr>
<td>Japan</td>
<td>12</td>
</tr>
<tr>
<td>ROW</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
</tr>
</tbody>
</table>

Geographical distribution of RBC demand by region, 2007

Worldwide annual blood collection by component

Automated versus Non-automated collection processes

<table>
<thead>
<tr>
<th>Blood loss segment</th>
<th>Units of RBCs (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Blood loss</td>
<td>50</td>
</tr>
<tr>
<td>Chronic Blood loss</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
</tr>
</tbody>
</table>

Data from market analyses - Creative Ceutical Report 2015

An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients

<table>
<thead>
<tr>
<th>Collection</th>
<th>Use of Place of Production (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>500,000</td>
</tr>
<tr>
<td>Plasma</td>
<td>120,000</td>
</tr>
<tr>
<td>Whole Blood</td>
<td>160,000</td>
</tr>
</tbody>
</table>

Worldwide demand for RBC for acute and chronic conditions, 2007

Collection and use of blood components across the EU (2010)

adapted from EDQM reports

Data from market analyses - Creative Ceutical Report 2015

An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients

<table>
<thead>
<tr>
<th>Region</th>
<th>Units of RBCs (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>10,000</td>
</tr>
<tr>
<td>Belgium</td>
<td>12,000</td>
</tr>
<tr>
<td>France</td>
<td>15,000</td>
</tr>
<tr>
<td>Germany</td>
<td>20,000</td>
</tr>
<tr>
<td>Ireland</td>
<td>8,000</td>
</tr>
<tr>
<td>Italy</td>
<td>12,000</td>
</tr>
<tr>
<td>Spain</td>
<td>15,000</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>20,000</td>
</tr>
<tr>
<td>Belgium (Flanders)</td>
<td>8,000</td>
</tr>
<tr>
<td>Belgium (Wallonia)</td>
<td>8,000</td>
</tr>
<tr>
<td>Belgium (Luxembourg)</td>
<td>8,000</td>
</tr>
</tbody>
</table>

Collection and use of blood components across the EU (2010)

adapted from EDQM reports
Data from market analyses - Creative Ceutical Report 2015

An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients

Collection of blood components across the EU (2012)
adapted from Implementation Survey 2013

<table>
<thead>
<tr>
<th>Country</th>
<th>Whole-blood donations</th>
<th>Blood-component collections (thousand)</th>
<th>Plasma derivatives (thousand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>530,356</td>
<td>46.5</td>
<td>13.671</td>
</tr>
<tr>
<td>Belgium</td>
<td>184,891</td>
<td>12.0</td>
<td>2.758</td>
</tr>
<tr>
<td>Croatia</td>
<td>170,205</td>
<td>41.0</td>
<td>2.648</td>
</tr>
<tr>
<td>Cyprus</td>
<td>57,027</td>
<td>43.8</td>
<td>279</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>420,164</td>
<td>38.9</td>
<td>13.775</td>
</tr>
<tr>
<td>Denmark</td>
<td>280,763</td>
<td>51.8</td>
<td>3.550</td>
</tr>
<tr>
<td>Estonia</td>
<td>5,652</td>
<td>4.8</td>
<td>109</td>
</tr>
<tr>
<td>Finland</td>
<td>280,434</td>
<td>45.6</td>
<td>483</td>
</tr>
<tr>
<td>France</td>
<td>2,042,700</td>
<td>40.5</td>
<td>131.875</td>
</tr>
<tr>
<td>Germany</td>
<td>4,785,048</td>
<td>51.6</td>
<td>196.156</td>
</tr>
<tr>
<td>Greece</td>
<td>406,008c</td>
<td>33.9</td>
<td>38.125</td>
</tr>
<tr>
<td>Hungary</td>
<td>425,417</td>
<td>41.9</td>
<td>3.378</td>
</tr>
<tr>
<td>Ireland</td>
<td>136,089</td>
<td>91.5</td>
<td>13.028</td>
</tr>
<tr>
<td>Italy</td>
<td>2,089,127</td>
<td>49.2</td>
<td>80.013</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>5,539</td>
<td>2.7</td>
<td>1,451</td>
</tr>
</tbody>
</table>

"Regular shortages" of platelets in patient care are reported in Europe.

Shortage means
a relative deficiency in the supply with blood, blood components and plasma derivatives for medical application, which requires creation of waiting lists or makes a certain therapy temporarily unavailable at national level.
### EDQM, CD-P-TS 2015

The collection, testing and use of Blood and Blood Components in Europe, 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>Units transfused per patient</th>
<th>Total</th>
<th>RBC</th>
<th>FFP</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>13.1</td>
<td>12.0</td>
<td>10.5</td>
<td>12.4</td>
<td>11.0</td>
</tr>
<tr>
<td>France</td>
<td>12.2</td>
<td>11.0</td>
<td>10.0</td>
<td>12.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Germany</td>
<td>11.8</td>
<td>10.0</td>
<td>10.0</td>
<td>11.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Italy</td>
<td>11.7</td>
<td>10.0</td>
<td>10.0</td>
<td>11.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Spain</td>
<td>11.1</td>
<td>10.0</td>
<td>10.0</td>
<td>11.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

### EDQM, Richardson C, 2014

Quality indicators for monitoring the clinical use of blood in Europe

Units transfused per transfused patient, separately for RBC, FFP and platelets, and in total

![Graph showing units transfused per transfused patient](image-url)
Quality indicators for monitoring the clinical use of blood in Europe

Blood units transfused per transfused patient, by clinical department

Chronic versus acute demand – Compatibility issues versus issues of supply logistics

AABB Blood survey report 2013

Estimated 2013 Collection and Transfusion by AABB US Member Blood Centers and Hospitals for Non-RBC-Components (expressed in thousands of units)

<table>
<thead>
<tr>
<th>Collection/Production</th>
<th>Blood Centers</th>
<th>Hospitals</th>
<th>2013 Combined Total</th>
<th>2011 Total</th>
<th>% Change 2011-2013</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis Platelets Collected and Processed</td>
<td>2,112</td>
<td>114</td>
<td>2,226</td>
<td>55</td>
<td>2,283</td>
<td>-2.5</td>
</tr>
<tr>
<td>Apheresis Platelets Distributed for Transfusion</td>
<td>1,908</td>
<td>94</td>
<td>2,002</td>
<td>50</td>
<td>2,090</td>
<td>-4.2</td>
</tr>
<tr>
<td>WB-Derived Platelets Concentrates Distributed†</td>
<td>154</td>
<td>9</td>
<td>164(819)</td>
<td>9</td>
<td>129(643)</td>
<td>27.1</td>
</tr>
<tr>
<td>Total Platelets Distributed for Transfusion</td>
<td>2,062</td>
<td>103</td>
<td>2,166</td>
<td>51</td>
<td>2,219</td>
<td>-2.4</td>
</tr>
<tr>
<td>Plasma Collected or Produced</td>
<td>3,956</td>
<td>283</td>
<td>4,279</td>
<td>115</td>
<td>5,734</td>
<td>-21.0</td>
</tr>
<tr>
<td>Plasma Distributed for Transfusion</td>
<td>3,286</td>
<td>291</td>
<td>3,458</td>
<td>76</td>
<td>4,405</td>
<td>-22.4</td>
</tr>
<tr>
<td>Cryoprecipitate Distributed for Transfusion†</td>
<td>1,218</td>
<td>117</td>
<td>1,335</td>
<td>70</td>
<td>867</td>
<td>54.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfusions</th>
<th>Blood Centers</th>
<th>Hospitals</th>
<th>2013 Combined Total</th>
<th>2011 Total</th>
<th>% Change 2011-2013</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis Platelets</td>
<td>0</td>
<td>1,143</td>
<td>1,143</td>
<td>104</td>
<td>1,019</td>
<td>12.2</td>
</tr>
<tr>
<td>WB-Derived Platelets Concentrates†</td>
<td>0</td>
<td>167</td>
<td>167(555)</td>
<td>53</td>
<td>116(658)</td>
<td>30.7</td>
</tr>
<tr>
<td>Total Platelets Transfused</td>
<td>0</td>
<td>1,210</td>
<td>1,310</td>
<td>121</td>
<td>1,135</td>
<td>15.4</td>
</tr>
<tr>
<td>Plasma</td>
<td>1</td>
<td>1,796</td>
<td>1,797</td>
<td>120</td>
<td>1,995</td>
<td>-9.9</td>
</tr>
<tr>
<td>Cryoprecipitate†</td>
<td>0</td>
<td>1,054</td>
<td>1,054</td>
<td>132</td>
<td>634</td>
<td>66.2</td>
</tr>
</tbody>
</table>

*Significantly different from 2011 data.
†Apheresis equivalent units; numbers in parentheses represent individual platelet concentrates produced from whole blood donations.
‡Includes individual units and pools expressed as individual units using weighted average units per pool as reported by the responding facilities.
AABB Blood survey report 2013
Apheresis platelets as percent of total platelets produced.

German data according to Transfusion Law §21, 2014
Manufacturing of platelet concentrates
German data according to Transfusion Law §21, 2014

Manufacturing of platelet concentrates in dependence of the legal organizational status of the manufacturer

Use and decay / expiry of platelet concentrates

Decay / expiry differentiated according to manufacturer and hospital / user
Availability of platelet concentrates in Europe – Summary

- Platelets” - Do we exactly know what we are talking about?
  - Wide variety of manufacturing processes.

- Data on manufacturing and use of platelets in Europe exist.
  - Data focus on the overall need of platelets per member state.
  - Data verify a wide variety of use of platelets among member states.
  - Data focus on the differentiation of the manufacturing process pool platelets versus apheresis platelets.
  - “Regular shortages” of platelets in patient care are reported in Europe.
  - Decay of platelet concentrates is an issue.
Collecting data for decision making:

Information content derived from available data?

Knowledge gaps as evident from consideration of available data

Platelet manufacturing processes

- We do not have data on the use of the different manufacturing protocols (e.g., EDQM Blood Guide monographs).
- Data don’t contribute to understanding the interdependencies of the manufacturing protocol with the parameter quality, safety, efficacy of the platelet concentrate manufactured.
- National data in the European context currently provide no parameters to allow for a solid comparison of data (e.g., data on different infrastructural aspects and financing of national health care systems).
- ....

Processes of platelet supply and transfusion

- We learn about magnitudes of transfused platelets, but we currently do not link them with epidemiological data in order to evaluate different practices of platelet use (e.g., incidence, prevalence of disease entities, infectious disease markers in the population under consideration).
- We learn about magnitudes of transfused platelets, but we currently do not link them with the underlying transfusion protocols and clinical data in order to evaluate different practices of platelet use (e.g., prevention of bleeding by prophylactic transfusion, transfusion trigger, transfusion thresholds, platelet doses, outcome parameters to decide on the continuation of transfusion therapy).
- We learn about shortages and decay of platelets, but we do not link these data with parameters to allow for a solid interpretation of shortages and decay (e.g., donor selection processes, donor characteristics, interdependencies of manufacturer and clinical units / hospitals).
Knowledge gaps as evident from consideration of available data

Platelet manufacturing processes

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- Data don’t contribute to understanding the interdependencies of the manufacturing protocol with the parameter quality, safety, efficacy of the platelet concentrate manufactured.
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- We learn about magnitudes of transfused platelets, but we currently do not link them with the underlying transfusion protocols and clinical data in order to evaluate different practices of platelet use (e.g. prevention of bleeding by prophylactic transfusion, transfusion trigger, transfusion thresholds, platelet doses, outcome parameter to decide on the continuation of transfusion therapy, …).
- We learn about shortages and decay of platelets, but we do not link these data with parameters to allow for a solid interpretation of shortages and decay (e.g. donor selection processes, donor characteristics, interdependencies of manufacturer and clinical units / hospitals, …).

Which kind of data / of data analysis would enhance the information needed?
Clinical studies and “Real world data” - EMA initiative on patient registries

cited from: Xavier Kurz, Head of Monitoring and Incidence Management, EMA // PPTA Conference 23 March 2016

Examples of use of disease registries in the regulatory environment versus prospective clinical studies

Clinical studies and “Real world data” – Retrospective analysis of clinical data

Example of French haemovigilance data

Apheresis platelets are more frequently associated with adverse reactions than pooled platelets both in recipients and in donors: a study from French hemovigilance data


STUDY DESIGN AND METHODS:
From the French national hemovigilance system, types and numbers of recipient adverse reactions were compared over a period from 2009 to 2011. Donor adverse reactions were available for 2010 and 2011. This study involved 23 of 26 French regions. Main outcomes were the rates of adverse reaction in recipients and serious adverse reaction in donors.

RESULTS:
There were 790,854 PLT transfusions during the study period (477,747 [60%] with APCs, 313,107 [40%] with PPCs). APCs were associated with more adverse reactions (6244 vs. 2469 per 1,000,000, p < 0.001) and more severe and life-threatening reactions (respectively, 241 vs. 131 per 1,000,000, p < 0.001; and 182 vs. 121 per 1,000,000, p = 0.04). Mortality rates due to an adverse transfusion reaction were similar (15 vs. 6 per 1,000,000, p = 0.5). In donors, the number of whole blood (WB) donations was 4,722,685 whereas 266,095 apheresis procedures were performed. Serious adverse reactions were more frequent for apheresis procedures than for WB donations (5445 vs. 803 per 1,000,000, p < 0.001).
Blocking neutrophil diapedesis prevents hemorrhage during thrombocytopenia

Hillgruber C et al., J Exp. Med. 2015; 212 : 1255 - 1266

Spontaneous organ hemorrhage is the major complication in thrombocytopenia with a potential fatal outcome. However, the exact mechanisms regulating vascular integrity are still unknown. Here, we demonstrate that neutrophils recruited to inflammatory sites are the cellular culprits inducing thrombocytopenic tissue hemorrhage. Exposure of thrombocytopenic mice to UVB light provokes cutaneous petechial bleeding. This phenomenon is also observed in immune–thrombocytopenic patients when tested for UVB tolerance. Mechanistically, we show, analyzing several inflammatory models, that it is neutrophil diapedesis through the endothelial barrier that is responsible for the bleeding defect. First, bleeding is triggered by neutrophil-mediated mechanisms, which act downstream of capturing, adhesion, and crawling on the blood vessel wall and require Gβγ signaling in neutrophils. Second, mutating Y731 in the cytoplasmic tail of VE-cadherin, known to selectively affect leukocyte diapedesis, but not the induction of vascular permeability, attenuates bleeding. Third, and in line with this, simply destabilizing endothelial junctions by histamine did not trigger bleeding. We conclude that specifically targeting neutrophil diapedesis through the endothelial barrier may represent a new therapeutic avenue to prevent fatal bleeding in immune–thrombocytopenic patients.

A stringent systems approach uncovers gene-specific mechanisms regulating inflammation

Tong AJ et al., Cell 2016; 165 : 165-179

Stringent analyses of nascent transcript RNA-seq, ChIP-seq, and transcription factor binding motif datasets associated with inflammatory gene induction uncover the extent to which unique mechanisms regulate individual genes. with key biological functions and allow a mechanistic understanding of transcriptional control at a genome-wide level.
Linking data with a broader scientific context
Systems biology approach, systems medicine approach

Effect of Blood Donor Characteristics on Transfusion Outcomes: A Systematic Review and Meta-Analysis
Chassé M et al., Transf Med Rev 2016

Optimal selection of blood donors is critical for ensuring the safety of blood products. The current selection process is concerned principally with the safety of the blood donor at the time of donation and of the recipient at the time of transfusion. Recent evidence suggests that the characteristics of the donor may affect short- and long-term transfusion outcomes for the transfused recipient. We conducted a systematic review with the primary objective of assessing the association between blood donor characteristics and red blood cell (RBC) transfusion outcomes. We searched MEDLINE, EMBASE, and Cochrane Central databases and performed manual searches of top transfusion journals for all available prospective and retrospective studies. We described study characteristics, methodological quality, and risk of bias and provided study-level effect estimates and, when appropriate, pooled estimates with 95% confidence intervals using the Mantel-Haenszel or inverse variance approach. The overall quality of the evidence was graded using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. From 613 citations identified by our literature search, 50 studies met our eligibility criteria (9 observational, 9 interventional). We identified the evaluation of association of 17 donor characteristics on RBC transfusion outcome. The risk of bias and confounding of the included studies was high. The quality of evidence was graded as very low to low for all 17 donor characteristics. Potential associations were observed for donor sex with reduced survival at 90 days and 6 months in male recipients who receive donated blood from females (hazard ratio 2.60 [1.09, 6.20] and hazard ratio 2.40 [1.10, 5.24], respectively; n = 1). Human Leukocyte Antigen - antigen D Related (HLA-DR) selected transfusions (odds ratio [OR] 0.39 [0.15, 0.99] for the risk of transplant aloimunization, n = 5), presence of antinuclear antibodies (OR 5.84 [1.66, 20.59] for risk of transfusion-related acute lung injury, n = 4), and donor RBC antigen selection (OR 0.26 [0.08, 0.52] for risk of alloimmunization, n = 4), based on low quality evidence, positive antinuclear antibodies, female donor to male recipients, HLA-DR selected RBC transfusion, or donor RBC antigen selection may affect RBC transfusion outcome. Our findings that donor characteristics may be associated with transfusion outcomes warrant establishing web-to-web data infrastructure to allow for large robust evaluations. PROSPERO registration number: CRD42012006726.

Linking data with infrastructural data of healthcare provision
Micro-/macroenvironment – Health analytics

Hematopoietic stem cell transplantation
Grathwohl A et al., JAMA 2010; 303 : 1617 – 1624; Niedenweiser D et al., Bone Marrow Transplant 2016; 1–8; Grathwohl A et al., EBioMedicine 2015; 2 : 2101-2109

HSCT is an accepted therapy today
- different use and needs worldwide
- Availability of resources, governmental support, access for patients to a team identified as key factors for higher transplant rates

Country- and center-specific economic factors
- are associated with distinct, significant, and clinically relevant effects on survival after HSCT.
- impact on center expertise in long-term disease and complication management.
- but associations, not causal effects are described.
Use of blood components dependent on patient’s need acute vs chronic
Example of a German University Clinic, Data collection 12 months - Here: Average / month

<table>
<thead>
<tr>
<th>Hematology / Oncology Unit</th>
<th>Internal Medicine Emergency Care</th>
<th>Clinic for General Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases / patients</td>
<td>150</td>
<td>236</td>
</tr>
</tbody>
</table>

Allocation at blood bank

<table>
<thead>
<tr>
<th>Component</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>257</td>
</tr>
<tr>
<td>Plasma</td>
<td>61</td>
</tr>
<tr>
<td>Platelets</td>
<td>240</td>
</tr>
</tbody>
</table>

Total: 558

Use of components

<table>
<thead>
<tr>
<th>Component</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>238</td>
</tr>
<tr>
<td>Plasma</td>
<td>61</td>
</tr>
<tr>
<td>Platelets</td>
<td>237</td>
</tr>
</tbody>
</table>

Total: 556

Allocation / Use (RBC)

<table>
<thead>
<tr>
<th>Allocation / Use</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC / 100 cases</td>
<td>72,30%</td>
</tr>
<tr>
<td>Plasma / 100 cases</td>
<td>99%</td>
</tr>
<tr>
<td>Platelets / 100 cases</td>
<td>30,60%</td>
</tr>
</tbody>
</table>

Total / 100 cases

Use of components

<table>
<thead>
<tr>
<th>Component</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC / 100 cases</td>
<td>238,89</td>
</tr>
<tr>
<td>Plasma / 100 cases</td>
<td>45,67</td>
</tr>
<tr>
<td>Platelets / 100 cases</td>
<td>108,99</td>
</tr>
</tbody>
</table>

Total / 100 cases: 452,56

Allocation / Use (Plasmas)

<table>
<thead>
<tr>
<th>Allocation / Use</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC / 100 cases</td>
<td>72,30%</td>
</tr>
<tr>
<td>Plasma / 100 cases</td>
<td>99%</td>
</tr>
<tr>
<td>Platelets / 100 cases</td>
<td>30,60%</td>
</tr>
</tbody>
</table>

Total / 100 cases

Availability of platelet concentrates in Europe – Summary 2

- Platelets - Do we exactly know what we are talking about?
  - Wide variety of manufacturing processes.

- Data on manufacturing and use of platelets in Europe exist.
  - Data focus on the overall need of platelets per member state.
  - Data verify a wide variety of use of platelets among member states.
  - Data focus on the differentiation of the manufacturing process pool platelets versus apheresis platelets.
  - “Regular shortages” of platelets in patient care are reported in Europe.
  - Decay of platelet concentrates is an issue.

- Data currently do not provide the information content necessary for decision-making in the field.
  - When thinking about recommendations resulting from this workshop, the need to clearly define parameters necessary to interpretate data in the European context should be considered.

- Data source and methods of data analysis
  - Clinical studies and retrospective analysis of clinical data are required. Registry data might be a helpful tool.
  - Data examination has to take into account aspects from systems biology and systems medicine approaches as well as from the micro- / macroenvironmental conditions of healthcare provision.
Discussion

Risikoadjustierte prozessorientierte Qualitätssicherung
Das der Risikobewertung zugrundeliegende Modell determiniert die Eingriffsschwelle.

- Szenarienbildung
- Kostenanalyse
- Formulierung einer Strategie zur Risikokontrolle
- Risikokommunikation
- Risikomanagement

Risk assessment models – Aggregated risk assessment

Kleinman S et al., Transfusion 2015

### TABLE 1. Patients receiving RBC transfusions get exposed to different numbers of RBC units with different time frames of exposure

<table>
<thead>
<tr>
<th>RBC transfusion category</th>
<th>Diagnosis or procedure</th>
<th>Number of transfusion episodes</th>
<th>Total RBC unit exposure + (time)</th>
<th>Immune suppressed</th>
<th>Use of irradiated blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Cardiac surgery&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td>Single</td>
<td>3±&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Intermittent</td>
<td>ICU&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Variable</td>
<td>3±&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Suppressed</td>
<td>No</td>
</tr>
<tr>
<td>Intermittent</td>
<td>Cardiovascular disease&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td>Variable</td>
<td>3±&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sustained over limited time frame</td>
<td>HBSCT&lt;sup&gt;11,12&lt;/sup&gt;</td>
<td>Multiple</td>
<td>36-20</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic but time-limited</td>
<td>MDS&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Multiple</td>
<td>3±&lt;/sup&gt;</td>
<td>Immunosuppressed</td>
<td>No&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic, Hb&lt;sup&gt;+&lt;/sup&gt;</td>
<td>SCD&lt;sup&gt;14,15&lt;/sup&gt;</td>
<td>Multiple</td>
<td>24±year (30 years&lt;sup&gt;16,17&lt;/sup&gt;)</td>
<td>Methemic</td>
<td>No&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> These data are taken from representative publications for each RBC transfusion category and may not be fully reflective of all practice patterns. Depending on how the data were presented in the cited publication(s), they are expressed as a mean, median, or range thereof.

<sup>2</sup> The data include only the patients who received transfusions.

<sup>3</sup> Median.

<sup>§</sup> Not routinely: may be irradiated if hospital-wide policies for hematology-oncology patients or for pediatric patients require.

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Risk assessment models – Aggregated risk assessment

Kleinman S et al., Transfusion 2015

### TABLE 4. Per unit risk in transfused RBC under current donor testing protocols in the United States

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Risk</th>
<th>Method of estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher-risk pathogens</td>
<td>0.076%</td>
<td></td>
</tr>
<tr>
<td>B. microti&lt;sup&gt;21&lt;/sup&gt;</td>
<td>0.00005% (1 in 1316)</td>
<td></td>
</tr>
<tr>
<td>CMV&lt;sup&gt;1,18&lt;/sup&gt;</td>
<td>Detection of infection in transfused recipients and PCR data in donors</td>
<td></td>
</tr>
<tr>
<td>EIA</td>
<td>Mathematical modeling&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Acute-type agent&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.005% (1 in 2000)</td>
<td></td>
</tr>
<tr>
<td>Chronic-type agent&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.0007% (1 in 1.5 million)</td>
<td></td>
</tr>
<tr>
<td>Lower-risk pathogens</td>
<td>0.0009%</td>
<td></td>
</tr>
<tr>
<td>Plasmodia—all species</td>
<td>Clinical case reporting (&lt;1 TT case per year in United States)</td>
<td></td>
</tr>
<tr>
<td>Bacteria&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Based on French and German data</td>
<td></td>
</tr>
<tr>
<td>A. phagocytophila&lt;sup&gt;23,24&lt;/sup&gt;</td>
<td>No documented clinical cases in the United States in past 5 years; may be more common for subclinical cases</td>
<td></td>
</tr>
<tr>
<td>HIV&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Clinical case reporting (&lt;1 TT case per year in United States)</td>
<td></td>
</tr>
<tr>
<td>HCV&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Mathematical modeling&lt;sup&gt;25&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>HBV&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Mathematical modeling&lt;sup&gt;25&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>WHV&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Clinical case reporting (&lt;1 TT case per year in United States)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Rare in nonendemic areas.

<sup>2</sup> Assumes that all PCR-positive donations, regardless of antibody status, would be infectious.

<sup>3</sup> Using data from previously detected EIAs.

<sup>4</sup> Using NRT donor screening data and a window period model.

<sup>5</sup> IND = investigational new drug.
### TABLE 5. Aggregate single-unit risks in transfused RBC under current donor testing protocols in the United States

<table>
<thead>
<tr>
<th>Aggregate risk category</th>
<th>Risk elements*</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>HIV = HCV = HBV</td>
<td>0.0003%</td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td>(1 in 322,600)</td>
</tr>
<tr>
<td>Minimum + CMV†</td>
<td>HIV = HCV = HBV</td>
<td>0.1033%</td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td>(1 in 998)</td>
</tr>
<tr>
<td>Maximum</td>
<td>HIV = HCV = HBV</td>
<td>0.1203%</td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td>(1 in 831)</td>
</tr>
<tr>
<td>Maximum CMV†</td>
<td>HIV = HCV = HBV</td>
<td>0.2033%</td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td>(1 in 454)</td>
</tr>
<tr>
<td></td>
<td>babesia-endemic area</td>
<td></td>
</tr>
<tr>
<td></td>
<td>babesia-nonendemic area</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rara-chronic EIA</td>
<td></td>
</tr>
</tbody>
</table>

* This column contains the components that are then summed together to provide the total risk (shown in the right-hand column), for each aggregate risk category. The numbers for each risk element are taken from Table 4.  
† (HSCT patients).

---

### TABLE 6. Aggregate lifetime patient risks due to RBC transfusion for different patient categories under current testing algorithms in the United States

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>RBC unit exposure</th>
<th>Minimum††</th>
<th>Maximum‡‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac surgery</td>
<td>3</td>
<td>0.0009 (1/107,000)</td>
<td>0.36 (1/277)</td>
</tr>
<tr>
<td>Trauma</td>
<td>5</td>
<td>0.0014 (1/66,000)</td>
<td>0.60 (1/167)</td>
</tr>
<tr>
<td>ICU</td>
<td>3.5</td>
<td>0.0011 (1/91,000)</td>
<td>0.42 (1/238)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>3</td>
<td>0.0009 (1/107,000)</td>
<td>0.36 (1/277)</td>
</tr>
<tr>
<td>HSCT</td>
<td>15</td>
<td>1.49 (1/87)</td>
<td>3.25 (1/31)</td>
</tr>
<tr>
<td>MDS</td>
<td>39</td>
<td>0.012 (1/80)</td>
<td>3.76 (1/27)</td>
</tr>
<tr>
<td>SCD</td>
<td>720</td>
<td>0.22 (1/450)</td>
<td>43.17 (1/2)</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>750</td>
<td>0.23 (1/430)</td>
<td>45.13 (1/2)</td>
</tr>
</tbody>
</table>

†† The method of calculating risk when large numbers of units are transfused as described by Kleinman et al.  
‡‡ Lifetime risks, except for cardiovascular disease and ICU patient groups. In the latter groups, risk is for a single hospitalization or ICU stay.  
Lifetime risk would increase for patients transfused on multiple occasions.  
Minimum per-unit risk is 0.0003% for all patient groups except for HSCT patients, where minimum risk is 0.1033% based on potential sequelae from TT-CMV infection.  
Maximum per-unit risk is 0.1203% for the first four patient groups and 0.2033% for HSCT patients. For patients with MDS, SCD, and thalassemia, risk is 0.1203% for a 1.5-year period (when a new acute EIA is in the blood supply) and 0.07031% (due to Babesia) when transfused during other time intervals.