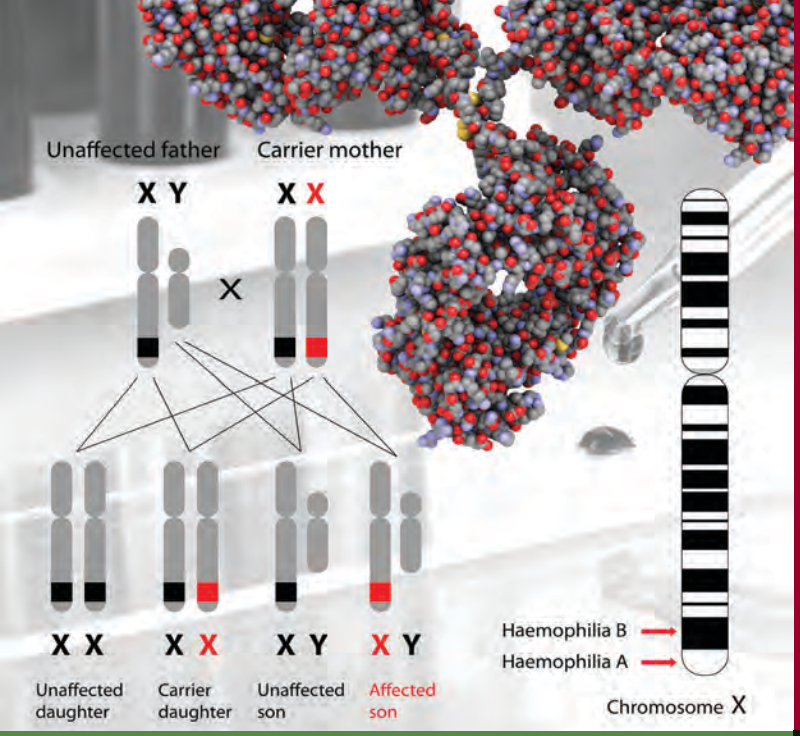
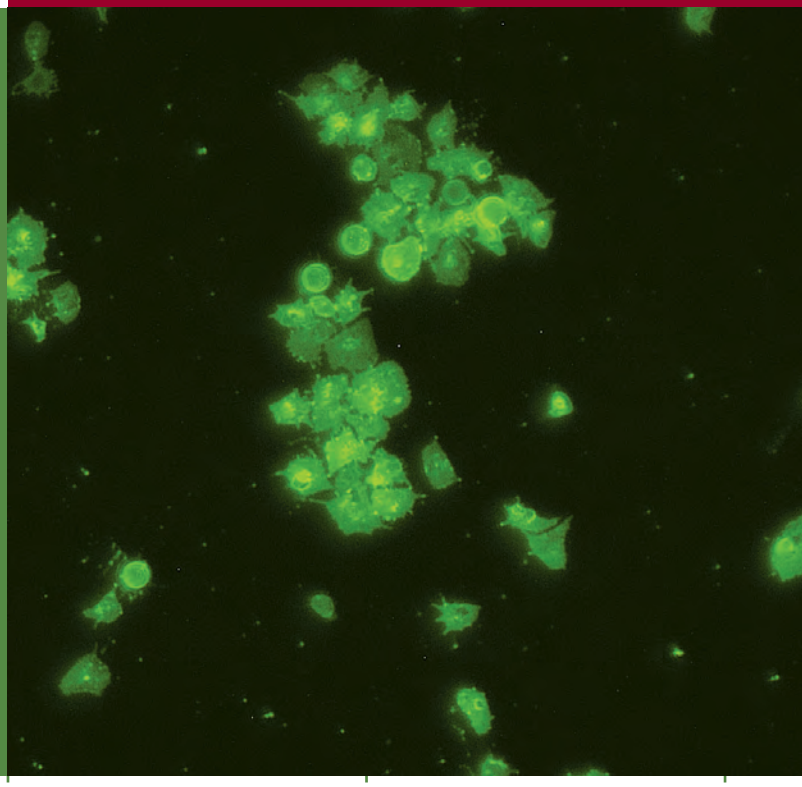


Optimal use of clotting factors and platelets



European symposium proceedings

Wildbad Kreuth
Initiative IV
Freising, Germany

European Directorate for the Quality of Medicines & HealthCare

6-7 May 2016

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Paul-Ehrlich-Institut

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Optimal use of clotting factors and platelets

European symposium proceedings
Wildbad Kreuth Initiative IV
Freising, Germany

European Directorate for the Quality of Medicines & HealthCare

Optimal use of clotting factors and platelets is published by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM).

Director of the publication: Dr S. Keitel

Page layout and cover: EDQM

European Directorate for the Quality of Medicines & HealthCare (EDQM)
Council of Europe
7 allée Kastner, CS 30026
F-67081 Strasbourg
France

Website: www.edqm.eu

Cover illustration:

Platelet adhesion to collagen under conditions of shear stress (20.16 dyn/cm²) and in the presence of thrombin receptor activating peptide 6 (5 µmol/L); platelet immunofluorescence staining was performed with CD41-FITC antibody; original magnification 630 ×.

Introduction

In continuation of the Wildbad Kreuth Initiative, the European symposium on "optimal use of clotting factors and platelets" took place on 6 and 7 May 2016 in the Bildungszentrum Kardinal-Döpfner-Haus in Freising, Germany. The new venue had been chosen since the original location in Wildbad Kreuth was no longer available, and it turned out to be a very good choice which provided an excellent environment for plenary sessions and workshops, and for getting together for many fruitful discussions.

The symposium was the fourth in the series of Wildbad Kreuth meetings on optimal use of blood products. These conferences provide a unique forum for delegates invited from the member states of the Council of Europe. The aim of the Kreuth symposia is to be not just another scientific meeting with presentations of the latest cutting-edge scientific findings, but to provide a platform for exchanging and discussing current practices and projections of future developments across the Council of Europe area and, through workshops, to formulate useful recommendations.

The outcomes of the previous three symposia in 1999, 2009 and 2013 published in the conference proceedings were very well received in the field. In particular, the recommendations drafted in 2013 were not only disseminated in scientific publications[1,2], finding considerable interest in the scientific community, but were also translated into resolutions of the Committee of Ministers of the Council of Europe[3,4].

The fourth symposium in Freising, like the previous Kreuth conferences, addressed the optimal use of clotting factors. While new products with extended half-life are entering the scene, there is still a need to evaluate the treatment of haemophilia across Europe and to promote further harmonisation of standards. Platelet transfusion was chosen as the second main topic since there are currently several issues and controversies concerning the choice of concentrates, indications, monitoring of transfusion and open questions to be explored by research.

---

[1] Giangrande P, Seitz R, Behr-Gross ME, Berger K, Hilger A, Klein H, Schramm W, Mannucci PM: Kreuth III: European consensus proposals for treatment of haemophilia with coagulation factor concentrates. Haemophilia 20:322-325 (2014)

[2] Sewell WAC, Kerr J, Behr-Gross ME, Peter HH, and on behalf of the Kreuth Ig Working Group (2014): European consensus proposal for immunoglobulin therapies. Eur J Immunol 44: 2207-2214

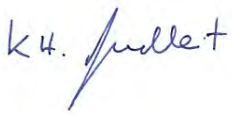
[3] Resolution CM/Res(2015)3 on principles concerning haemophilia therapies

[4] Resolution CM/Res(2015)2 on principles concerning human normal immunoglobulin therapies for immunodeficiency and other diseases

The National Authorities and the interested parties of 34 countries nominated 109 experts who accepted an invitation to meet in Freising on 6-7 May 2016 in order to exchange their experiences with the aim of developing an international consensus on the clinical use of clotting factors in haemophilia treatment and platelets transfusion.
This volume of proceedings reproduces the presentations, summaries of sessions, and the recommendations of the 2016 conference.

Prof Wolfgang Schramm
(LMU)

Prof Rainer Seitz
(PEI)



Dr Karl-Heinz Buchheit
(EDQM)

Contents

EUROPEAN SYMPOSIUM

IV Wildbad Kreuth Initiative - Optimal use of clotting factors and platelets

6-7 May 2016, Freising, Germany

Duration: 2,5 days. Working language: English

***

FINAL PROGRAMME

THURSDAY 5 MAY 2016

16:00-18:00

- Registration for participants
- Pre-meeting for speakers

19:00-21:30

- Buffet Dinner

FRIDAY 6 MAY 2016

8:00 Welcome

Prof Dr Karl-Walter Jauch, Medical Director, University Munich
Dr Michael Wierer, EDQM, Council of Europe

SESSION 1 (Plenary): Clinical use of clotting factors and platelets - Challenges

Moderators & Rapporteurs: *Pier Mannucci, Rainer Seitz, Michael Wierer*

8:30-8:50 **Optimal use of blood components – rationale for Wildbad-Kreuth Initiative IV**
***Wolfgang Schramm**, University of Munich, DE*

8:50-9:10 **Continuing the Kreuth Initiative: Current controversies in clinical use of blood components**
***Rainer Seitz**, Paul Ehrlich Institut, Langen, DE*

9:10-9:30 **Quality indicators for monitoring the Clinical Use of Blood**
***Constantina Politis,** Coordinating Haemovigilance Centre, Athens, GR*

9:30-9:50 **How novel drugs change treatment in haemophilia**
***Flora Peyvandi**, University of Milan, IT*

9:50-10:10 **Current challenges using platelet concentrates**
***Jean-Pierre Cazenave**, ARMESA, Strasbourg, FR*

10:10-10:40 Bavarian break

10:40-11:00 **Regulatory and health technology assessment requirements**
***Jan Müller-Berghaus**, Paul Ehrlich Institut, Langen, DE*

11:00-11:20 **Current challenges of benefit/effectiveness/risk assessment (haemophilia and platelets)**
***Karin Berger**, University Hospital of Munich, DE*

11:20-11:40 **Patients organisations' view**
***Brian O'Mahony,** European Haemophilia Consortium (EHC), Dublin, IE*

11:40-13:00 Lunch break

WORKSHOPS (parallel sessions)

SESSION 2: Clotting Factors: Impulse Presentations (parallel session)

Moderators & Rapporteurs: *Paul Giangrande, Pier Mannucci, Brian O'Mahony, Flora Peyvandi*

13:00-13:20 **Clinical trials of clotting factors/regulatory aspects**
***Anneliese Hilger**, Paul Ehrlich Institut, Langen, DE*

13:20-13:40 **Inhibitor development in PUPs – a comparison of previous studies and the Sippet study**
***Frits Rosendaal,** Leids Universitair Medisch Centrum, NL*

13:40-14:00 **Inhibitors: Prophylaxis and Immune Tolerance Induction (ITI)**
***Hervé Chambost,** University Hospital of Marseille, FR*

14:00-14:20 **Access: supply, procurement, tenders**
***Paul Giangrande,** University of Oxford, UK*

14:20-14:40 **Haemophilia care in Europe and USA – 2014/15 data and future trends**
***Patrick Robert**, the Marketing Research Bureau Inc, Orange, USA*

SESSION 3: Platelets: Impulse Presentations (parallel session)

Moderators & Rapporteurs: *Karin Berger, Jean-Pierre Cazenave, Sheila MacLennan, Dorothea Stahl*

13:00-13:20 **Current practice in platelet transfusion**
***Gregor Bein**, University Hospital of Giessen & Marburg, DE*

13:20-13:40 **How do we assess clinical efficacy of platelet transfusion?**
***Miguel Lozano,** Hospital Clinic of Barcelona, ES*

13:40-14:00 **Infectious risk: Testing strategies, pathogen inactivation**
***Sheila MacLennan**, National Health Service, Leeds, UK*

14:00-14:20 **Immunogenicity: process related issues**
***Olivier Garraud**, National Institute of Blood Transfusion (INTS), Paris, FR*

14:20-14:40 **Availability of platelet concentrates in Europe**
***Dorothea Stahl,** Paul Ehrlich Institut, Langen, DE*

14:40-15:00 Coffee break

15:00-17:00 **Working Groups**

Working Group 1: Clotting factor concentrates
Moderators & Rapporteurs: *Paul Giangrande, Pier Mannucci, Flora Peyvandi, Brian O'Mahony*

Working Group 2: Platelet-concentrates
Moderators & Rapporteurs: *Jean-Pierre Cazenave, Sheila MacLennan, Dorothea Stahl, Karin Berger*

17:00-17:30 **Preparation of interim reports**

SESSION 4 (Plenary): Summary of discussions – Interim reports of the Working Groups sessions

17:30-18:00 **Presentation and synthesis of workshops**

18:00 Close of meeting

20:00 Evening Dinner

SATURDAY 7 MAY 2016 – (Only open to public sector organisations representatives)

8:00-10:00 **Discussion in the Working Groups (parallel sessions), preparation of final reports**

10:00-10:30 Coffee break

10:30-12:30 **Final reports from the Working Groups**
Moderators: *Rainer Seitz & Michael Wierer*

- **Working Group 1: Clotting factors**
- **Working Group 2: Platelets**

12:30-13:30 Lunch break

13:30-16:00 **Conclusions and Recommendations**

SCIENTIFIC PROGRAMME COMMITTEE

Prof Dr Rainer SEITZ
Dr Marie-Emmanuelle BEHR-GROSS
Dr Karl-Heinz BUCHHEIT
Prof Dr Wolfgang SCHRAMM
Dr Karin BERGER
Dr Anneliese HILGER
PD Dr Dorothea STAHL
Dr Michael WIERER

Meeting Venue: see http://www.bildungszentrum-freising.de/

List of Participants

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REICHERT Anja	Baxalta Deutschland GmbH	Germany
ROBERT Patrick	The Marketing Research Bureau, Inc	U.S.A
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STRBAC Nina	Blood Transfusion Institute of Serbia	Serbia
STREIF Werner	Medical University Innsbruck	Austria
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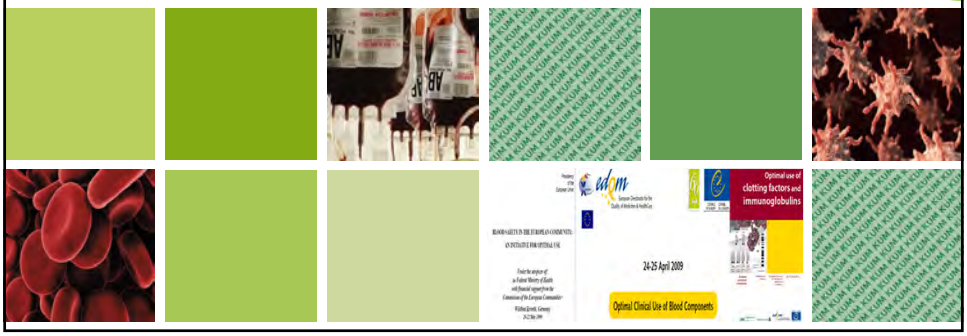
ZACHARI Eleni	EDQM	France

Presentations

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
CAMPUS GROSSHADERN
CAMPUS INNENSTADT
ÄRZTLICHER DIREKTOR

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

Prof. Karl-Walter Jauch



UNIVERSITY HOSPITAL LMU MUNICH

WE CAN MEDICINE

KLINIKUM DER UNIVERSITÄT MÜNCHEN – DOWNTOWN

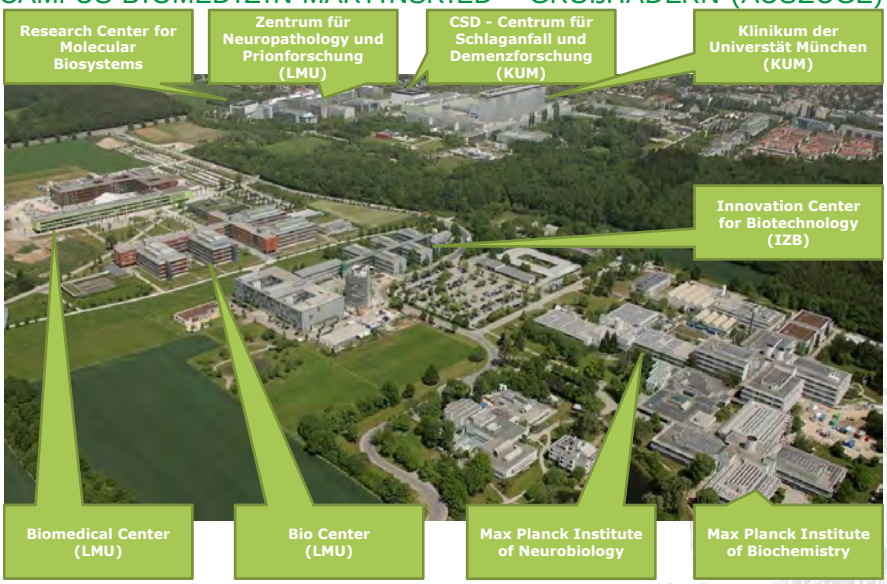
Downtown:

1st. Hospital 1813: „Allgemeines Krankenhaus“

Between 1843 und 1929:

- Many Buildings and Institutes from the University

CAMPUS BIOMEDIZIN MARTINSRIED – GROßHADERN (AUSZÜGE)



Quelle: IZB Fördergesellschaft mbH

KEY DATA

46 Clinical Departments, Institutes and Divisions

ca. 8.000 full-time employees

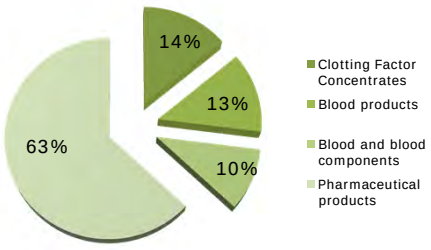
144 Wards

approx. 120 Professors in Medical Care

92 Mio. € Third-party funds

1066 Mio. € Total Revenue 2015

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.

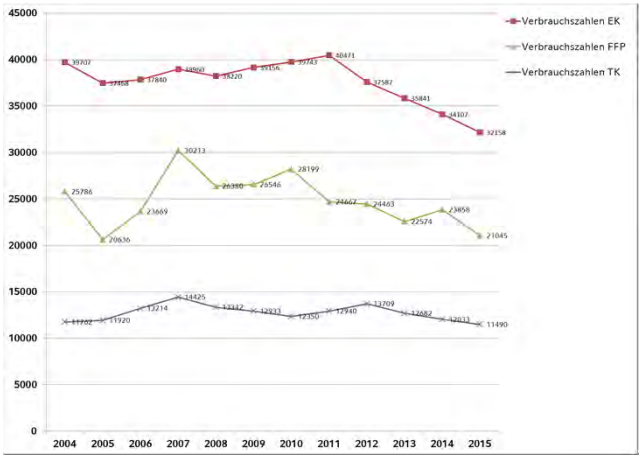
SAFETY IS AN ULTIMATE GOAL OF BLOOD PROVISION IN ROUTINE CARE

German Transfusion law regulates since 1998

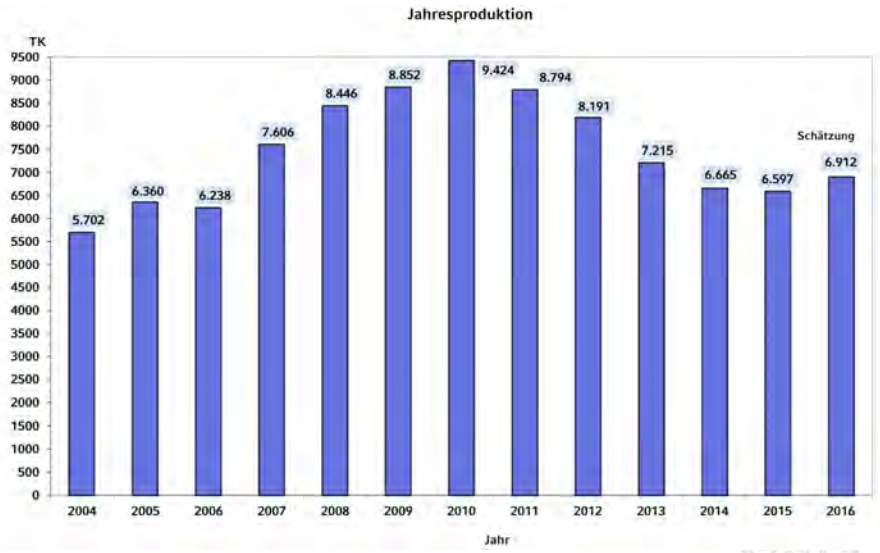
- Transfusion commission
- Transfusion officer
- Transfusion representative
- Obligation of documentation

→ 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



TC- OWN PRODUCTION



PLATELET PRODUCTION AT THE UNIVERSITY HOSPITAL OF MUNICH

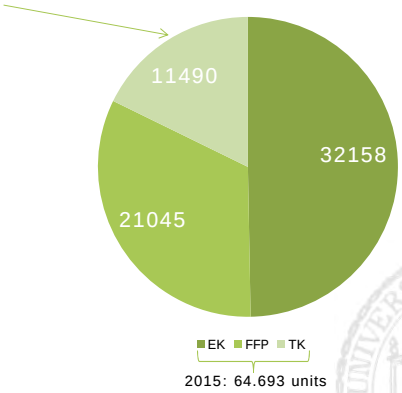
Approx 6.500 apheresis platelets per year are produced inhouse

- Secures a stable donor pool
- Indepence (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)

Haematology / Oncology	48%
Surgery	11%
Paediatric Clinic	10%
Cardiac Surgery	9%
Intensive care unit	8%

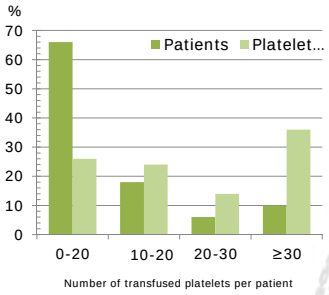


PLATELET TRANSFUSIONS IN ONCOLOGY HAEMAOLOGICAL PATIENTS

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

Karin Berger[1], Georg Wittmann[2], Christina Rieger[1], Helmut Ostermann[1]
[1]Medizinische Klinik and Poliklinik III, University Hospital of Munich, Germany
[2]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.



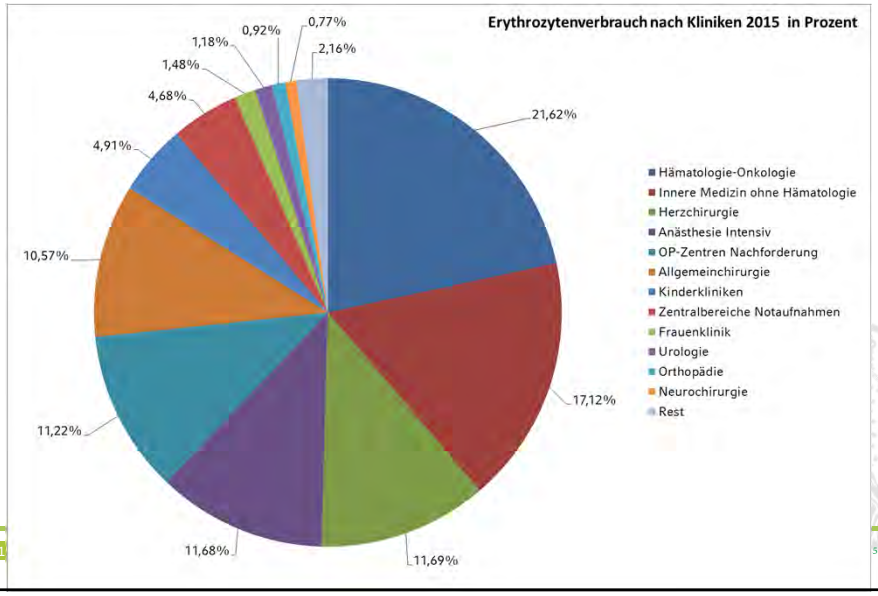
OPTIMAL USE OF BLOOD AND BLOOD PRODUCTS IS NECESSARY FROM ETHICAL, MORAL AND SOCIAL ASPECTS

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

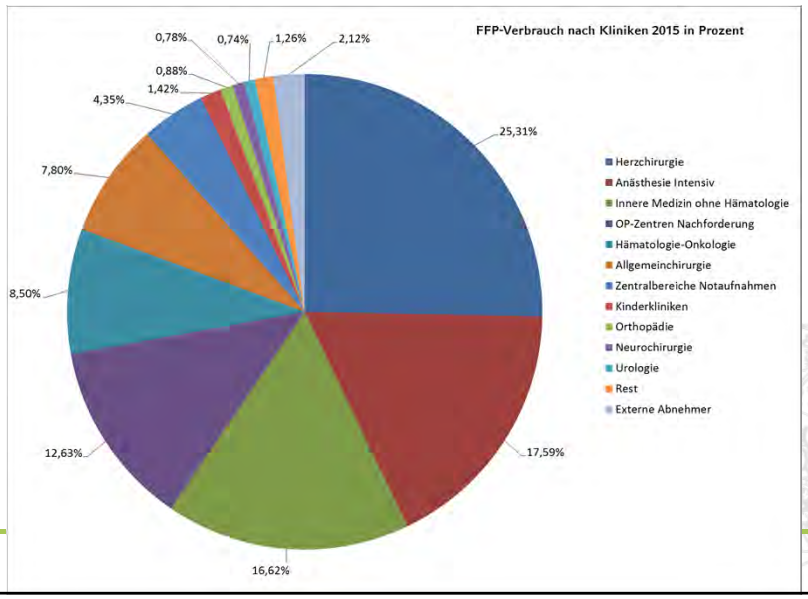
WHO (2001) - The clinical use of blood - Handbook

VIELEN DANK FÜR IHRE AUFMERKSAMKEIT

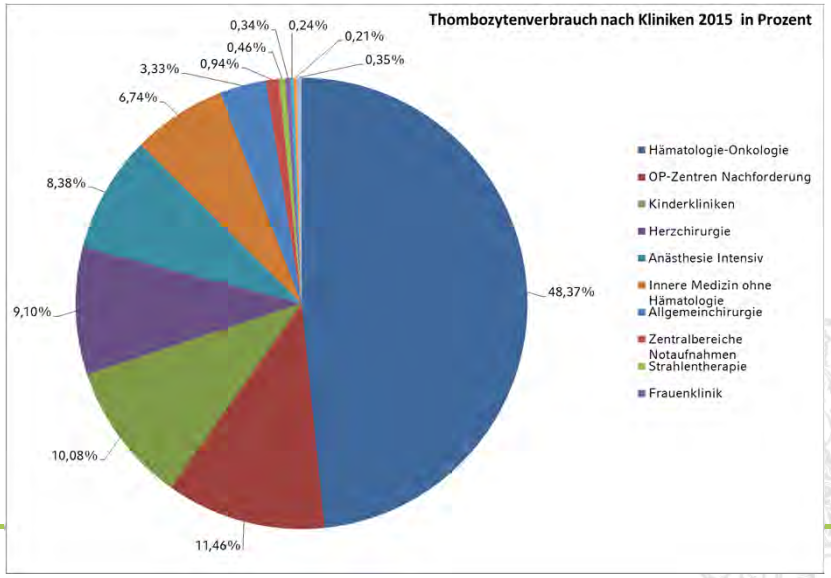
EK-VERBRAUCHER 2015



FFP-VERBRAUCHER 2015



TK-VERBRAUCHER 2015



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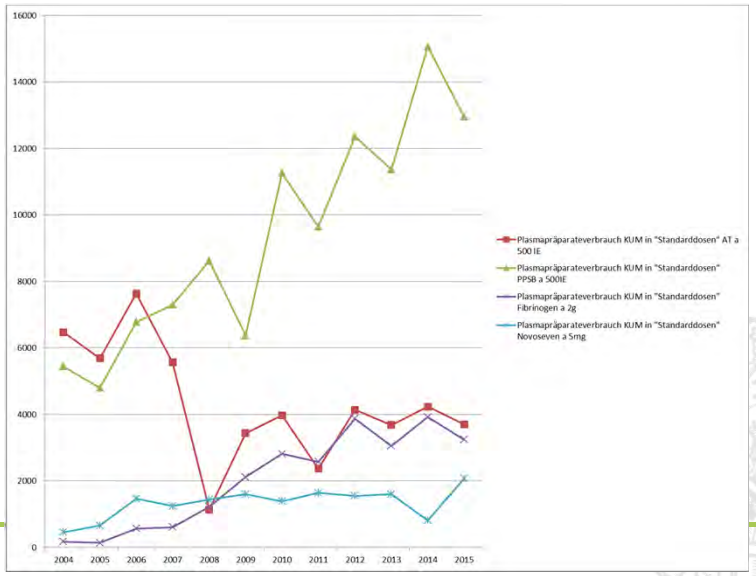
PLASMAPRÄPARATE VERLAUF OHNE „BLUTER"



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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

	Title	Topics addressed
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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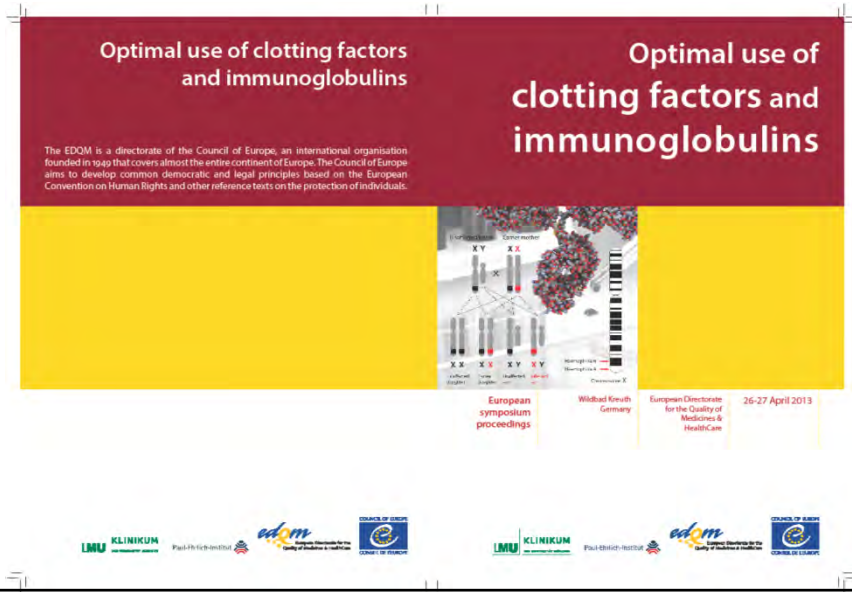
Kreuth III Proceedings



Follow-up activities to Kreuth III

- **Haemophilia treatment recommandations**
  - Kreuth III: European consensus proposals for treatment of haemophilia with coagulation factor concentrates. Haemophilia (2014), 20, 322–5
  - 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**
  - European consensus proposal for immunoglobulin therapies Eur. J. Immunol. 2014. 44: 2207–2214

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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

CM/Res(2015)3E

Resolution on principles concerning haemophilia therapies

CM/Res(2015)2E

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

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Mrs B. Hovanyecz(EDQM)

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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 Safety in the European Community – Optimal use of blood components: Wildbad Kreuth Initiatives 1999 - 2016

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Frame of the Wildbad Kreuth Initiatives

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 AVOID[1] ...

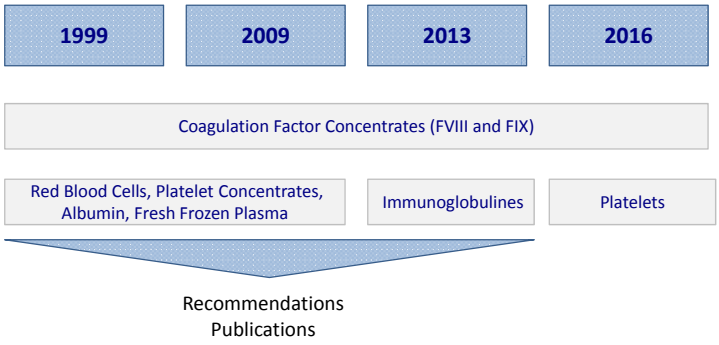
- Overuse
- Underuse
- Inappropriate use

OPTIMAL USE IN HAEMOPHILIA CARE REQUIRES[2] ...

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

[1]Advisory Council on the Assessment of Developments in the Health Care System: Report Appropriateness and Efficiency 2000/2001, Addendum
[2]Wildbad Kreuth Initiative: Conclusions and Recommendations No 71

Optimal Use of Blood and Blood Products in Europe
Wildbad Kreuth Initiatives (WBK) 1999-2016



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Kreuth III: European consensus proposals for treatment of haemophilia with coagulation factor concentrates

Haemophilia (2014), 20, 322–325
DOI: 10.1111/hae.12440

P. GIANGRANDE,*† R. SEITZ,‡ M. E. BEHR-GROSS,§ K. BERGER,¶ A. HILGER,‡ H. KLEIN,** W. SCHRAMM†† and P. M. MANNUCCI‡‡

Recommendations

- To optimize the organization of haemophilia care nationally, it is recommended that a formal body be established in each country to include the relevant clinicians, national haemophilia patient organisation, health ministry, paying authority and (if appropriate) regulatory authorities.
- The minimum factor VIII consumption level in a country should be 3 I.U. per capita.
- Decisions on whether to adopt a new product should not be based solely on cost.
- Prophylaxis for children with severe haemophilia is already recognized as the optimum therapy. Ongoing prophylaxis for individual adults should also be provided when required based on clinical decision making by the clinician in consultation with the patient.
- Children with inhibitors who have failed, or who are not suitable for, immune tolerance therapy (ITI) should be offered prophylaxis with bypassing agents.
- Single factor concentrates should be used as therapy wherever possible in patients with rare bleeding disorders.
- Orphan drug designation for a factor concentrate should not be used to hinder the development, licencing and marketing of other products for the same condition which have demonstrably different protein modification or enhancement.

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Major health political consequence of WBK III

COMMITTEE OF MINISTERS COMITÉ DES MINISTRES
COUNCIL OF EUROPE CONSEIL DE L'EUROPE

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;****

*http://www.consilium.europa.eu/en/council-eu/conclusions-resolutions/
**https://www.edqm.eu/sites/default/files/resolution_cm_res_2015_3_on_principles_concerning_haemophilia_therapies.pdf

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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

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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 eldery 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)?

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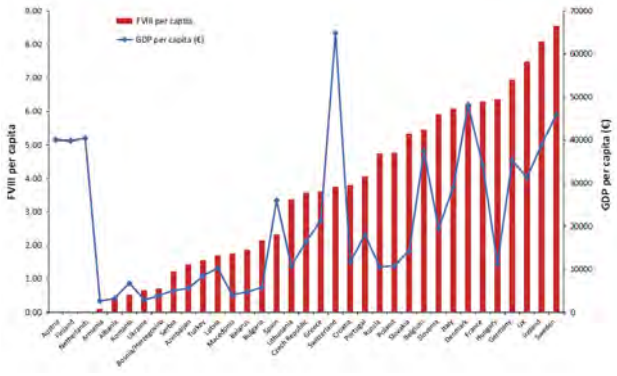

Comparision of GDP per capita (€) and factor VIII per capita use.

O'Mahony B et al. *Haemophilia* 2013, 19: e239-247.

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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

- Clinical relevance?
- Benefits?
- Cost-Effectiveness?

*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

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How to get access to optimal treatment?

Securing reimbursement for patient centered haemophilia care: major collaborative efforts are needed

Karin C. Berger,[1] Brian M. Feldman,[2] Joan Wasserman,[3] Wolfgang Schramm,[4] Victor Blanchette,[5] and Kathelijn Fischer on behalf of the Outcome Measures Expert Working Group of the International Prophylaxis Study Group (IPSG)

haematologica | 2016; 101(3)

- 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.

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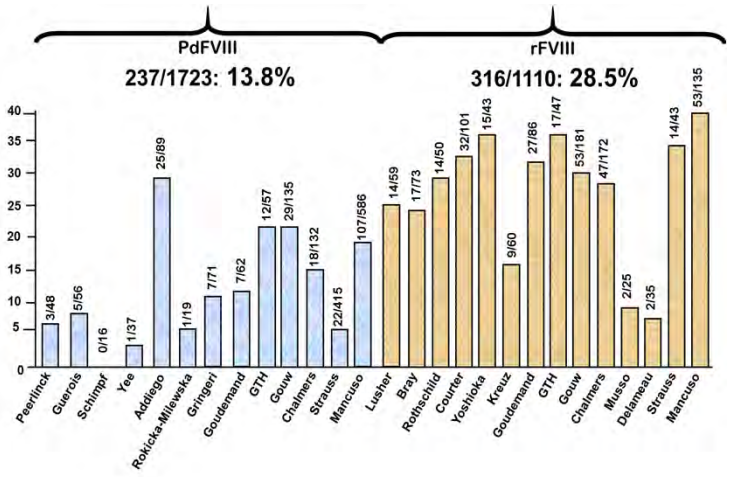
Uncerntainties on the impact of pd vs rec factor usage on inhibitor incidence



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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

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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?

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

How much blood is needed?

E. Seifried,[1] H. Klueter,[2] C. Weidmann,[3] T. Staudenmaier,[4] H. Schrezenmeier,[4] R. Henschler,[1] A. Greinacher,[5] & M. M. Mueller[1]

Vox Sanguinis (2011) **100**, 10–21

Demographic Changes: The Impact for Safe Blood Supply

Andreas Greinacher[a] Konstanze Fendrich[a] Wolfgang Hoffmann[b]

Transfus Med Hemother 2010;37:141–148

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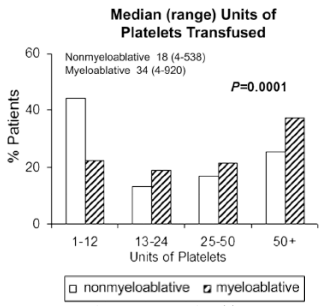
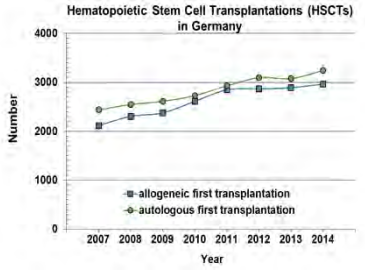
Contemporary representative real world data (epi data, blood usage) are required to predict future needs

Patiens ungergoing HSCT require a considerable amounts of plt transfusions

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



Wang et al. 2010 Br J Haematol 149 (1):101-110



Jahresbericht 2014 DRST Deutsches Register für Stammzelltransplantationen (German registry for stem cell transplantations) www.drst.de

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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

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Platelet production varies considerably in EU

Country	Proportion of PPC / APC production number (percent)		Changes in total PC production	Changes in total PC production	Population-related
	2014		2012 to 2013	2013 to 2014	2014
	Pooled PCs	Apheresis PCs	Percent	Percent	PCs / 1 000 population
France	161 896 (53.0%)	143 568 (47.0%)	+ 1.8%	-0.3%	4.77
Germany	231 139 (39.7%)	351 728 (60.3%)	- 1.9%	+0.9%	7.18
Switzerland	9 892 (28.0%)	25 436 (72.0%)	+ 1.4%	+ 1.7%	4.29
United Kingdom*	76 094 (26.6%)	210 256 (73.4%)	+ 2.6%	+ 0.4%	4.43

*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.

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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
http://www.nhsbt.nhs.uk/download/blood-2020.pdf

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Challenges: Spreading and Emerging Pathogens

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Continuing the Kreuth Initiative: Current controversies in clinical use of blood components

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Kreuth Initiative: Symposia 1999, 2009, 2013

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

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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

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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?

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Designated Orphan MP for haemophilia A

#	Product	Sponsor	Date
1	Pegylated rh FVIIa	Novo Nordisc	4/6/2008
2	Liposomal rh FVIII	Bayer Pharma AG	24/7/2009 (withdrawn)
3	Sequence-modified rhFVIIa	Bayer Pharma AG	9 October 2009
4	Recombinant porcine factor VIII (B domain deleted)	Inspiration Biopharmaceuticals	20 September 2010
5	Recombinant fusion protein FVIII attached to Fc of IgG1	Biogen Idec	20 September 2010
6	Pegylated rh BDD sequence-modified FVIII	Bayer Pharma AG	23 February 2011
7	Recombinant fusion protein FVIIa with albumin	CSL Behring	15 April 2011
8	Pegylated rH FVIII	Novo Nordisk	26 April 2012
9	Vatreptacog alfa (activated)	Novo Nordisk	9 August 2012
10	Hum. moAb TFPI	Novo Nordisk	10 October 2012
11	Hum. bispecific moAb targeting F IX, IXa, X and Xa	Chugai Pharma Europe Ltd	16 January 2014
12	Synth. siRNA against antithrombin mRNA + ligand with 3 N-acetylgalactosamine	Alnylam UK Limited	29 July 2014
13	rh FVIIa modified (repeats from β chain of human chorionic gonadotropin)	Richardson Associates Regulatory Affairs	22 August 2014
14	A combination of peptides (H-Lys-Lys-Gly-Pro-Arg…]	Apitope International NV	19 November 2014

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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)


Haemophilia The Official Journal of the World Federation of Hemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society

REVIEW ARTICLE

Evolution of the European guidelines for the clinical development of factor VIII products: little progress towards improved patient management

P. M. MANNUCCI


Haemophilia The Official Journal of the World Federation of Hemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society

COMMENTARY

Comment on: Mannucci, P. M. Evolution of the European guidelines for the clinical development of factor VIII products

A. HILGER,* C. ARRAS-REITER,* B. KELLER-STANISLAWSKI,* B. LJUNGBERG,† C. MALE,‡ D. MENTZER,* R. SEITZ* and G. SILVESTER§

*Paul-Ehrlich-Institut, Langen, Germany; †Läkemedelsverket, Uppsala, Sweden; ‡Medizinische Universität Wien, Vienna, Austria; and §European Medicines Agency, London, UK

** Blood Product Working Party; Chair: A. Hilger*

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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?

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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."*
  *The **Sanguis Study** Group: Use of blood products for elective surgery in 43 European hospitals. Transfusion Medicine 4:251-268;**1994***

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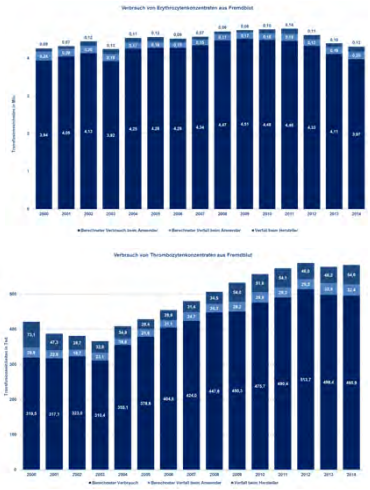
Where are we now?

- 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

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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)

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Controversies in clinical use of red cells?

- 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

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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


VoxSanguinis
SHORT REPORT
Clinical practice of platelet transfusions in haemato-oncology

- 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

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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

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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."*
  Garraud O. Improving platelet transfusion safety: biomedical and technical considerationsBlood Transfus. 14:109-22;2016
- 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


The Growing Number of Hemophilia Registries: Quantity vs. Quality
CLINICAL PHARMACOLOGY & THERAPEUTICS
C Kreuz[1], J Hesse[1,2], B Haschberger[2,3], M Heiden[4], R Seitz[4], HM van den Berg[5], A Hilger[1] and on behalf of the ABIRISK Consortium

- Clinical data collection of patients receiving platelets would also be valuable
  Pendry K. The use of big data in transfusion medicine. Transfus Med 25:129-131;2015

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

Continuing the Kreuth initiative

- 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

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

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
  - Implementation of Annual performance indicators of use of blood based on Rec(2002)11
- 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.
Implementation of annual performance indicators of use of blood and blood products based on the Rec(2002)11 of the Council of Europe

- 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

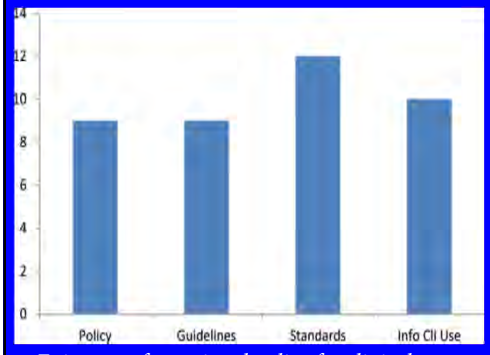
- Laboratory parameters
- Outcome in terms of morbidity
- Outcomes in terms of mortality
- Outcomes in terms of time
- Outcomes in terms of disease groups

Cost-effectiveness, cost-benefit analysis, cost-recovery evaluation

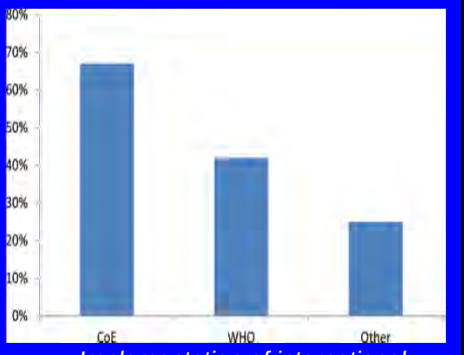
Other indicators

RESULTS

National policy for clinical use of blood

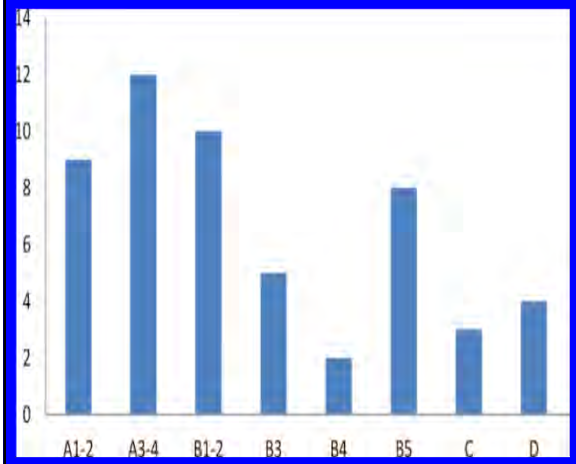


Existence of a national policy for clinical transfusion medicine, guidelines and quality standards

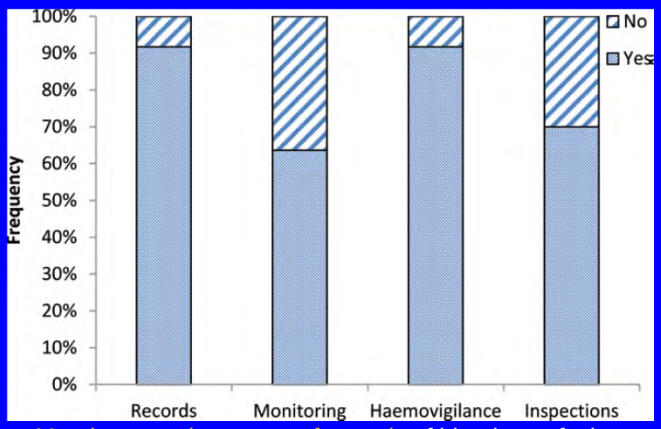


Implementation of international guidelines for the optimal use of blood and blood components

Numbers of countries providing responses to each section of the questionnaire

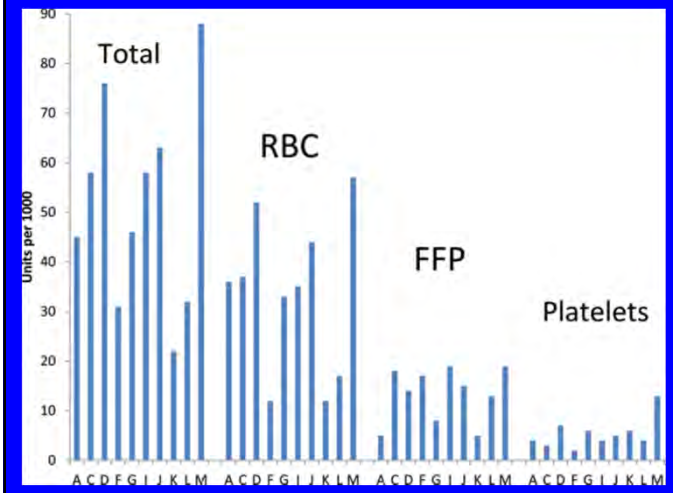


- A1-2: General information
- A3-4: National policy for the clinical use of blood
- B1-2: Indicators of use of the blood and blood components (red cells, fresh
- frozen plasma, platelets): national level
- B3: Evaluation of the use of blood at local (hospital) level
- B4: Benchmarking between institutions 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

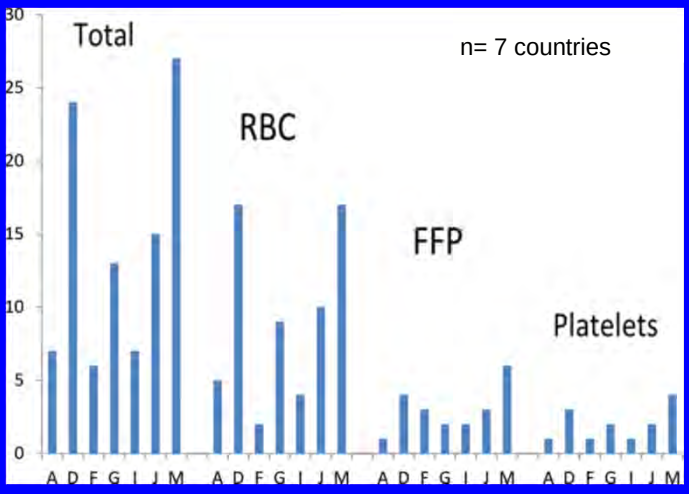
Units (total, RBC, FFP and platelets) transfused per 1 000 population, by country



The Excel worksheet into which the data were entered calculates automatically certain rates from these data

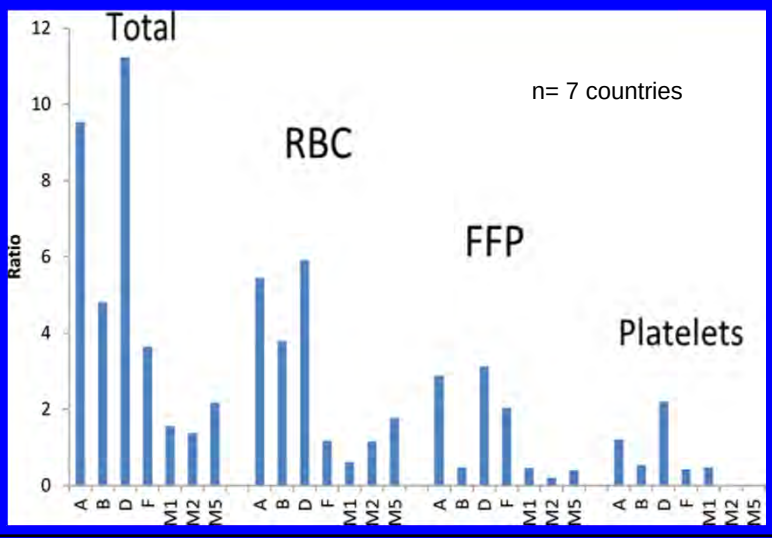
n= 10 countries

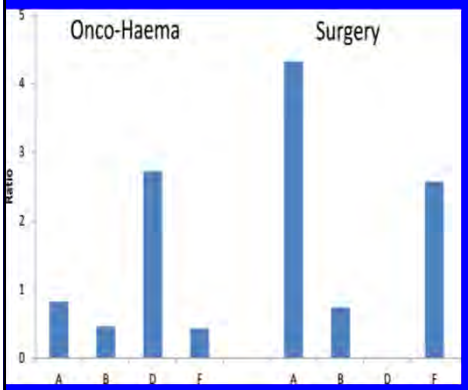
Units (total, RBC, FFP and platelets) transfused per hospital bed



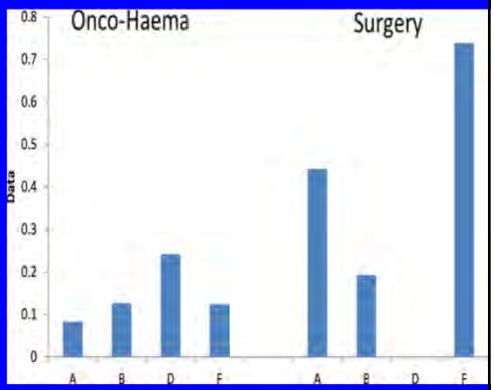
n= 7 countries

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



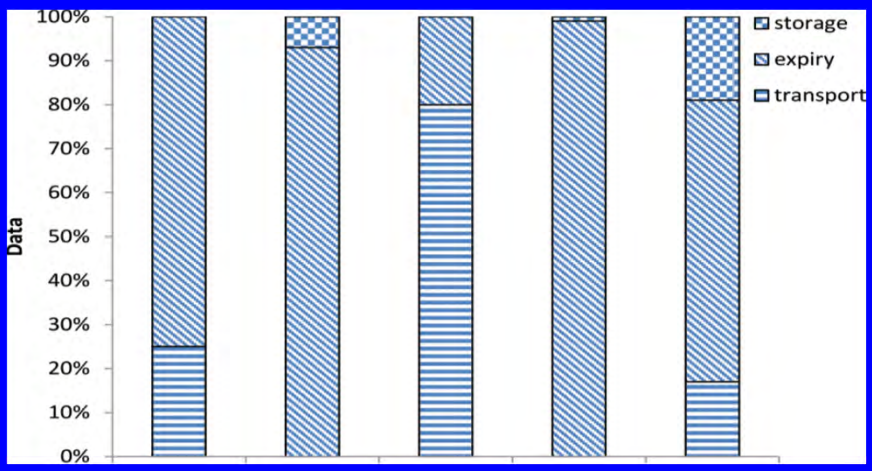


Units transfused per transfused patient, by clinical department



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

Percentage distribution of cause of discarding blood units (poor storage, expiry or poor transportation)



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)

Ratio $\frac{FFP}{RBC}$: 0.4 $(range\ 0.03 - 1.5\ median\ 0.31)$ 1:3

$\frac{Whole\ Blood\ Derived\ Platelets}{Apheresis\ Platelets} = \frac{64}{36}$ % 1.8 (0.0-85% 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)

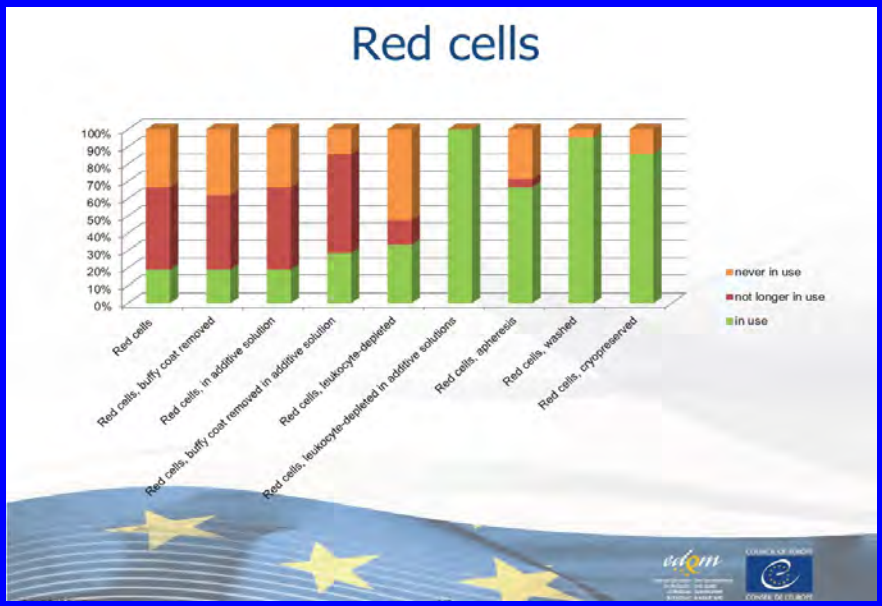
  71% recovered plasma (range 11-100% median 72%)
- Human albumin (17 MS)

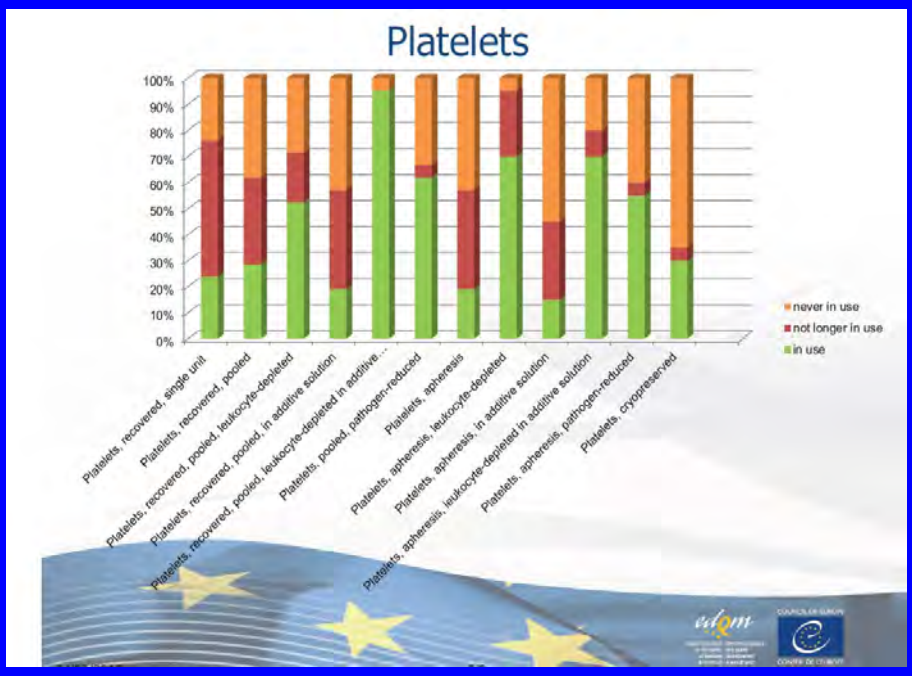
  Average use = 5088 kg (range= 0.0 - 35,379 kg, median 1,139 kg)
- Manufactured albumin (13 MS)

  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)





Comments I

- 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

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

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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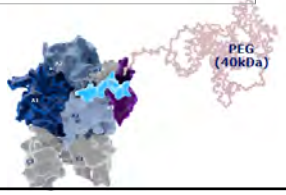
Novel products
rFVIII extended half-life

Product	Technology	Half-lfe $t_{1/2}$	Estimated time to 1% after 50IU/kg
BAY94-9027	Site-directed PEGylation	**1.4–1.6 fold**	~5 days
N8-GP	Site-directed glycoPEGylation		6,5 days
BAX855 (Adynovate)	Controlled PEGylation		4 days
rFVIII-Fc (Eloctate, Elocta)	Fc-fusion		4,9 days



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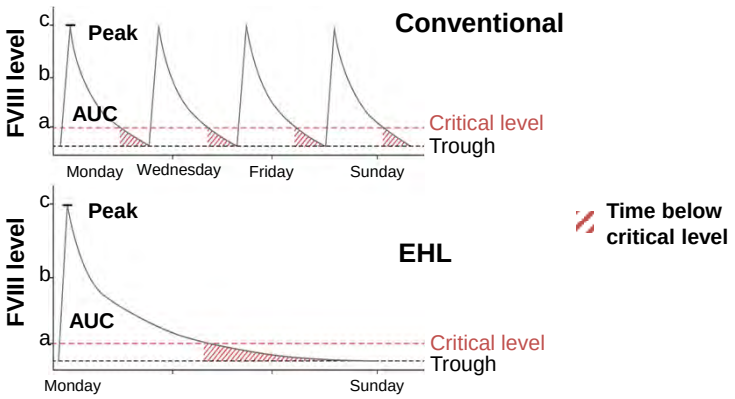
Impact of reduction of injections

- 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



(Adapted from Mahdi et al. Br J Haematol. 2015 ;169:768-76)

Product	Dose (IU/kg)	Treatment regimen	Median ABR, bleeds·patient^{-1}·year^{-1}	Patients with no bleeding episodes, %
Long-acting rFVIII Products				
BAY94-9027	45–60 IU/kg	every 5 days	**1,9**	44
	60 IU/kg	every 7 days	**3,9**	37
rFVIII-Fc (Eloctate)	25–65 IU/kg	every 3 - 5 days	**1,6**	45,3
	65 IU/kg	every 7 days	**3,6**	17,4
BAX 855 (Adynovate)	45 IU/kg	2xweek	**1,9**	39,6

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

(Powell et al. N Engl J Med 2013;369:2313-23 ; Powell J et al. Haemophilia 2014;20;(Suppl.3):187; Mahlangu et al. Blood 2014;123:317-325); Konkle BA et al. Blood 2015;126:1078-1085)

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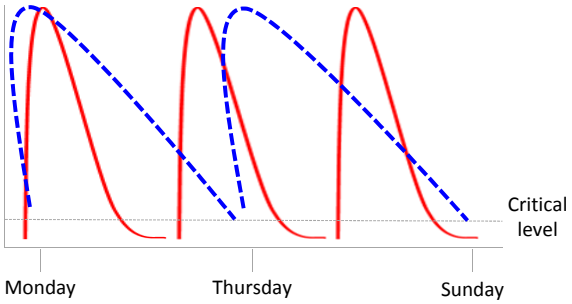
Efficacy - rFVIII extended half-life

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

- Standard products → three infusions/week
- **rFVIII extended half-life** → two infusions/week

- Reduction in injection frequency → **30 - 35%**
- Higher trough level



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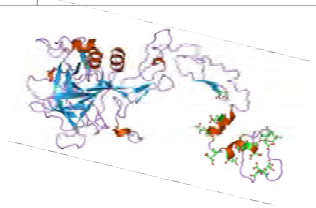
Novel products
rFIX extended half-life

Product	Technology	Half-lfe $t_{1/2}$	Estimated time to 1% after 50IU/kg
N9-GP	Site-directed glycoPEGylation	**3-5 fold**	22 days
rFIX-Fc (Alprolix)	Fc-fusion		10 days
rIX-FP (Idelvion)	Albumin-fusion		1-2 weeks



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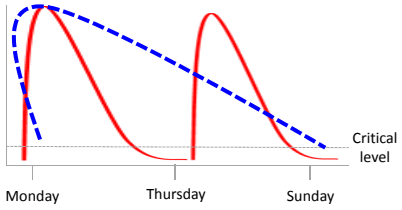
Efficacy - rFIX extended half-life

- 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%**



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Status clinical trials of extended half-life

Product	Status	Pediatric trials	PUPs trials
rFVIII Products			
BAY94-9027	Phase III completed	Ongoing	//
N8-GP	Phase III completed	Active, not recruiting	Ongoing
BAX855 (Adynovate)	Approved by FDA at 2015	Completed	Ongoing
rFVIIIFc (Eloctate)	Approved by FDA at 2014 Approved by EMA at 2015	Completed	Ongoing
rFIX Products			
N9-GP	Phase III completed	Active, not recruiting	Ongoing
rFIXFc (Alprolix)	Approved by FDA at 2014	Completed	Ongoing
rIX-FP (Idelvion)	Approved by FDA at 2016	Completed	Ongoing

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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

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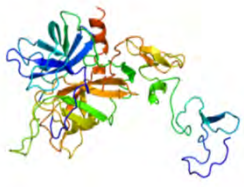
Novel rFVIIa products

Fc-fusion	Albumin-fusion	CTP-fusion
Fusion of the Fc domain of human IgG	Fusion of the human albumine	Fusion of the C terminus peptide of human chorionic gonadotropin (hCG)
rFVIIa		
rFVIIa-FC	rVIIa-FP	Factor VIIa-CTP



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Novel rFVIIa products

Product	Half-lfe $t_{1/2}$	Somministration
rFVIIa-Fc	5,5 fold (in mice)	Intravenous
rFVIIa-FP (CSL689)	3- to 4-fold	Intravenous
rFVIIa-CTP	3-fold	Intravenous and subcutaneous injection

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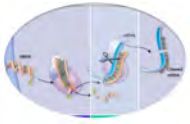
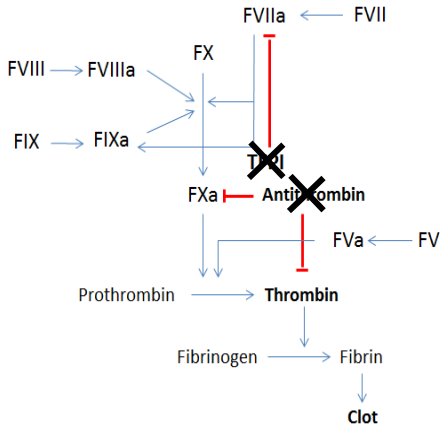
Novel products
Non-replacement products

- **Inhibition of TFPI**
  - monoclonal antibody (anti-TFPI)
- **Inhibition of antithrombin (AT)**
  - small interference RNA (siRNA)





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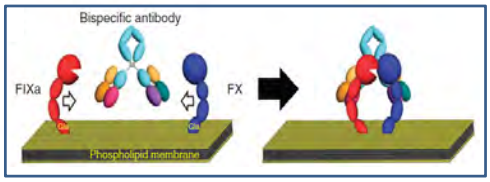
Bispecific antibody - ACE910 (Emicizumab)

- **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



(Kitazawa et al Nat Med 2012;18:1570-1574; Sampei et al. Plos One 2013;8:e57479)

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Non-replacement products

	Product	Technology	Half-life	Somministration
Inhibition of natural anticoagulants				
	Concizumab (NN7415)	anti-TFPI Antibody	once weekly	Intravenous and subcutaneous injections
	ALN-AT3 (Fitusiran)	RNA interference (RNAi) against AT	once weekly or montly	Subcutaneous injections
Promotion of thrombin generation by mimicking the cofactor activity of FVIII				
	ACE910 (Emicizumab)	Bispecific antibody to FIXa/FX	once weekly	Subcutaneous injections

Flora Peyvandi

Status clinical trials of non-replacement products

Product	Status	Patients enrolled
Inhibition of natural anticoagulants		
Concizumab (NN7415)	Phase I Ongoing (NCT02490787)	Hemophilia A and B
ALN-AT3 (Fitusiran)	Phase I/II Ongoing (NCT02554773)	Hemophilia A and B Hemophilia patients with inhibitor
Promotion of thrombin generation by mimicking the cofactor activity of FVIII		
ACE910 (Emicizumab)	Phase III Ongoing (NCT02622321)	Hemophilia A Hemophilia patients with inhibitor

Flora Peyvandi

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

(Chowdary P et al J Thromb Haemost 2015; 13: 743–54; Pasi KJ et al Blood 2015; 126 (23) 57th ASH Annual Meeting)

(Uchida N et al Blood 2016; 127:1633-1641)

Flora Peyvandi

Paradigm shift in hemophilia treatment?

rFVIII extented 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

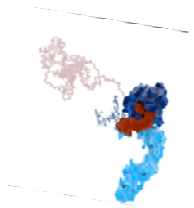
Flora Peyvandi

Paradigm shift in hemophilia treatment?

rFIX extented 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



Flora Peyvandi

Paradigm shift in hemophilia treatment?

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

Flora Peyvandi

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Seminar
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The past and future of haemophilia: diagnosis, treatments, and its complications

Flora Peyvandi, Isabella Garagiola, Guy Young

Haemophilia A and B are hereditary haemorrhagic disorders characterised by deficiency or dysfunction of coagulation protein factors VIII and IX, respectively. Recurrent joint and muscle bleeds lead to severe and progressive musculoskeletal damage. Existing treatment relies on replacement therapy with clotting factors, either at the time of bleeding (ie, on demand) or as part of a prophylactic schedule. The major complication of such therapy is the development of neutralising antibodies (ie, inhibitors), which is most frequent in haemophilia A. Treatment might improve considerably with the availability of new modified drugs, which might overcome existing prophylaxis limitations by reducing dosing frequency and thereby rendering therapy less distressing for the patient. Subcutaneous administration of some new therapies would also simplify prophylaxis in children with poor venous access. Gene therapy has the potential for a definitive cure, and important results have been obtained in haemophilia B. Despite improvements in haemophilia care, the availability of clotting factor concentrates for all affected individuals worldwide remains the biggest challenge.

Published Online
February 17, 2016
http://dx.doi.org/10.1016/
S0140-6736(15)01123-X

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

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 forsee the risk of an emerging pathogen transmitted by transfusion. This type of risk needs a proactive approach according to the principle of precaution

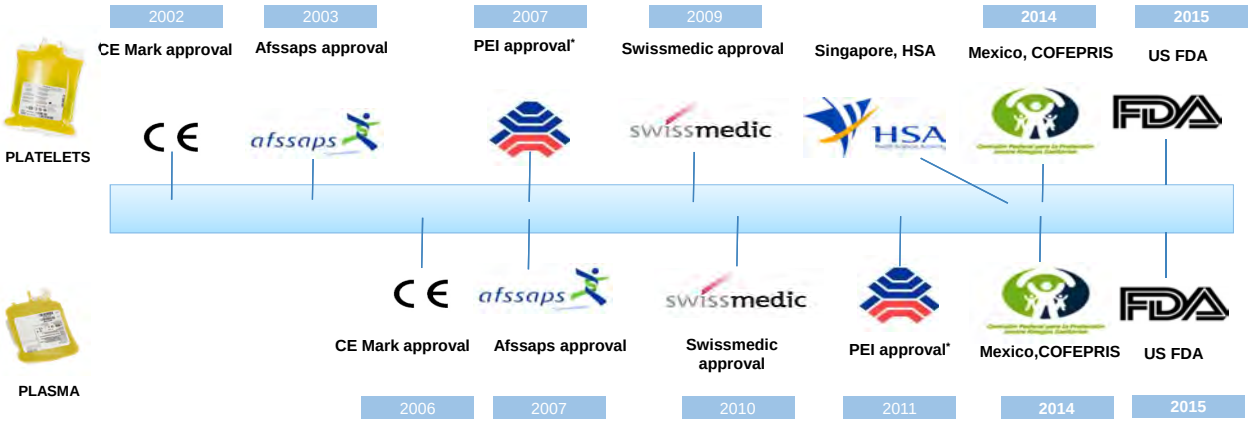
1. PI implementation for 100% of blood components
2. PI implementation should not wait its availability for all 3 blood components (platelets, plasma, RBC)
3. PI should be implemented when safe methods of inactivation for large spectrum of pathogens are available
4. Use of PI should be universal for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

* Webert KE, Cserti CM, Hannon J, Lin Y, Pavenski K, Pendergrast JM, Blajchman MA. Proceedings of a Consensus Conference: pathogen inactivation-making decisions about new technologies. Transfusion Medicine Reviews, 2008, 22, 1-34.

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



1O Years of use for Intercept Blood System™ components

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 x 10^{11}/10 kg body weight
- Posology for neonates: 0.1-0.2 x 10^{11}/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

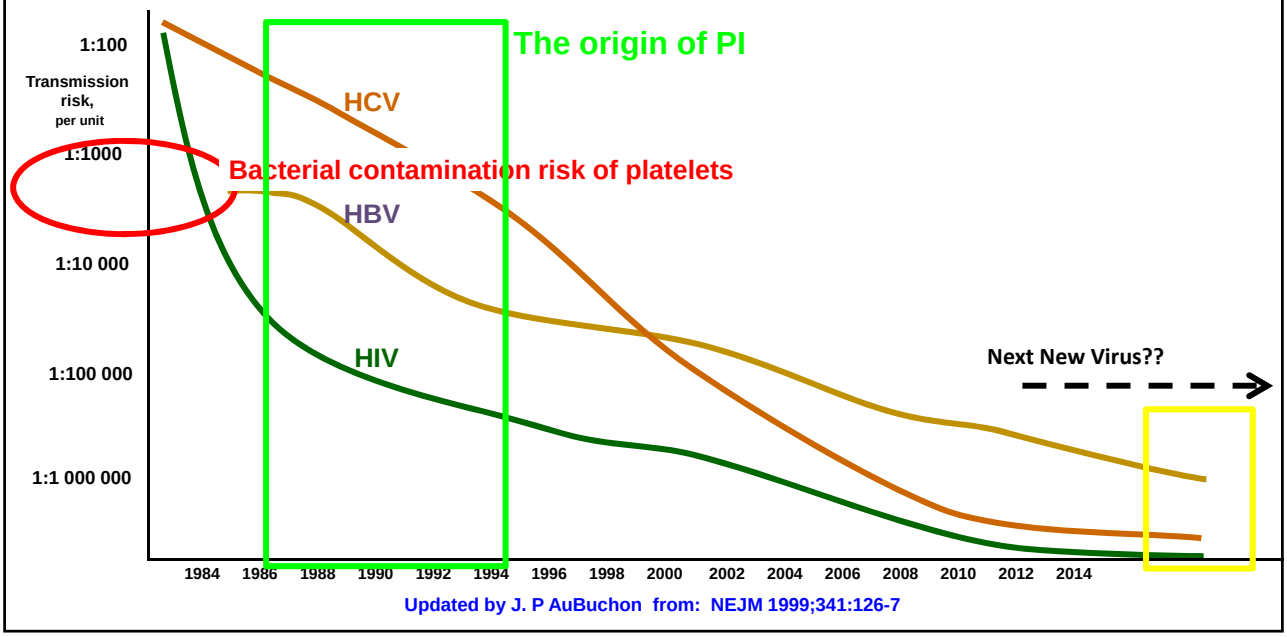
	N	Dose	1 Hr CI	1 Hr CCI	Interval	Grade 2 (%)
PLADO-Low	417	2.0	10	10.0	1.1	58
PLADOMedium	423	4.0	19	10.0	1.9	59
PLADO-High	432	8.0	38	11.0	2.9	60
SPRINT- IA[1]	318	3.7	21	11.1	1.9	59
SPRINT-C[2]	327	4.0	34	16.0	2.4	58
EUROSP-IA[1]	52	3.9	28	13.1	3.0	73[3]
EUROSP-C	51	4.3	35	14.9	3.4	69[3]
HOVON-IA[1]	87	3.4	20	11.4	2.5	7
HOVON-C[2]	99	3.9	34	17.1	3.4	Group

[1]Plasma inactivated amotosalen + UVA

[2]Plasma Control

[3]Grade 1 and 2 bleeding combined as mild bleeding

The evolution of transfusion risks



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

Enveloped viruses
- HIV-1
- HIV-2
- HBV
- DHBV
- HCV
- BVDV
- HTVL-I
- HTLV-II
- CMV/EBV/HHV-8
- WNV
- SARS
- Vaccinia
- Chikungunya
- Dengue
- Zika virus
- Influenza virus (H1N1)
- Avian flu virus (H5N1)
- XMRV

Non-enveloped viruses
- Bluetongue virus 11
- Simian Adenovirus-15
- Feline calicivirus
- Parvovirus B19
- Human adenovirus 5

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 minutissimum*
- *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*

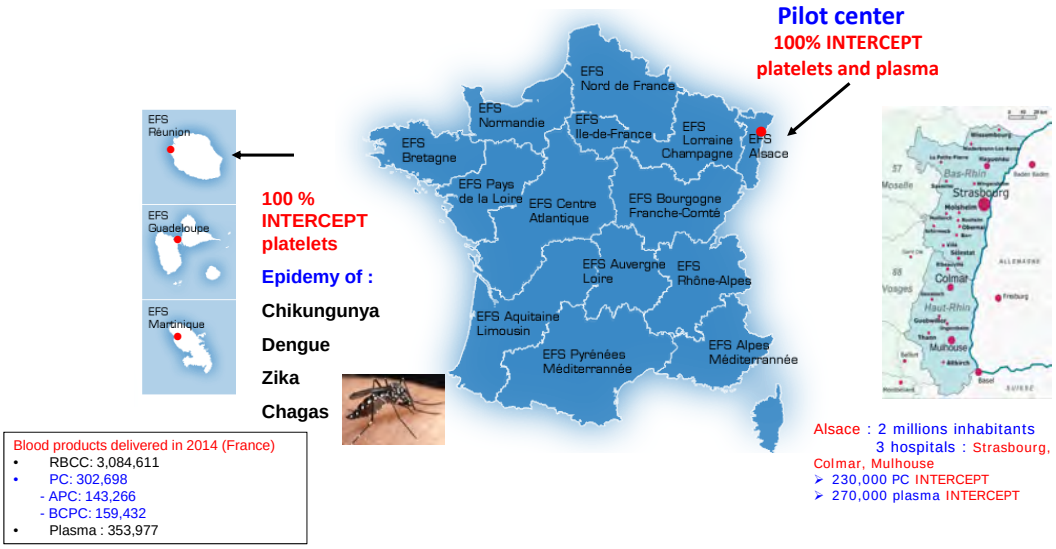
Residual leukocytes
T lymphocytes, cytokines

Bacterial spores resistant

Prions resistant

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

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



Blood products delivered in 2014 (France)
- RBCC: 3,084,611
- PC: 302,698
  - APC: 143,266
  - BCPC: 159,432
- Plasma : 353,977

Alsace : 2 millions inhabitants
3 hospitals : Strasbourg, Colmar, Mulhouse
- 230,000 PC INTERCEPT
- 270,000 plasma INTERCEPT

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)

Intercept components transfused in Alsace		Components (n)	Patients (n)
PC-IA (20/07/2006-31/07/2014)	Total	140,990	20,921 - 404 newborns - 823 children - 19,694 adults
	BCPC-IA	89,954	
	APC-IA	51,036	
FFP-IA (03/09/2007-31/07/2014)	Total Units (200 mL/unit)	124,724	17,960 - 658 newborns - 786 children - 16,516 adults
	Pools for plasma exchange therapy	3,753 (corresponding to 33,046 units of 200mL)	321 - 9 children - 312 adults

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, DENGV, 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

Frequency of Transfusion Transmitted Bacterial Infections (TTBI) of conventional-PC and of Intercept-PC in France (2006-2015)

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

AFSSAPS/ANSM Hemovigilance and EFS Activity reports (2006-2014) (gravity 1-4, imputability 2 (ex 3) and 3 (ex 4). 9 deaths (7 LR-APC/2 LR-BCPC conventional PC).
*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 Barthélémy (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: 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

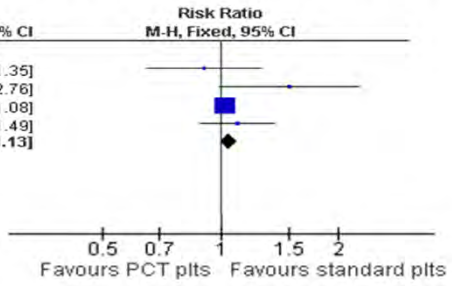
Pathogen-reduced platelets for the prevention of bleeding (Review)

Butler C, Doree C, Estcourt LJ, Trivella M, Hopewell S, Brunskill SJ, Stanworth S, Murphy MF

Figure 4. Forest plot of comparison: 1 Pathogen-reduced platelets versus standard platelets, outcome: 1.2 Number of participants with 'any bleeding' event(s) (WHO grade 1-4 or equivalent) - follow-up > 7 days.

Study or Subgroup	PCT Plts Events	Total	Standard Plts Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Intercept plts vs standard plts - multiple platelet transfusion studies						
Janetzko 2005	14	22	15	21	4.0%	0.89 [0.59, 1.35]
Kerkhoffs 2010	27	85	19	99	4.6%	1.66 [0.99, 2.76]
McCullough 2004	296	318	295	327	76.6%	1.03 [0.98, 1.08]
van Rhenen 2003	37	52	32	51	8.5%	1.13 [0.86, 1.49]
Subtotal (95% CI)		**477**		**498**	**93.8%**	**1.07 [1.01, 1.13]**
Total events	374		361			

Heterogeneity: Chi² = 5.62, df = 3 (P = 0.13); I² = 47%
Test for overall effect: Z = 2.17 (P = 0.03)



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

MERCI DE VOTRE ATTENTION
THANK YOU FOR YOUR ATTENTION

Conflict of interest disclosure of Jean-Pierre Cazenave

Cerus Corporation (The Netherlands)

Co-Investigator of clinical trials

Honoraria for presentations

Research contracts

Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

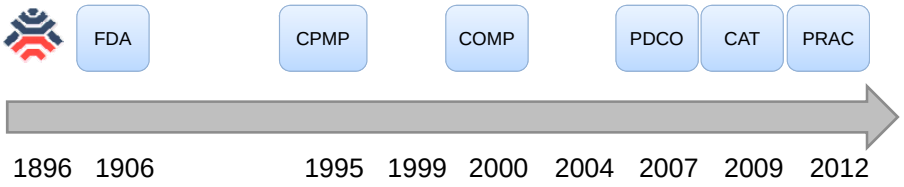
Regulatory and health technology assessment requirements

Jan Müller-Berghaus

Outline

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

History



CAT: Committee for Advanced Therapies,
CPMP/CHMP: Committee for Medicinal Products for Human Use,
PRAC: Pharmacovigilance Risk Assessment Committee
PDCO: Paediatric Committee
PRAC: Pharmacovigilance Risk Assessment Committee
COMP: Committee for Orphan Medicinal Products

Criteria for an marketing authorisation

- Demonstration of efficacy
- Favourable benefit/risk balance

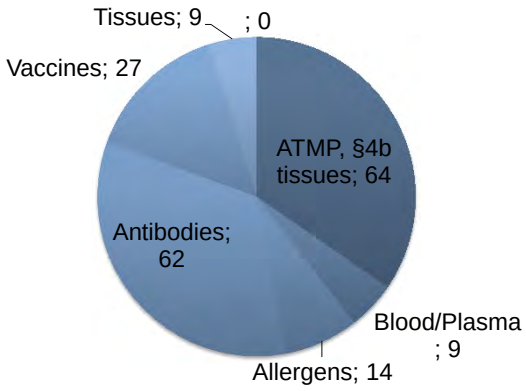
- Relative efficacy not necessarily required or evaluated (by law)
- Regardless of possible costs (by law)

Outline

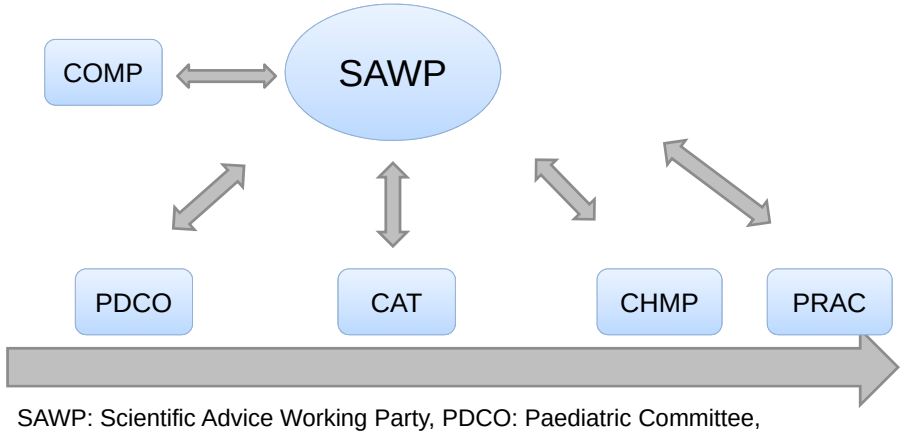
- A bit of history
- Scientific Advice
- The German system for deciding on reimbursement
- A way forward?

National support for developers
Scientific Advice at PEI 2015

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

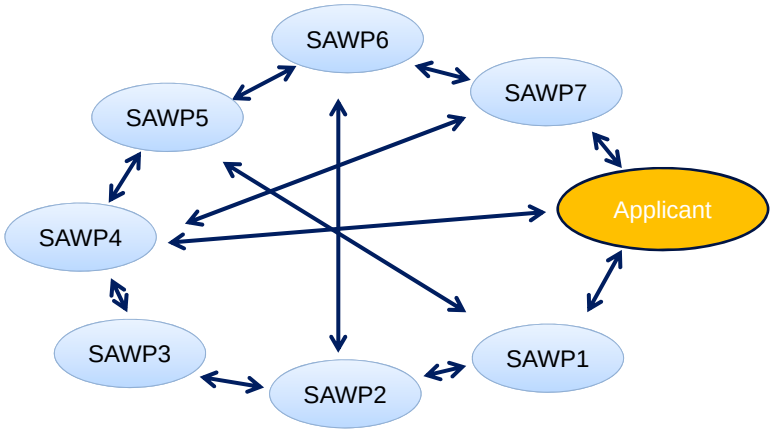


European support for developers



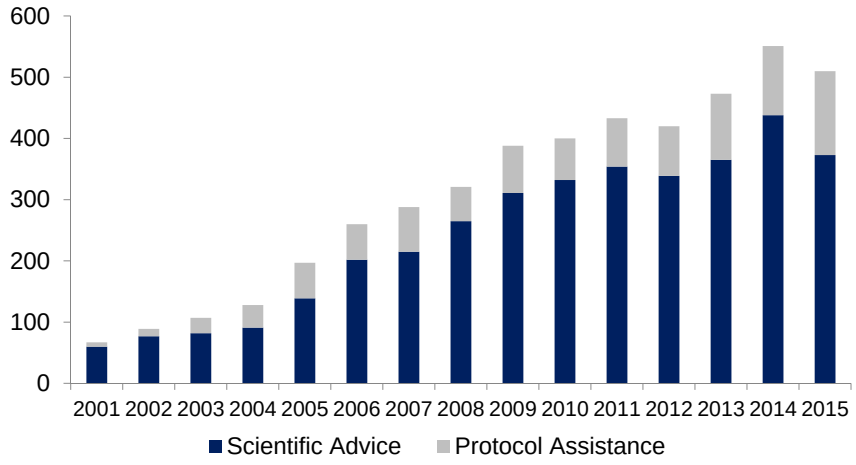
SAWP: Scientific Advice Working Party, PDCO: Paediatric Committee,
CAT: Committee for Advanced Therapies,
CHMP: Committee for Medicinal Products for Human Use,
PRAC: Pharmacovigilance Risk Assessment Committee
COMP: Committe for Orphan Medicinal Products

CHMP scientific advice



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

Centralised Scientific Advice



Outline

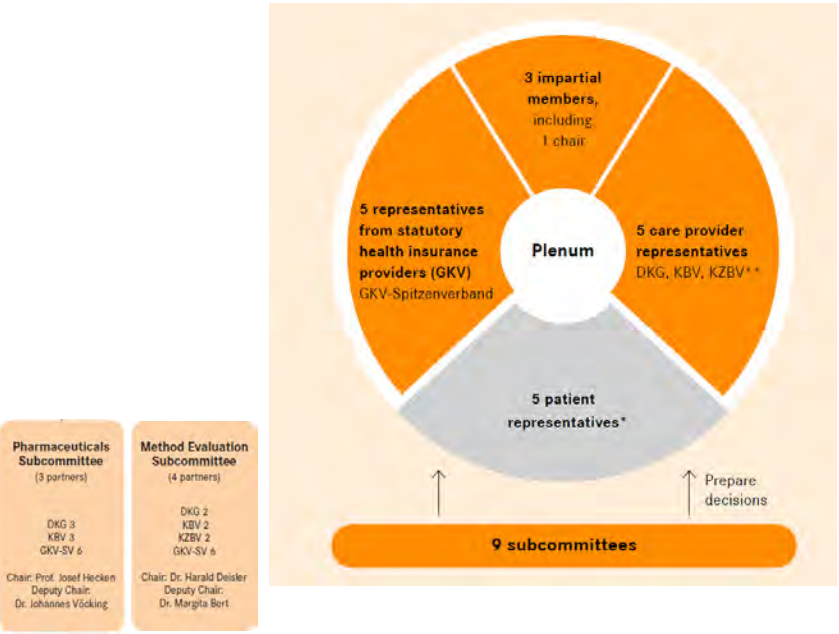
- A bit of history
- Scientific Advice
- The German system for deciding on reimbursement
- A way forward?

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

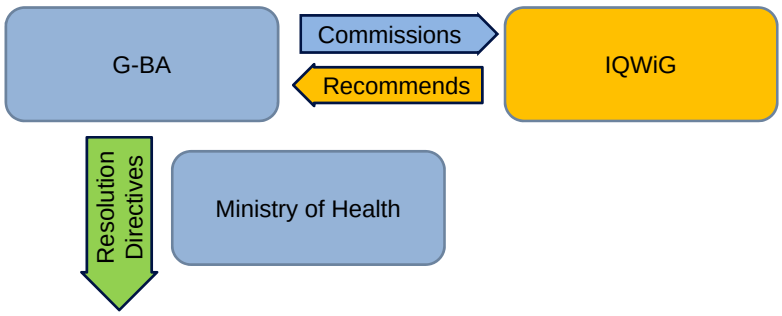


Organisational Aspects

- 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

		Outcome category			
		All-cause mortality	**Serious** *(or severe)* **symptoms** *(or late complications)* **and adverse events**	*Health-related quality of life*	**Non-serious** *(or non-severe)* **symptoms** *(or late complications)* **and adverse events**
Extent category	**Major** **sustained and great improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Major increase in survival time	Long-term freedom or extensive avoidance	*Major improvement*	*Not applicable*
	Considerable **marked improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	Moderate increase in survival time	Alleviation or relevant avoidance	*Important improvement*	Important avoidance
	Minor **moderate and not only marginal improvement** in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator therapy	*Any increase in survival time*	*Any reduction*	*Relevant improvement*	Relevant avoidance

a: Amendments to the ANV in *italics*.
ANV: Arzneimittel-Nutzenbewertungsverordnung (Regulation 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

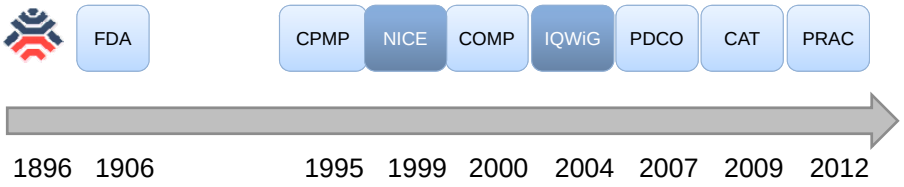
Hurdles to access

Pharmaceutical Quality

Efficacy Favourable B/R

Reimbursement Cost/Effectiveness Added benefit

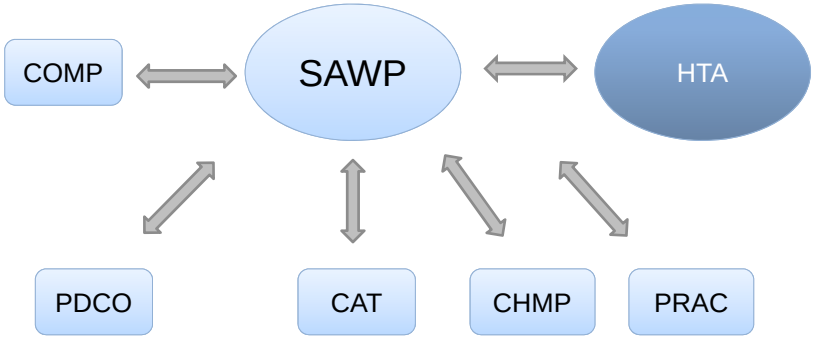
History



Outline

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

European support for developers

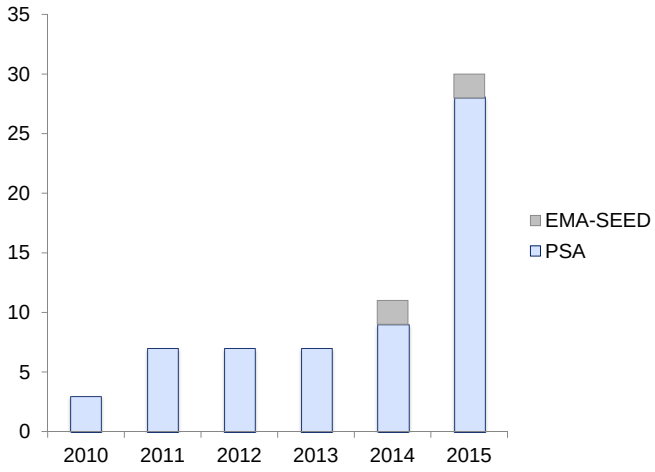


SAWP: Scientific Advice Working Party, PDCO: Paediatric Committee,
CAT: Committee for Advanced Therapies,
CHMP: Committee for Medicinal Products for Human Use,
PRAC: Pharmacovigilance Risk Assessment Committee
COMP: Committee for Orphan Medicinal Products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2016
EMA/695874/2015
Human Medicines Research and Development Support Division

Report of the pilot on parallel regulatory-health technology assessment scientific advice



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› G-BA, BfArM und PEI vereinbaren strukturierte Zusammenarbeit

G-BA, BfArM und PEI vereinbaren strukturierte Zusammenarbeit

Gemeinsame Pressemitteilung des Gemeinsamen Bundesaussschusses (G-BA), Paul-Ehrlich-Instituts (PEI) und Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

09 / 2016

Mit dem Ziel, möglichst frühzeitig eng und strukturiert bei gemeinsamen Fragestellungen hinsichtlich der Zulassung von Arzneimitteln einerseits und der frühen Nutzenbewertung von Arzneimitteln andererseits zusammenzuarbeiten, haben der Gemeinsame Bundesausschuss (G-BA), das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) und das Paul-Ehrlich-Institut (PEI) eine Vereinbarung getroffen. Dies teilten der G-BA und die beiden Bundesoberbehörden anlässlich des Abschlusses des Pharmadialogs am Dienstag in Berlin mit. Im Kern geht es darum, im Rahmen der Durchführung von klinischen Arzneimittelstudien gute Evidenz sowohl für die Beurteilung der arzneimittelrechtlichen Fragestellungen (Zulassung) als auch für die Beurteilung der sozialversicherungsrechtlichen Fragestellungen (frühe Nutzenbewertung) zu generieren.

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

- die wechselseitige Beteiligung von Experten der jeweiligen Institutionen im Vorfeld der Planung klinischer Studien bei den Beratungen der pharmazeutischen Unternehmer („Joint Scientific Advice");
- die wechselseitige Kenntnisgabe von Protokollen durchgeführter Beratungsgespräche;
- die Fortführung der schon etablierten Beteiligungsverfahren im Rahmen der frühen Nutzenbewertung
- regelmäßige wechselseitige Hospitation von Mitarbeiterinnen und Mitarbeitern, um die jeweils relevanten unterschiedlichen Fragestellungen in den Verfahren noch besser kennenzulernen und die bestehende gute Zusammenarbeit zu vertiefen und zu festigen.

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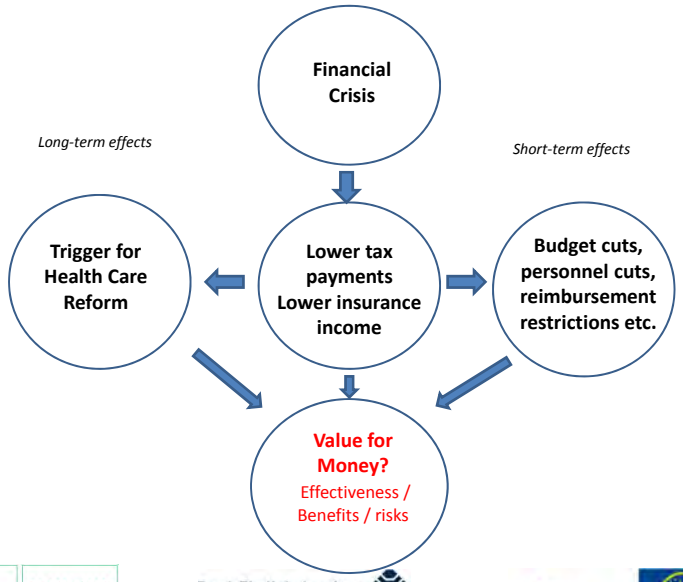
Email: Karin Berger@med.uni-muenchen.de

Agenda

- Why benefit / effectiveness and risk assessment?
- Challenges: benefit / risk assessment for clotting factor and platelet usage
- Open Questions & Outlook

Shortened Health Care Budgets



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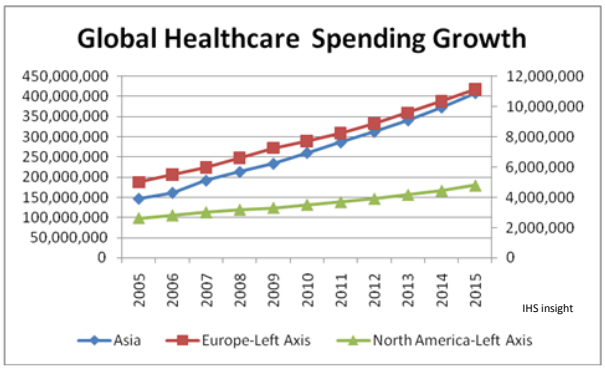
3

Cost constrained healthcare systems



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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*

ADR related Hospital costs

€636 million

€400 million.

€706 million.

http://antidote-europe.org/en/adverse-drug-reactions-kill-197000-europeans-annually/
*European Commission

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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**

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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

Pre-Authorisation	Post-Authorisation
Market Authorization	Access
How things work	Doing the right thing
Efficacy studies – condition-specific endpoints – strong links to the mechanism of action – short-term horizon – Small sample size	**Effectiveness studies** – comprehensive patient-relevant endpoints • Clinical • PROs – relatively longer-term horizons – Large sample size

European Network for HTA

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

How is the patient?

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 reserach: Endpoints

Clotting Factor Concentr.	Platelets
Patient relevant endpoints - Bleeds - Arthropathy - Osteoporosis - Mortality **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

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Haemophilia-associated patient-relevant *clinical* outcomes

GTH

Clinical Outcomes	Parameter	Measurement
Bleeds	frequency, localisation, severity	patient survey, patient diary
Target Joints	4 or more bleeds in one joint within 6 months*	patient survey, patient diary
Arthropathy	mobility, function, joint replacement, arthrodesis	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
Osteoporosis	fracture	patient survey, patient record
Therapy-related infectious diseases	hepatitis, HIV, clotting factor concentrates used	laboratory values, patient survey, patient record
Development of inhibitors	duration and intensity of treatment, gene mutations, clotting factor concentrates used	patient survey, patient record
Mortality	cause of death	death certificate, patient record

*Valentino L.A. Haemophilia (2009), 15 (Suppl. 2), 5-22.

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Haemophilia-associated *Patient Reported Outcomes (PROs)*

Patient Reported Outcomes	Parameter	Measurement
Disease-specific quality of life	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]	Haemophilia-QoL (adults and children), Haemo-QoL-A, Haem-A-QoL, Children Haemophilia Outcome (CHO)-Kids Assessment Tool (KLAT)
Health-related quality of life	Example: Euro-QoL-5D-questionnaire with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression[2]	EQ-5D, SF-36, SF-12
Activity	FISH (8 activities: eating, grooming, dressing, chair transfer, squatting, walking, step climbing, running[3]) or HAL (7 domains[4])	Functional Independence Score (FISH), Haemophilia Activities List (HAL; PedHAL)
Social integration	education, work, days absent, hospital stays	patient survey
Adherence and compliance	continuous treatment according to therapeutic guidelines	patient survey, patient diary

[1]Bullinger M. et al. Value in Health (2009) 12; 5: 808-820. [2]Moock J. Phys Rehab Kur Med 2008; 18(5): 245-249.
[3]http://www.wfh.org/en/page.aspx?pid=884; [4]http://www.wfh.org/en/page.aspx?pid=875

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

Clinical Outcomes	Measurement	Prioritization			
		un-important	moderately important	important	very important
Bleeds	patient survey, patient diary			1	13
Target Joints	patient survey, patient diary				14
Arthropathy	clinical joint status, Haemophilia Joint Health Score (HJHS), WFH Physical Examination Score (Gilbert Score)			6	8
	radiological joint status (Petterson Score)		8	2	1
	Magnetic Resonance Imaging (MRI)		5		
	ultrasound	2	4	3	
Osteoporosis	patient survey, patient record	9	1	2	
Therapy-related infectious diseases	laboratory values, patient survey, patient record			2	10
Development of inhibitors	patient survey, patient record				14
Mortality	death certificate, patient record				14

A total of 14 physicians prioritized health outcomes taking into consideration the ability of their assessment in clinical routine care.

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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.

The Growing Number of Hemophilia Registries: Quantity vs. Quality

C Keipert[1], J Hesse[1,2], B Haschberger[1,2], M Heiden[1], R Seitz[1], HM van den Berg[3], A Hilger[1]
on behalf of the ABIRISK Consortium

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 97 NUMBER 5 | MAY 2015

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 acces to most of the registries, therefore unclear what data is collected

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

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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

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Do these registries collect appropriate data for relative effectiveness reserach?

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?

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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?

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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 transfuion“
  - access to data required

SMART DATA

A chance for relative effectiveness research in coagulation factor and platelet usage?

Thank you for your attention !

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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

Brian O Mahony 2016

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

Brian O Mahony 2016

Access to home treatment (2015 survey)

Levels of access in %

- **76-100%**
- **51-75%**
- **10-50%**
- **<10%**
- **0%**
- **Unanswered**

Brian O Mahony 2016

Increase in access to prophylaxis

Increase in access to prophylaxis

In <u>children</u> (in 6 countries)

- Azerbaijan, Bulgaria, Romania, Russia, Serbia and Ukraine

In <u>adults</u> (in 7 countries):

- Belgium, Czech Republic, Ireland, Lithuania, the Netherlands, Poland and Spain

In both <u>children</u> **AND** <u>adults</u> (in 6 countries)

- Austria, Italy, Latvia, Portugal, Slovenia and Turkey

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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

Brian O Mahony 2016

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 countires
  - never or rarely available in 6 countries

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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

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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

	NHC	Min 3 IU/capita FVIII	Prophylaxis in children	Prophylaxis for adults when required
Implemented in	18 countries	18 countries	33 countries	31 countries
Not implemented in	19 countries	8 countries	4 countries	6 countries
No data for	8 countries	19 countries	8 countries	8 countries

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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

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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**

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

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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:

	Previous product	Test product ED1	Test product ED10-15	Test product ED50-75	Test product ED~100
Inhibitor*	x	x†	x	x	x
Recovery	x	x	x	x	x

*after washout period (see Explanatory Note); storage of back up blood sample is recommended
#new patients = not recruited for pre-authorisation studies
†baseline inhibitor testing prior to first infusion of test product

EMA/CHMP/BPWP/144533/2009 rev.1

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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

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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)

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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**

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GCP Trials in Haemophilia ….April 2016

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

Total CT Haemophilia	147
Ongoing	92
OD	26

CT Haemophilia PUP	15
CT Haemophilia PUP ongoing	12
CT HA PUP	12
CT HB PUP	3

CT Haemophilia PTP	60
CT Haemophilia PTP ongoing	41
CT HA PTP ongoing	30
CT HB PTP ongoing	11

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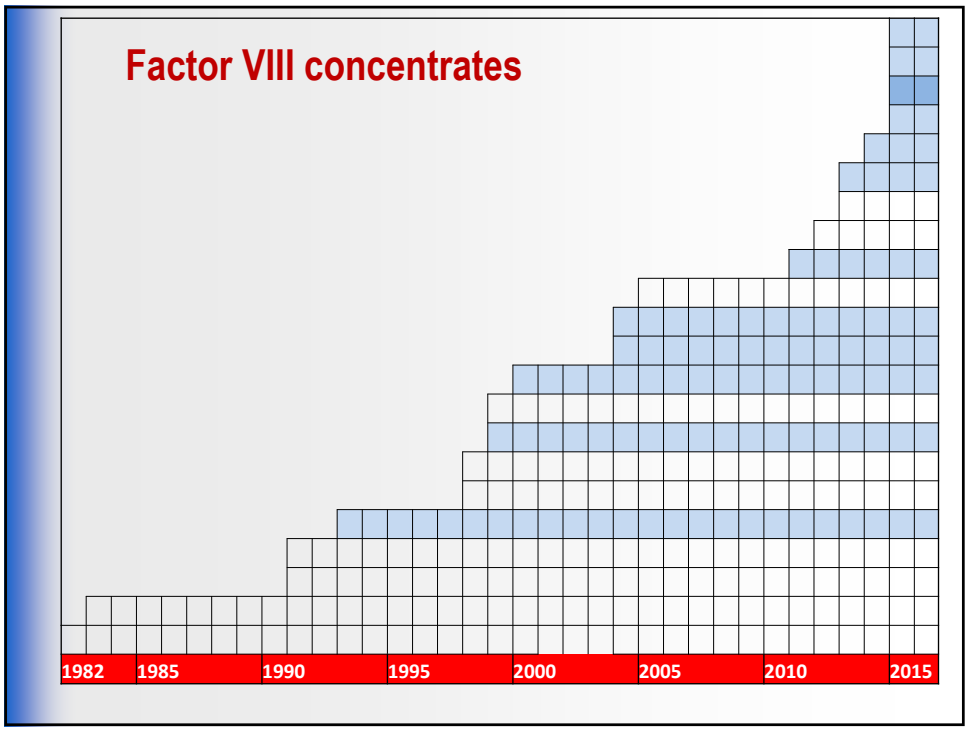
Pro's and Con's

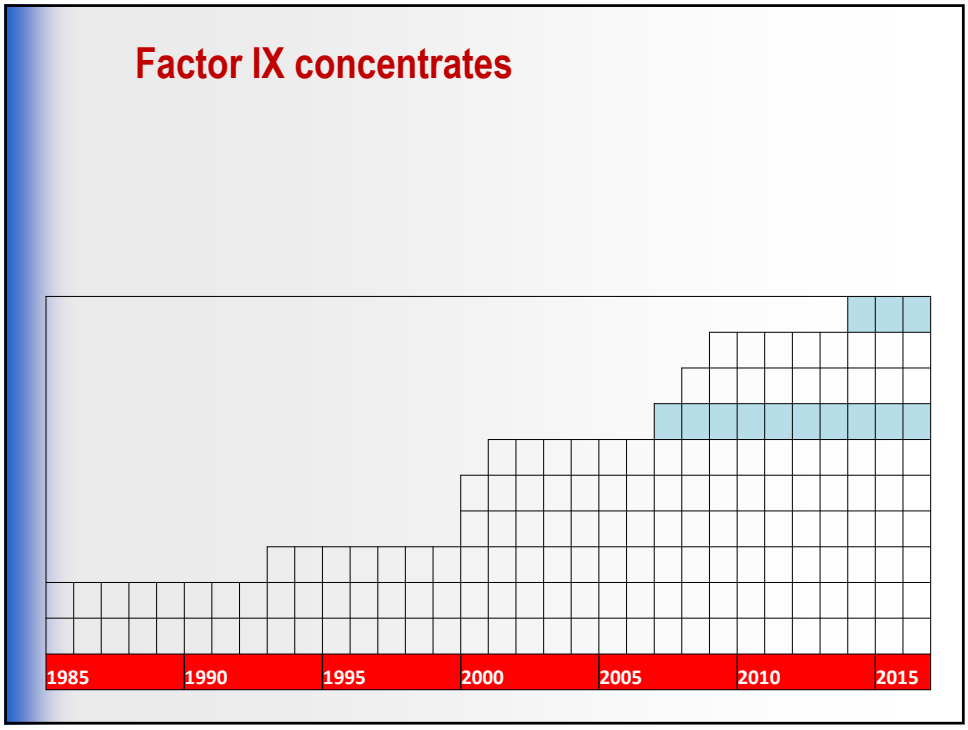
Clinical Trials

☑ 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
– volontary
– unknown confounding
– no standardized dataset yet
– Regulators do have no access to data


Factor VIII concentrates
1982
1985
1990
1995
2000
2005
2010
2015


Factor IX concentrates
1985
1990
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2005
2010
2015

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

(Rocino, Haemophilia 2016; Abbonizio, Haemophilia 2014; DeKoven, Haemophilia 2014; Darby, J Thromb Haemost 2004; Plug, J Thromb Haemost 2006))

Risk factors inhibitors

F8 mutation
family history of inhibitor
immunomodulatory genetic variants
intensity of initial treatment
prophylaxis (↓)
type of FVIII product

age at first treatment
ethnicity

(Schwaab, Thromb Haemost 1995; Astermark, Haemophilia 2001; Hay, Thromb Haemost 1997; Oldenburg, Thromb Haemost 1997; Astermark, Blood 2006; Gouw, Blood 2007; Gouw, Blood 2013; Gouw, N Engl J Med 2013; Aledort, Haemophilia 1998)

FVIII product and inhibitors

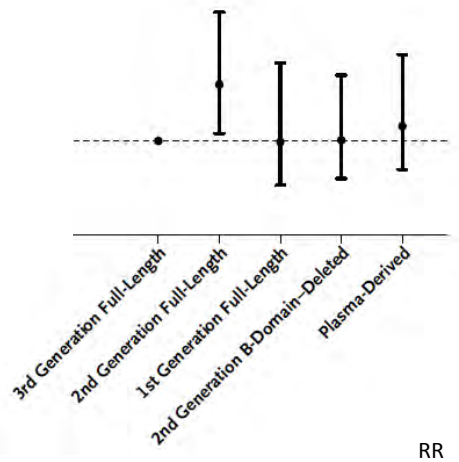
Previously untreated patients

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

(Peerlinck, Blood 1993; Guérois, Thromb Haemost 1995; Gouw, Blood 2007; Vermylen, Acta Clin Belg 1991; Rosendaal, Blood 1993; Gouw N Engl J Med 2013)



	RR	CI95
all	1.60	1.08-2.37
high-titre	1.79	1.09-2.94

(Gouw, N Engl J Med 2013)

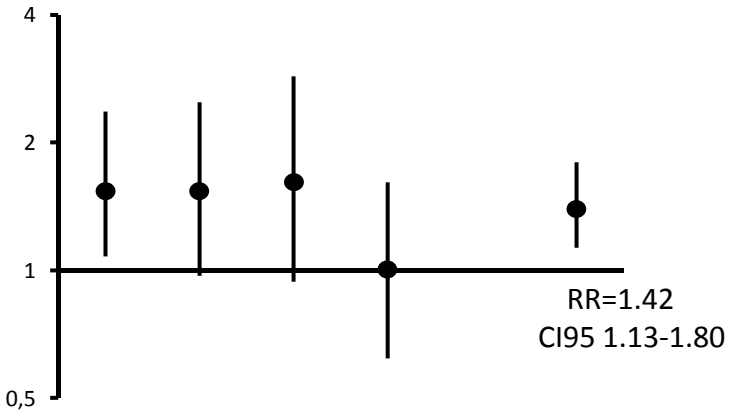
Replication: four studies

	design	period	countries	N*	adjustment
RODIN	cohort	2000-2010	14	574	mutation, age, +
FCN	cohort	1993-2014	1	353	mutation, age, +
UKHCDO	cohort	2000-2011	1	407	mutation, age, +
EUHASS	case-series	2008-2012	26	417	none

(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

Four studies meta-analysed

- all inhibitors -



(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

Four studies

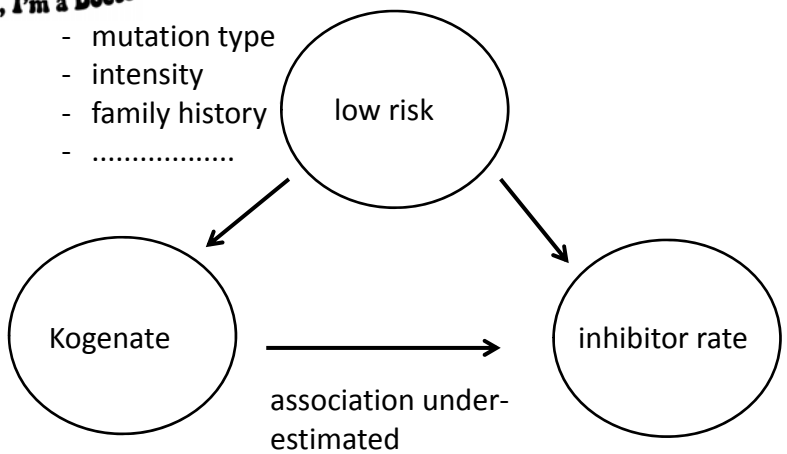
- Adjustment for confounding -

	unadjusted	adjusted
RODIN	1.37	1.60
FCN	1.61	1.55
UKHCDO	1.60	1.64
EUHASS	0.99	n.d.

(Gouw, N Engl J Med 2013; Calvez, Blood 2014; Collins, Blood 2014; Fischer, Thromb Haemost 2015)

Confounding

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



Confounding

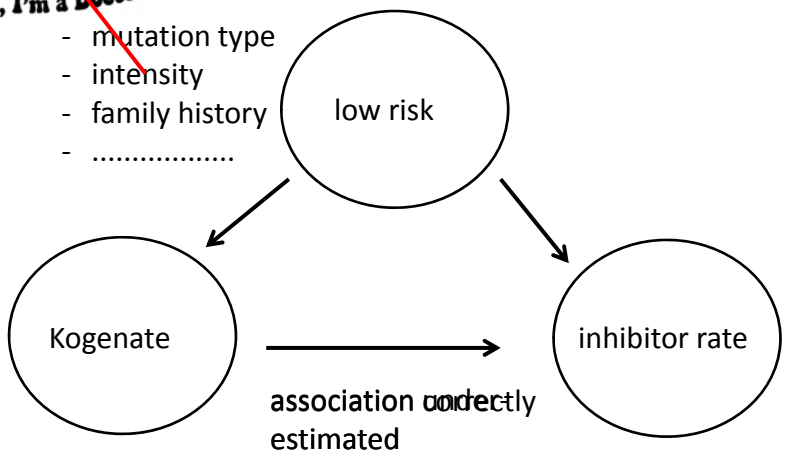
- the main problem of observational studies
  - mnemonic: grey hair and death risk
- a main cause is the physician: confounding by indication

- 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

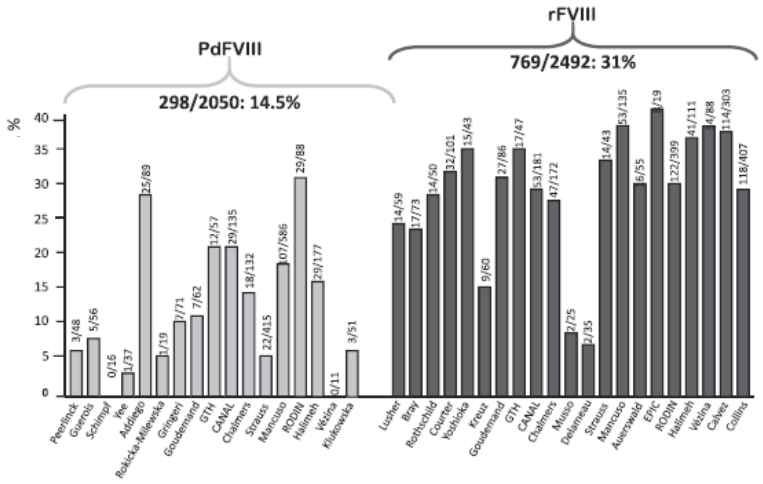
- when likelihood of subtle unknown or unmeasurable factors
  - confounding remains, unless influence physician removed
  - this is done by randomisation

Confounding

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



Overview of studies rFVIII vs pdFVIII



(Mannucci, Thromb Haemost 2015)

Meta-analyses rFVIII vs pdFVIII

	rFVIII	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 immunogenecity 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

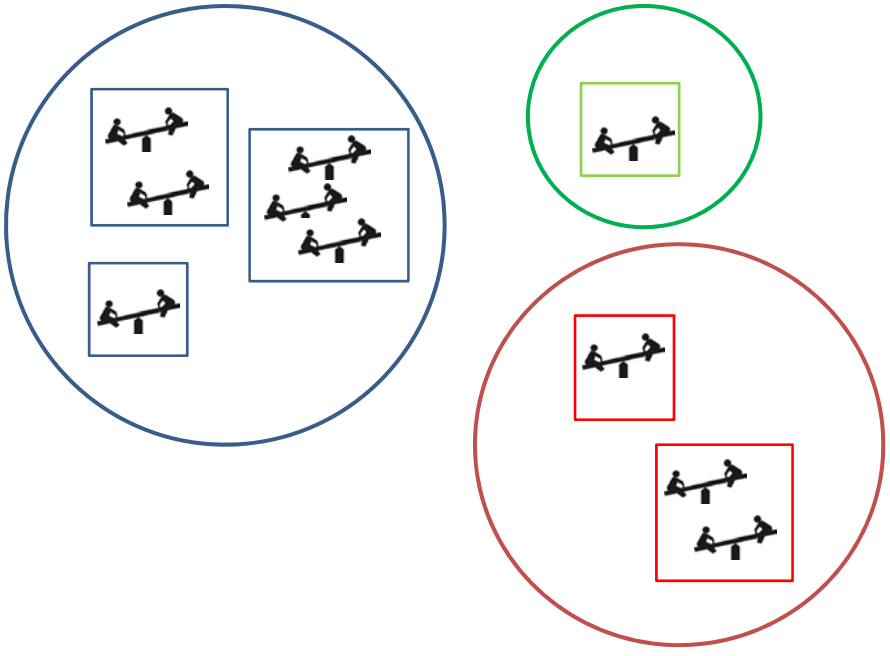
- randomised
- international multicenter
- open label
- blocked (block size 1:1)

- 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

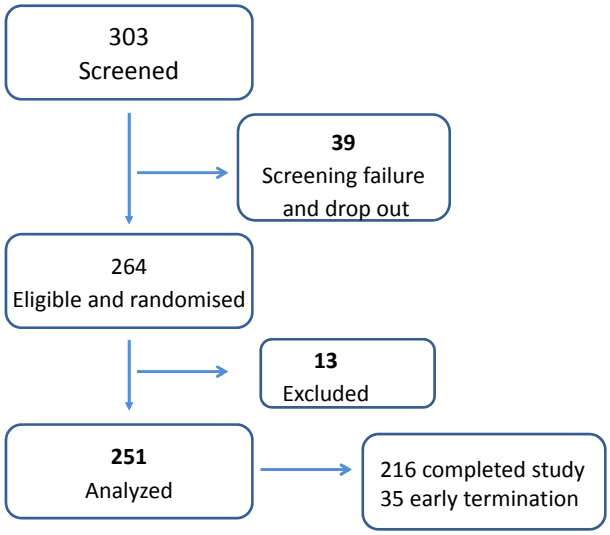
- Per country only one brand of pdFVIII and rFVIII available
  - only licensed brands
- Per centre randomisation between pdFVIII and rFVIII
- Ties brand, treatment preferences and ethnicity to country
- Balances these factors optimally between rFVIII and pdFVIII



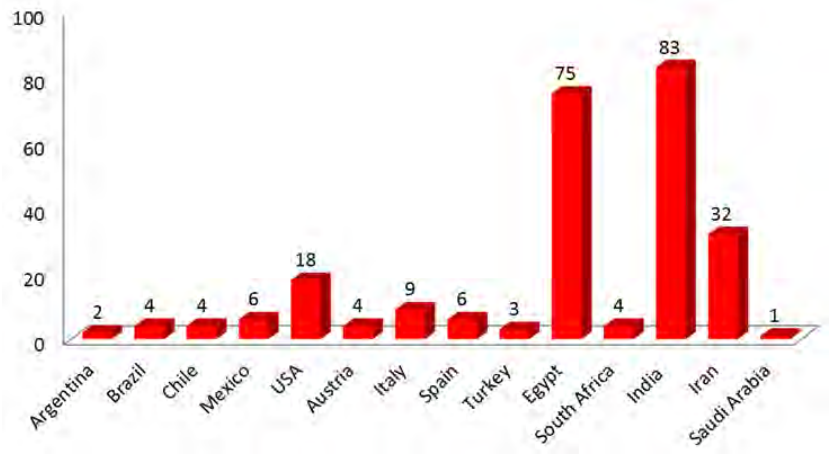
Analysis

- 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



Geographical distribution



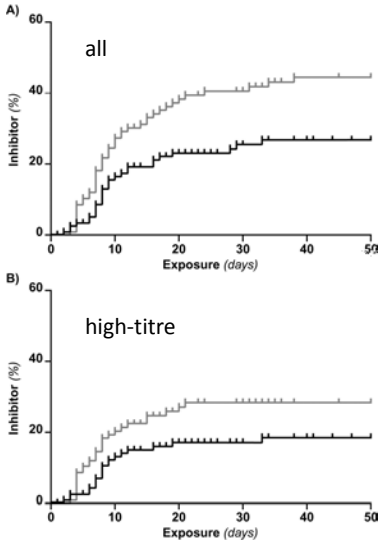
Baseline characteristics

	pdFVIII n=125	rFVIII n=126
median age (mo.)	14.0	15.0
null mutation	86.3%	81.4%
family history haemophilia	47.6%	42.6%
family history inhibitor	11.5%	10.1%
previous treatment	44.8%	42.1%
treatment regimen		
on-demand	48.8%	44.4%
standard pophylaxis	16.8%	15.1%
modified prophylaxis	34.3%	40.5%

Inhibitor occurrence

	pdFVIII n=125	rFVIII n=126
all	29	47
high-titre	20	30
persistent	74.4%	72.2%
peak titre		
peak (median)	12	16
range	0.8-1100	0.7-1850

Cumulative incidence by arm



44.5% (CI95 34.7-54.3)

26.8% (CI95 18.3-35.2)

28.4% (CI95 19.6-37.2)

18.6% (CI95 11.1-26.9)

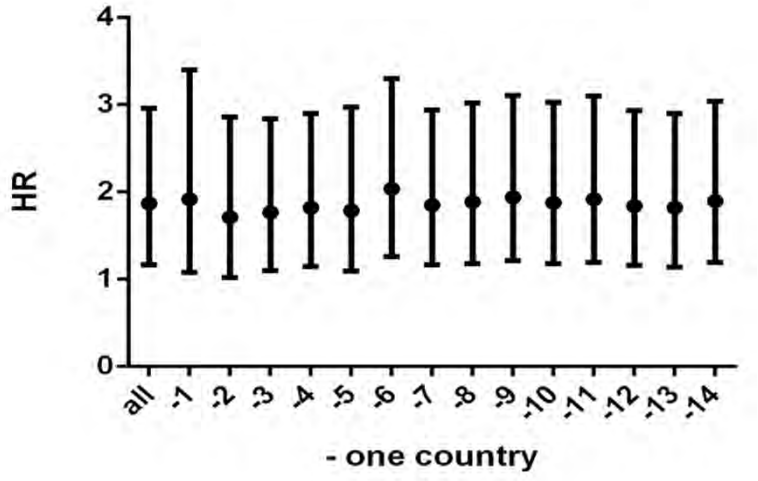
Cox regression

	hazard ratio	CI95
all	1.87	1.17-2.96
high titre	1.69	0.96-2.98

adjusted HRs similar to crude HRs

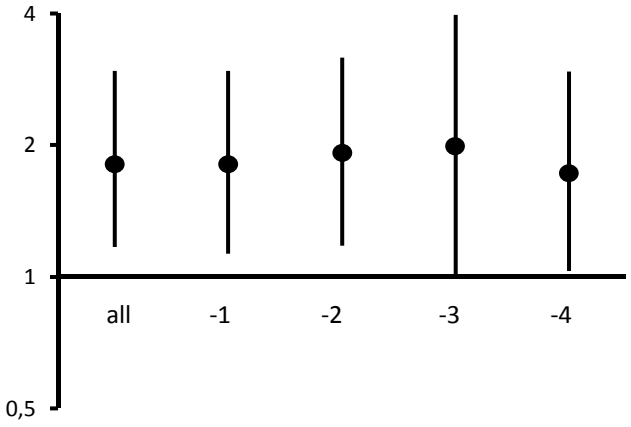
Sensitivity analysis

- country -



Sensitivity analysis

- rFVIII concentrate -



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

	pdFVIII	rFVIII	Number needed to Harm
all	26.8%	44.5%	5
high-risk**	30.7%	46.5%	6.3
low-risk	9.5%	38.2%	3.4

** presence of null mutation

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Pier Mannucci

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- DMSB
- Syntesi Research
- Patients and parents

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Ministero della Salute

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LFB, France

EUROPEAN SYMPOSIUM

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

Inhibitors in Haemophilia

Prophylaxis – Immune Tolerance Induction

Pr Hervé Chambost

Haemophilia Reference Care Centre – Haematology Oncology Department University

Children Hospital La Timone – Marseille – France

EUROPEAN SYMPOSIUM

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

Disclosure for Hervé CHAMBOST

(none related to this presentation)

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Paid Instructor	**No relevant conflicts of interest to declare**
Speaker bureau	**No relevant conflicts of interest to declare**
Clinical trials (PI)	**Bayer Healthcare, Biogen, CSL Behring, NovoNordisk, Octapharma**

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

Inhibitors
in the French Cohort

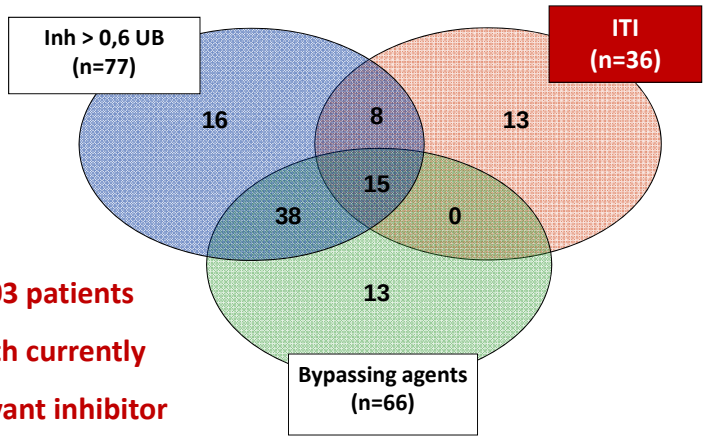
Inhibitor history recorded at the last follow-up in the whole cohort

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

* Inhibitors confirmed by the specific working party

The current Burden of Inhibitors in FranceCoag

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

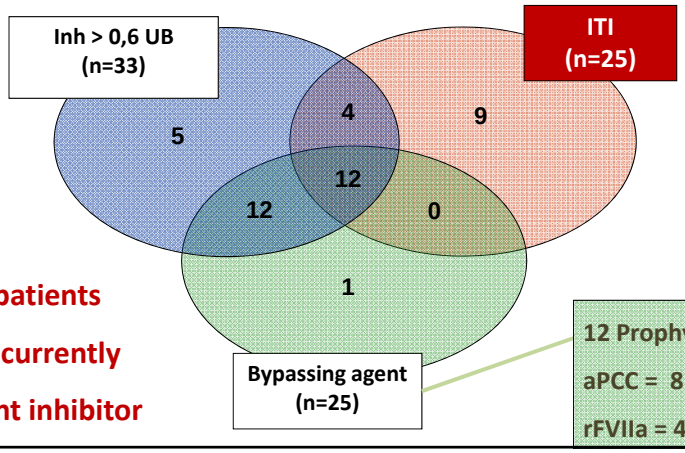


103 patients with currently relevant inhibitor

Inhibitors in the PUPs' HA Cohort

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

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



43 patients with currently relevant inhibitor

12 Prophylaxis
aPCC = 8 (4 ITI+)
rFVIIa = 4 (3 ITI+)

Treatment of bleedings
in haemophilia patient with inhibitor

Low titers, low responding, transient inhibitors …

- ✓ Treatment / FVIII concentrates (higher dose)
- ✓ Prophylactic objectives are achievable

High titers, high responding, anamnesis …

- ✓ Bypassing agents (BPA) = rFVIIa or aPCC*
- ✓ Possible poor response, life-threatening bleedings
- ✓ Disability, impaired quality of life, absence at school, impaired academic achievement and productivity ...

**** FENOC Study : Astermark et al, Blood 2007***

Immunotolerance Induction

Treatment of inhibitor

Immunotolerance Induction : the rationale

Series with heterogeneous protocols in the literature

Large international Registries

Risk factors for response - 50 to 80 % of tolerance

One randomized trial (International ITI)

Plenary paper

blood

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

Charles R. M. Hay[1] and Donna M. DiMichele,[2] on behalf of the International Immune Tolerance Study

BLOOD, 9 FEBRUARY 2012 • VOLUME 119, NUMBER 6

Cochrane

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)

ORIGINAL ARTICLE

Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors

B. A. KONKLE,* L. S. EBBESEN,† E. ERHARDTSEN,† R. P. BIANCO,‡ T. LISSITCHKOV,§ L. RUSEN¶ and M. A. SERBAN**

J Thromb Haemost 2007; **5**: 1904–13

Reference/study design	No. patients, age at start of prophylaxis, prestudy bleeding frequency
55; prospective study with 3-mo lead-in on-demand period (control period) followed by randomization to 2 doses of rFVIIa for a 3-mo treatment period	22 5.1-50.5 y ≥2 bleeds/mo during 3-mo preprophylaxis period

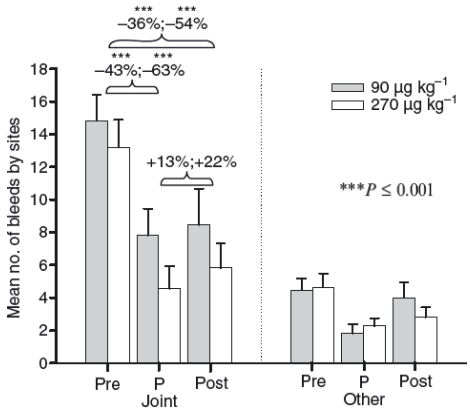


Fig. 3. Number of bleeds by site per trial period. The bracketed data

The NEW ENGLAND JOURNAL of MEDICINE

Anti-Inhibitor Coagulant Complex Prophylaxis in Hemophilia with Inhibitors

Cindy Leissinger, M.D., Alessandro Gringeri, M.D., Bülent Antmen, M.D., Erik Berntorp, M.D., Chiara Biasoli, M.D., Shannon Carpenter, M.D.,

N Engl J Med 2011;365:1684-92.

Reference/study design	No. patients, age at start of prophylaxis, prestudy bleeding frequency	BAP dose	Duration of BAP (range)	Efficacy
56; randomized crossover study of 6 mo of aPCC prophylaxis followed by 6 mo of on-demand therapy or vice versa	26 2.8-62.8 y ≥6 bleeds requiring bypassing therapy in 6 mo before study enrollment	aPCC 85 U/kg ± 15% on 3 nonconsecutive d/wk	6 mo	62% reduction in all bleeding events* 61% reduction in hemarthroses* 72% reduction in target joint bleeding* Significantly fewer absences from school/work during prophylaxis*

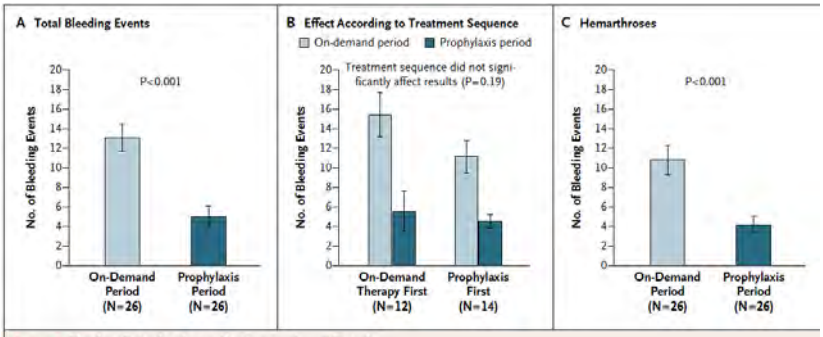


Figure 2. Bleeding Episodes during the Two Treatment Periods.

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

S. V. ANTUNES,* S. TANGADA,† O. STASYSHYN,‡ V. MAMONOV,§ J. PHILLIPS,¶ N. GUZMAN-BECERRA,† A. GRIGORIAN,† B. EWENSTEIN† and W.-Y. WONG†

Haemophilia (2014), 20, 65–72

Reference/study design	No. patients, age at start of prophylaxis, prestudy bleeding frequency	BAP dose	Duration of BAP (range)	Efficacy
57; randomized control trial comparing 12 mo of aPCC prophylaxis with 12 mo of on-demand therapy	36 7-56 y ≥12 bleeds in 12 mo before study enrollment	aPCC 85 ± 15 U/kg every other day	12 mo	72.5% reduction in annual bleeding rate

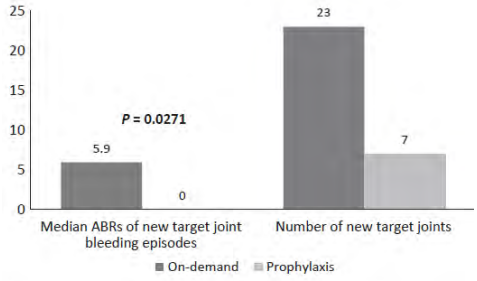


Fig. 3. New target joints and associated bleeding episodes.

How I Treat

blood

How I use bypassing therapy for prophylaxis in patients with hemophilia A and inhibitors

Cindy A. Leissinger,[1] Tammuella Singleton,[1] and Rebecca Kruse-Jarres[2]

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

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

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 Aet 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)

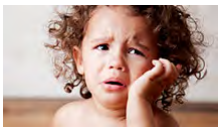
Overtreatment ? Unjustified TRT ?

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 at10 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

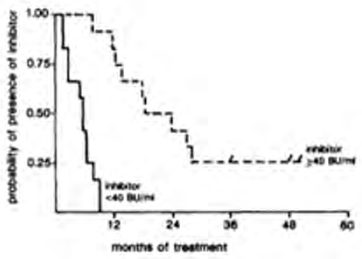
LR: 50-100 IU FVIII/kg body weight/d, every other day or 3 times per week
HR: 100 IU FVIII/kg bw i.v. twice daily and FEIBA 50 IU /kg bw i.v. twice daily

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

	Pre-ITI titer [BU] Median (range)	Time to BU <1 [mo]	Time to complete success [mo]	Succeess rate in HR [%]
Kreuz et al., Haemophilia 1995	**42** (0.8-1052)	**2.5**	**4** (0.5-42)	14/16 **(87%)**
Brackmann et al, Vox Sang 1996	**89** (0.8-520)	**7** (0.7-15)	**14.5** (4.1-25.4)	21/22 **(95%)**

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

Bonn protocol	Malmo protocol	van Creveld
FVIII 100 U/kg BID	Immunoadsorption using protein A column	FVIII 25-50 IU/kg BID for 1-2 weeks
FEIBA 100 U/kg BID	if inhibitor titer >10 BU/mL	then 25 IU/kg every other day
	Cyclophosphamide 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

blood

How I use bypassing therapy for prophylaxis in patients with hemophilia A and inhibitors

Cindy A. Leissinger,[1] Tammuella Singleton,[1] and Rebecca Kruse-Jarres[2]

[1]Louisiana Center for Bleeding and Clotting Disorders, Tulane University Medical Center, New Orleans, LA; and [2]Washington 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

Reference/study design	No. patients, age at start of prophylaxis, prestudy bleeding frequency	BAP dose	Duration of BAP (range)	Efficacy
55; prospective study with 3-mo lead-in on-demand period (control period) followed by randomization to 2 doses of rFVIIa for a 3-mo treatment period	22 5.1-50.5 y ≥2 bleeds/mo during 3-mo preprophylaxis period	rFVIIa 90 μg/kg per day or rFVIIa 270 μg/kg per day	3 mo	45% reduction in bleeding in patients treated with 90 μg/kg per day 59% reduction in bleeding in patients treated with 270 μg/kg per day (not statistically significant compared with 90 μg/kg dose) Significantly fewer hospital admissions and absences from school/work during prophylaxis
56; randomized crossover study of 6 mo of aPCC prophylaxis followed by 6 mo of on-demand therapy or vice versa	26 2.8-62.8 y ≥6 bleeds requiring bypassing therapy in 6 mo before study enrollment	aPCC 85 U/kg ± 15% on 3 nonconsecutive d/wk	6 mo	62% reduction in all bleeding events* 61% reduction in hemarthroses* 72% reduction in target joint bleeding* Significantly fewer absences from school/work during prophylaxis*
57; randomized control trial comparing 12 mo of aPCC prophylaxis with 12 mo of on-demand therapy	36 7-56 y ≥12 bleeds in 12 mo before study enrollment	aPCC 85 ± 15 U/kg every other day	12 mo	72.5% reduction in annual bleeding rate

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)

Haemophilia
The Official Journal of the World Federation of Hemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society

Haemophilia (2015), 21, 436–443 DOI: 10.1111/hae.12720

ORIGINAL ARTICLE *Clinical haemophilia*

Survey of coagulation factor concentrates tender and procurement procedures in 38 European Countries

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Introduction: Procurement of coagulation factor concentrates (CFCs) for the treatment of haemophilia is a vital process that determines the quantity and quality of factor replacement therapy. **Aim:** The aim of this study was to examine the different tender and procurement systems used in Europe for the procurement of CFCs and the outcomes produced by the various systems. **Methods:** The survey questionnaire consisted of 30 items and explored various aspects of the procurement process including the prices of CFCs. In 2014, the survey was sent out by the European Haemophilia Consortium (EHC) to 45 national haemophilia patient organizations affiliated to the EHC in all European countries as well as to a designated clinician familiar with the procurement process. **Results:** The survey was completed by 38 European countries. Nineteen countries use a tender process, 17 an alternative procurement process and 2 use a combination of methods. A wide variety of agencies and individuals are involved in the process. Factors associated with optimum outcome and lower prices include a tender process with a specific legal framework and a tender board including haemophilia clinicians and patient organization representatives. Safety was reported as the most important selection criterion but given the safety profile of almost all currently licensed products, price was the main criterion used in many countries. **Conclusion:** The involvement of both clinicians and patient organizations greatly improves the outcome of a tender or procurement process, as does the presence of a legal framework that governs the process.

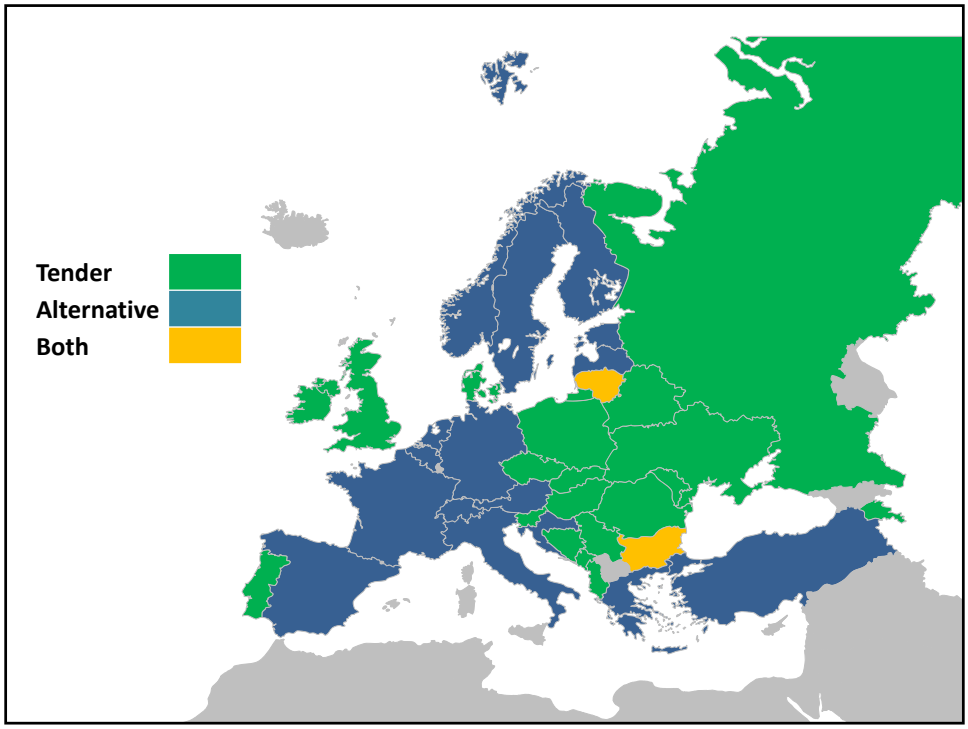
Keywords: factor concentrate, procurement, tender

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)		Alternative (17)		Both (2)
Albania	Poland	Austria	Kyrgyzstan	Bulgaria
Azerbaijan	Portugal	Belgium	Latvia	Lithuania
Belarus	Romania	Croatia	Netherlands	
Bosnia & Herzegovina	Russia	Estonia	Norway	
Czech Republic	Serbia	Finland	Spain	
Denmark	Slovak Republic	France	Sweden	
Hungary	Slovenia	Germany	Switzerland	
Ireland	Ukraine	Greece	Turkey	
Moldova	United Kingdom	Italy		
Montenegro				



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:

Health Insurance funds	Medicines agencies or pharmacies	Hospitals or blood centres	Ministries of Health	Clinicians or Haemophilia Centres	Patient Organisation
Involved in all aspects of the process					
Bosnia& Herzegovina	Denmark	Albania	Albania	Ireland	Ireland
Hungary	United Kingdom	Czech Republic	Azerbaijan	Denmark	Serbia
Montenegro, Serbia Slovak Rep.	Azerbaijan Romania Belarus	Ireland Portugal Romania	Belarus Ireland Russia	Montenegro Serbia United Kingdom	
Involved only in scientific and technical aspects of the process					
				Romania Portugal Bosnia & Herzegovina Moldova	Portugal Slovenia United Kingdom

Main representatives on procurement boards:

Health Insurance funds	Medicines agencies or pharmacies	Procurement Agencies	Ministries of Health or Local authorities	Clinicians or Haemophilia Centres	Patient Organisation
Involved in all aspects of the Process					
Kyrgyzstan	France		Kyrgyzstan		Kyrgyzstan
	Belgium		Italy		
Croatia	Kyrgyzstan				
	Sweden				
Involved only in Scientific and Technical aspects of the process					
			Turkey	France	
				Kyrgyzstan	
				Estonia	

Tender /Procurement Boards:
duration of terms of office and contracts

		N	Years
Term of office of the committee	Tender	9	2.3
	Alternative	3	1.5
Typical duration of the contract awarded	Tender	18	1.4
	Alternative	7	1.9

Outcomes:

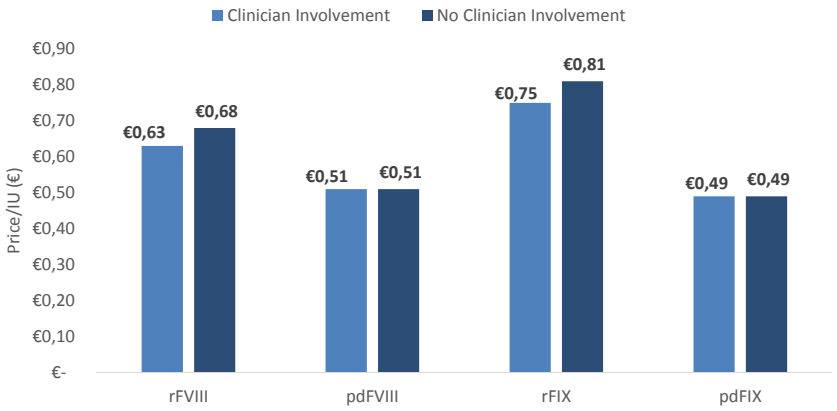
Lower prices obtained for most products when using tender system compared to alternative procurement process:

- 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)

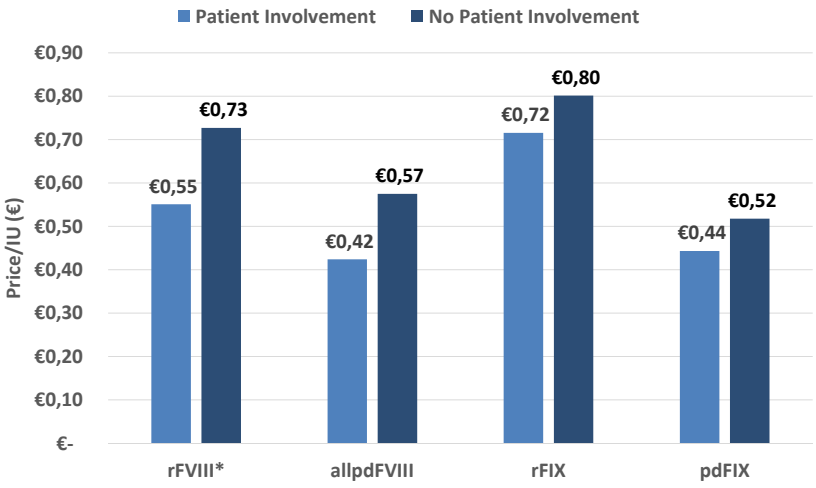
	Tender			Alternative Process		
	n	Median (€)	Range (€)	n	Median (€)	Range (€)
Recombinant FVIII*	12	0.56	0.28 -1.05	17	0.69	0.39 -1.06
Plasma-Derived FVIII	15	0.40	0.16 -1.16	16	0.64	0.18 - 0.90
Recombinant FIX	6	0.73		12	0.72	
Plasma-Derived FIX*	15	0.40	0.18 -0.83	17	0.54	0.38 -0.88

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

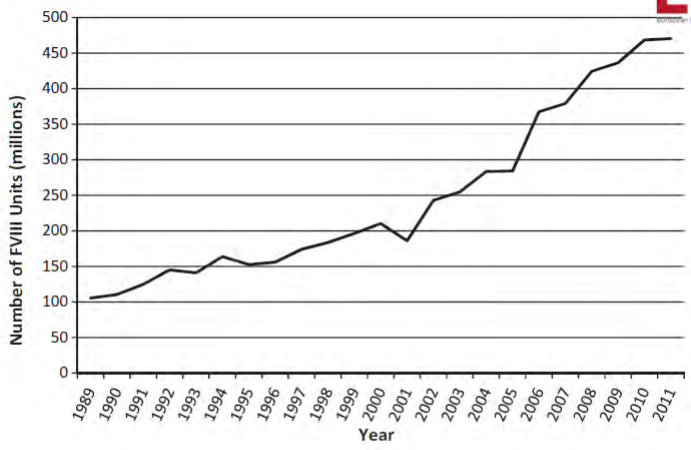


Fig. 1. Annual UK factor VIII usage per calendar year, 1989–2011, inclusive. This shows a greater than fourfold increase in factor VIII consumption over two decades. The dip in usage in 2001 corresponded to the interruption in supply of Kogenate and Helixate, which halved the UK supply of rFVIII for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

Hay CRM. Haemophilia 19: 660-667 (2013)

UK tender process:

Hay CRM. Haemophilia 19: 660-667 (2013)

- 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:

Hay CRM. Haemophilia 19: 660-667 (2013)

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

Hay C et al. Haemophilia 21: 219-226 (2015)

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

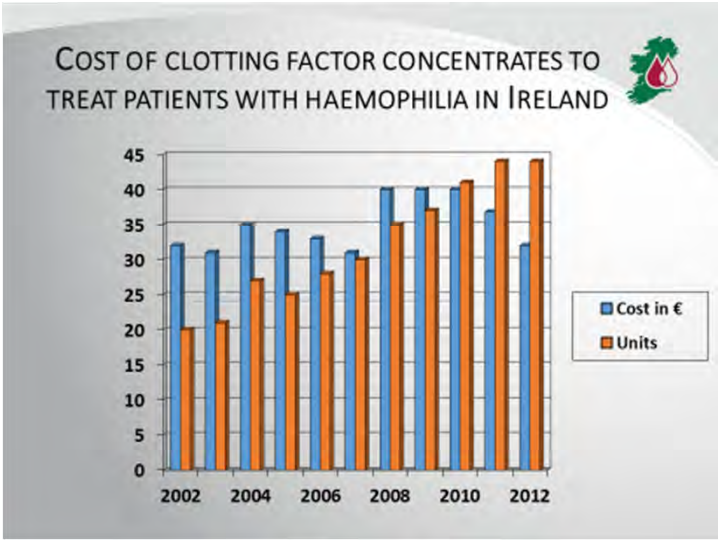
Provide feedback on service:

- 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

	QUESTIONS					
		Excellent	Good	Average	Poor	Very Poor	N/A
1	How would you rate the Customer Service provided by the supplier?				X		
2	How would you rate the handling of complaints by the supplier?			X			
3	How would you rate your local representative?	X					
4	How would you rate the support you receive from your local representative?	X					
5	How would you rate timeliness of deliveries?					X	
6	How would you rate the accuracy of the deliveries?			X			
7	How would you rate order fulfilment?				X		
8	How would you rate the invoicing process?			X			
9	How would you rate the value added services offered by the supplier?			X			
10	How would you rate the supplier's overall performance?				X		
	ADDITIONAL QUESTION						
		Excellent	Good	Average	Poor	Very Poor	N/A
11	How would you rate your homecare delivery supplier?		X				



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

Portuguese Association of Hemophilia denounces economic criteria in the treatment of disease

"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 a 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."

Press release, APH, World Haemophilia Day 2015

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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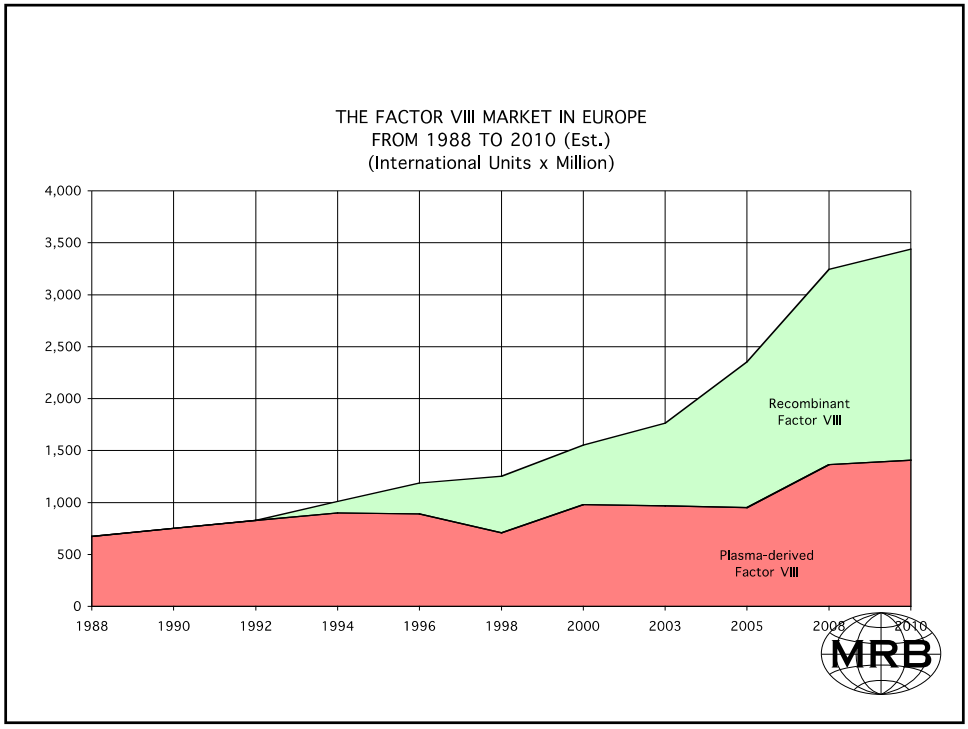
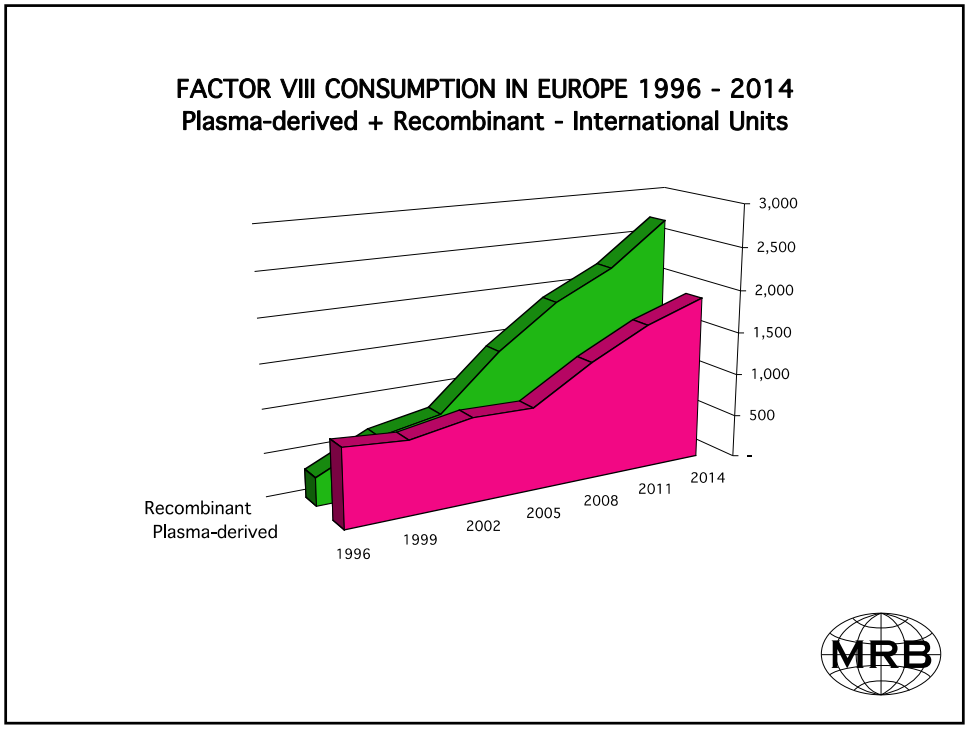

THE FACTOR VIII MARKET IN EUROPE
FROM 1988 TO 2010 (Est.)
(International Units x Million)
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
1988
1990
1992
1994
1996
1998
2000
2003
2005
2008
2010
Recombinant
Factor VIII
Plasma-derived
Factor VIII
MRB


FACTOR VIII CONSUMPTION IN EUROPE 1996 - 2014
Plasma-derived + Recombinant - International Units
3,000
2,500
2,000
1,500
1,000
500
-
Recombinant
Plasma-derived
1996
1999
2002
2005
2008
2011
2014
MRB

Factor VIII Consumption in Europe 1996 - 2014
(International Units, Plasma-derived and recombinant)

	1996	1999	2002	2005	2008	2011	2014	Growth
Plasma-derived (Units x 000)	891	838	960	948	1,352	1,684	1,911	
Annual Growth Rate		*-2.0%*	*4.7%*	*-0.4%*	*12.6%*	*7.6%*	*4.3%*	*4.3%*
Recombinant (Units x 000)	322	655	788	1,402	1,882	2,206	2,701	
Annual Growth Rate		26.7%	6.3%	21.2%	10.3%	5.4%	7.0%	*12.5%*
Plasma-derived+Recombinant	1,213	1,493	1,748	2,350	3,234	3,889	4,612	
Annual Growth Rate		*7.2%*	*5.4%*	*10.4%*	*11.2%*	*6.3%*	*5.8%*	*7.7%*

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.

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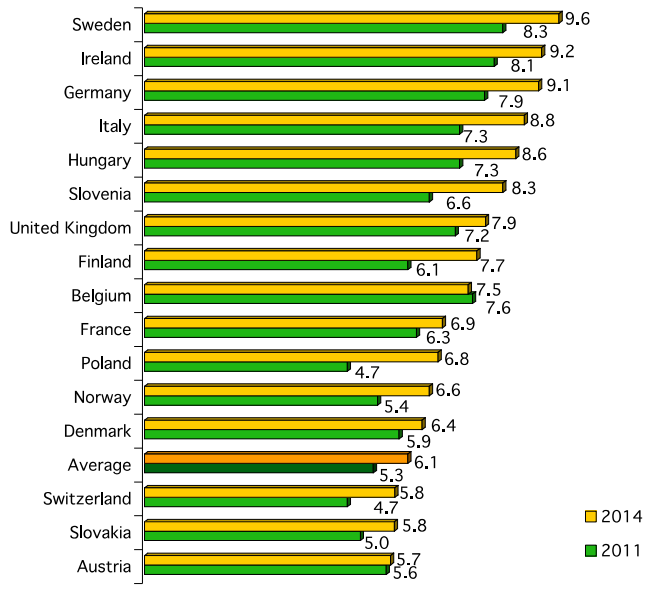
THE PLASMA PROTEINS MARKET IN EUROPE - 2014
FACTOR VIII CONSUMPTION PER CAPITA IN EUROPE 2011 & 2014



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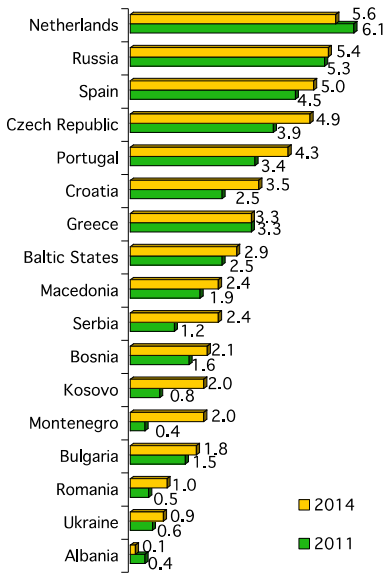
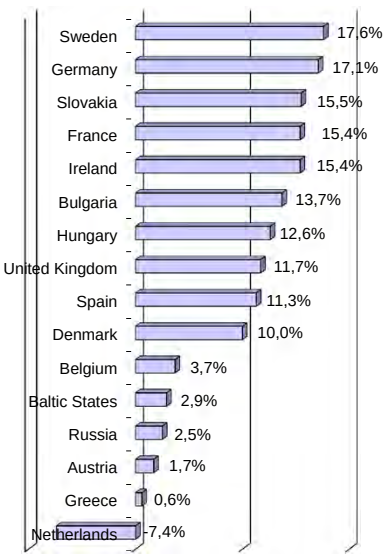
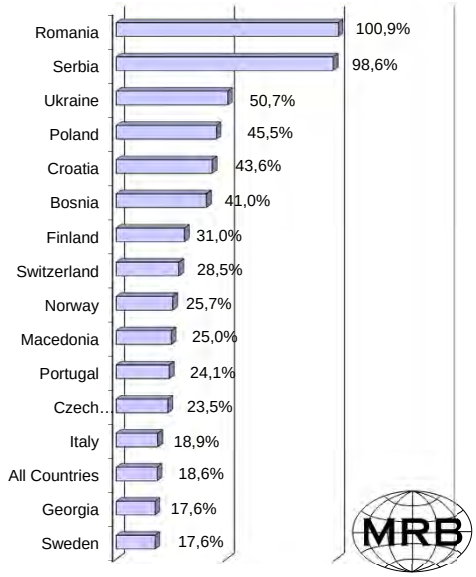
THE PLASMA PROTEINS MARKET IN EUROPE - 2014
FACTOR VIII CONSUMPTION PER CAPITA IN EUROPE 2011 & 2014



THE PLASMA PROTEINS MARKET IN EUROPE - 2014
CHANGE IN FACTOR VIII CONSUMPTION BETWEEN 2011 AND 2014
(Recombinant & Plasma-derived Factor VIII)





Factor IX Consumption in Europe 1996 - 2014
(International Units, Plasma-derived and recombinant)

	1996	1999	2002	2005	2008	2011	2014	Growth
plasma-derived (Units x 000)	188	171	161	160	202	283	344	
Annual Growth Rate		*-3.2%*	*-1.9%*	*-0.2%*	*8.0%*	*11.9%*	*6.7%*	*3.4%*
Recombinant (Units x 000)	-	34	78	158	191	224	260	
Annual Growth Rate			32.8%	26.3%	6.5%	5.5%	5.0%	*14.6%*
Plasma-derived+Recombinant	188	204	240	318	392	507	604	
Annual Growth Rate		*2.8%*	*5.5%*	*9.9%*	*7.2%*	*8.9%*	*6.0%*	*6.7%*

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 – 2914, 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.

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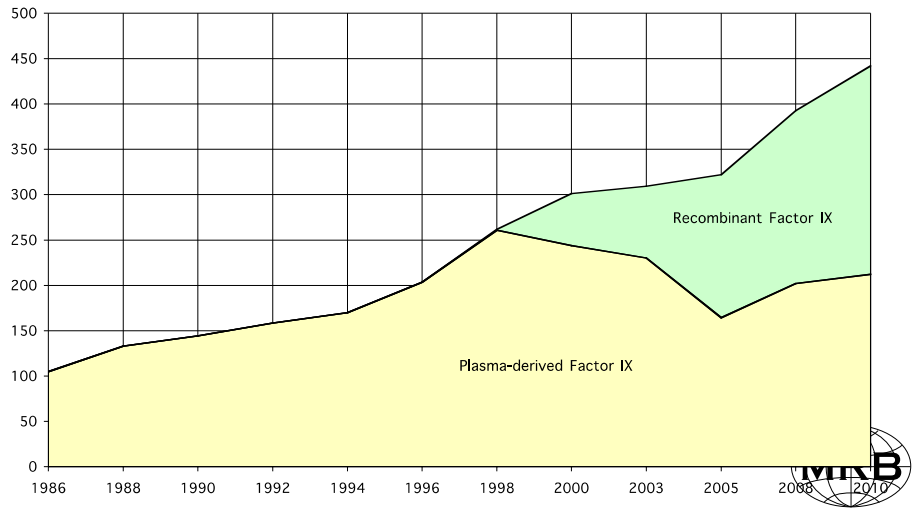
THE FACTOR IX MARKET IN EUROPE
FROM 1986 TO 2010 (Est.)
(International Units x Million)



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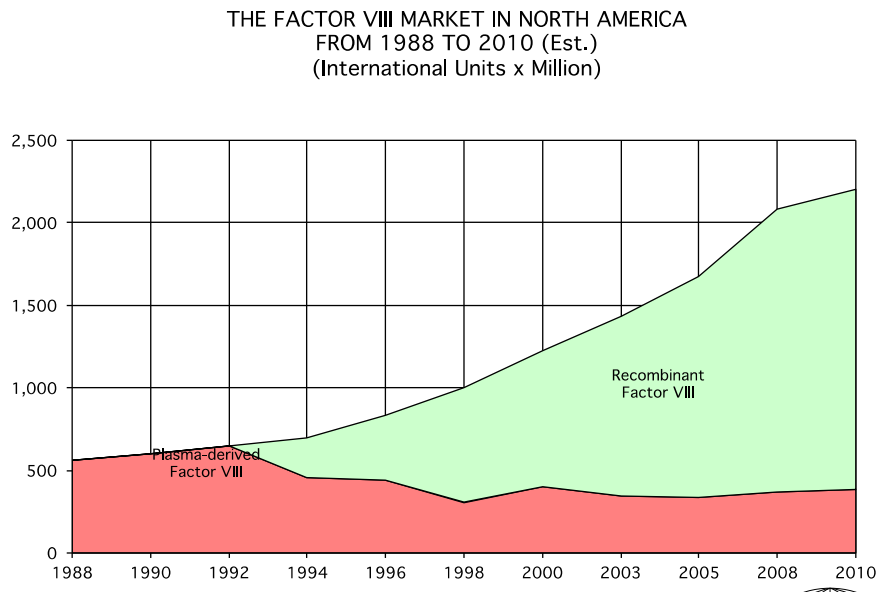
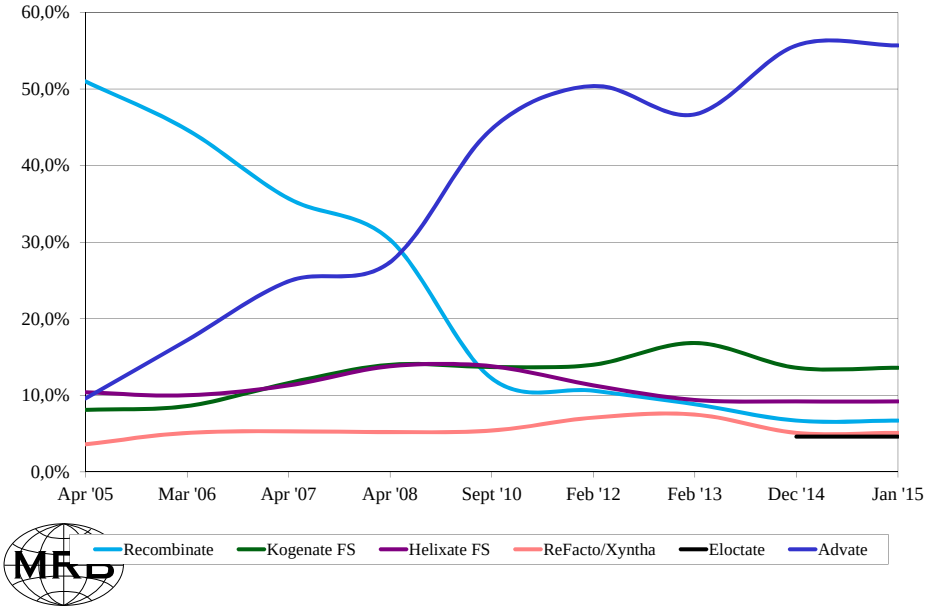
- Current Market: Europe
- **Current Market: United States**
- Future trends

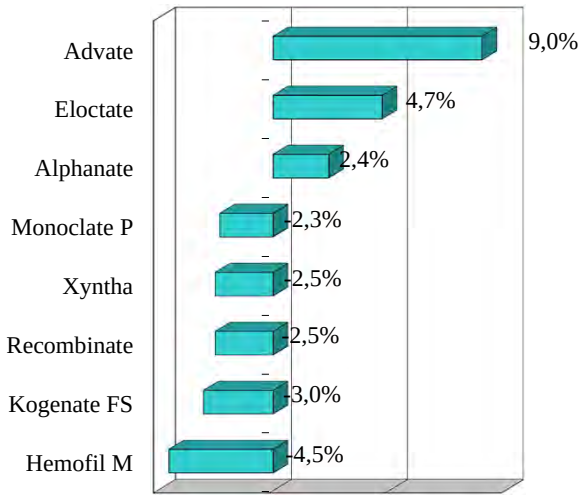


Recombinant factor VIII was adopted faster in the United States than in Europe

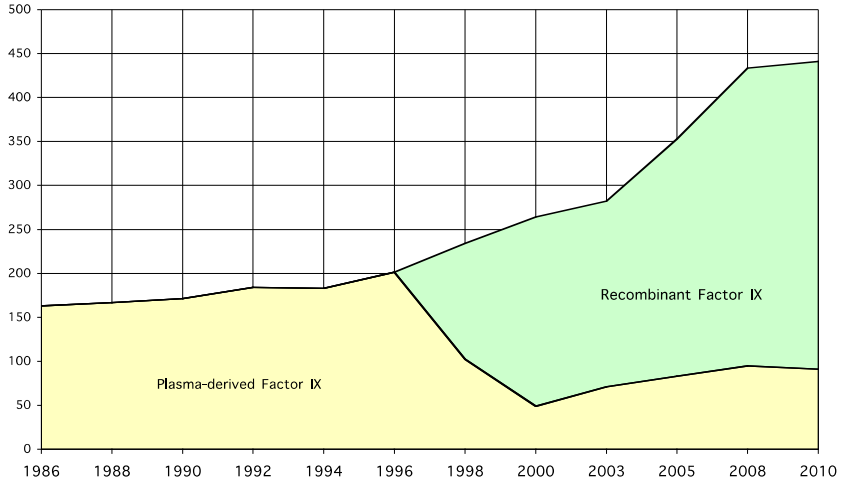
MARKET PENETRATION OF RECOMBINANT FACTOR VIII 2005 - 2015
(Percent of Patients in the Sample)



MARKET SHARE CHANGE BETWEEN Q1/13 AND Q4/14 - FACTOR VIII CONCENTRATES
(Percentage of Patients in the Sample)



THE FACTOR IX MARKET IN NORTH AMERICA
FROM 1986 TO 2010 (Est.)
(International Units x Million)



Recombinant factor IX was adopted quickly in the United States than in Europe because of plasma-derived FIX shortage in 1999

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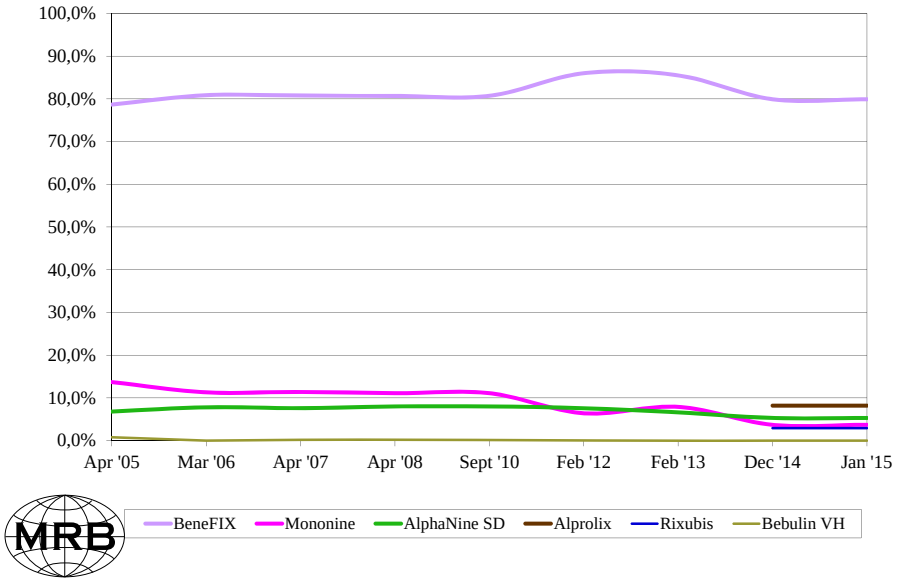
MARKET SHARES OF RECOMBINANT FACTOR IX 2005 - 2015
(Percentage of Patients in the Sample)



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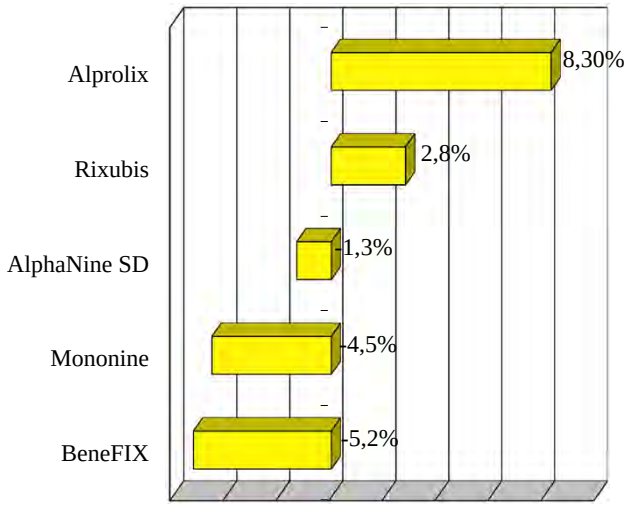
MARKET SHARE VARIATIONS BETWEEN Q1/13 AND Q4/14 - FACTOR IX CONCENTRATES (Percentage of Patients in the Sample)



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

	Percentage of Patients								
Type of Prophylaxis	February 2012	September 2010	April 2008	April 2007	March 2006	March 2005	January 2004	January 2003	January 2002
Permanent	33.1%	30.9%	13.2%	12.4%	12.1%	8.8%	13.2%	7.9%	7.3%
Temporary	16.6%	15.8%	17.8%	17.3%	15.9%	16.4%	14.4%	14.6%	13.1%
Total	49.7%	46.7%	31.0%	29.7%	27.9%	25.2%	27.6%	22.5%	20.4%

Source: The Marketing Research Bureau, Inc. - Hemophilia Care & Price Monitoring, Wave 21, 2013

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*)

Distribution of Inhibitor Treatment Hemophilia A Patients in Survey Sample - February 2012 and February 2013

Type of Treatment	February 2013		Feb. '13 vs. Feb. '12	February 2012
	Patients	Percent	Change	Percent
rFVIII	62	68.9%	7.0%	61.9%
Alphanate	18	20.0%	-7.0%	27.0%
Humate P	7	7.8%	-1.7%	9.5%
Koate DVI	1	1.1%	-0.5%	1.6%
Wilate	2	2.2%	2.2%	0.0%
Total ITI Patients	90	100.0%		100.0%

Mode of Treatments for Hemophilia A Patients with Inhibitors - 2002 to 2013

	Type of Treatment	February 2013		February 2012	September 2010	April 2008	April 2007	March 2006	March 2005	January 2004	January 2003	January 2002
		Patients	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent	Percent
Inihibitor Treatments	Immune Tol.	80	43.5%	23.5%	39.0%	39.2%	38.7%	32.5%	25.4%	29.9%	26.7%	25.3%
	PCC	0	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.8%	0.4%	0.5%	0.5%
	FEIBA	43	23.4%	32.3%	29.4%	29.0%	29.1%	32.9%	39.8%	34.9%	37.8%	37.8%
	Novoseven	51	27.7%	39.5%	31.6%	31.8%	31.9%	34.6%	33.2%	29.5%	29.0%	29.4%
	Autoplex T	0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	5.4%	6.0%	6.9%
	Sub-Total	174	94.6%	95.3%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.8%

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

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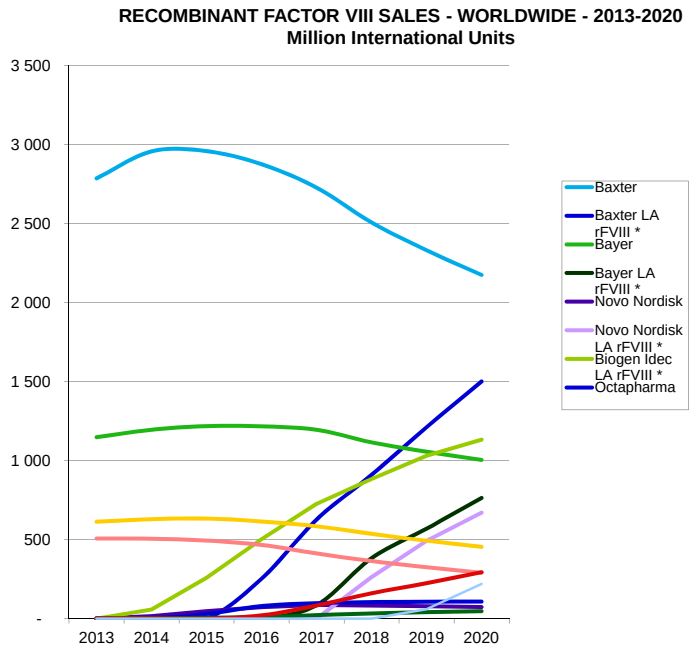
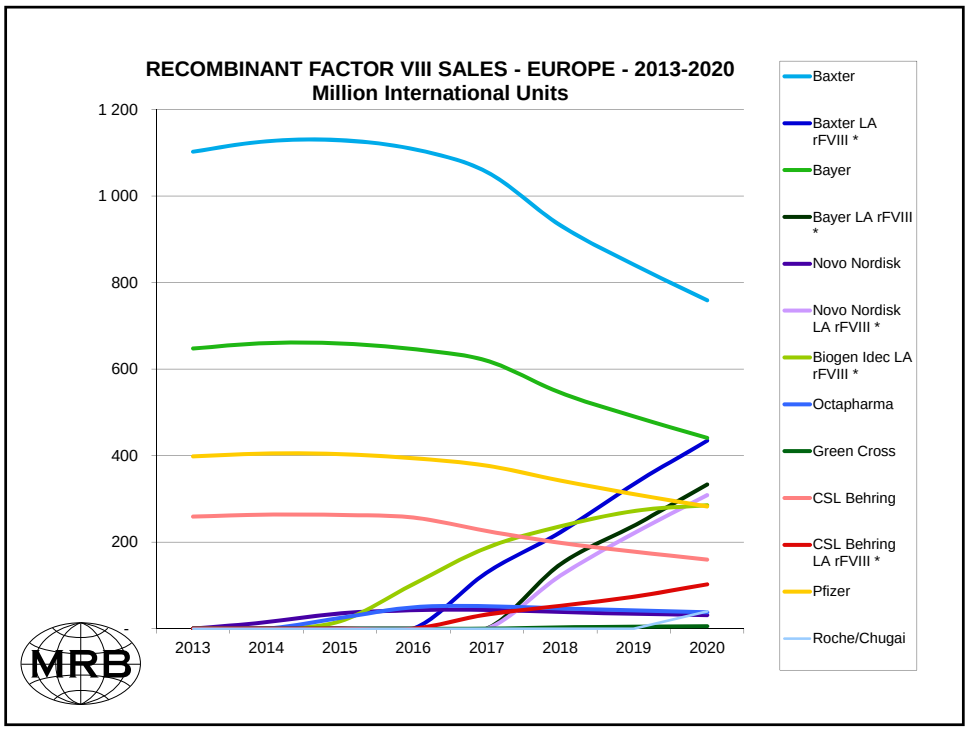
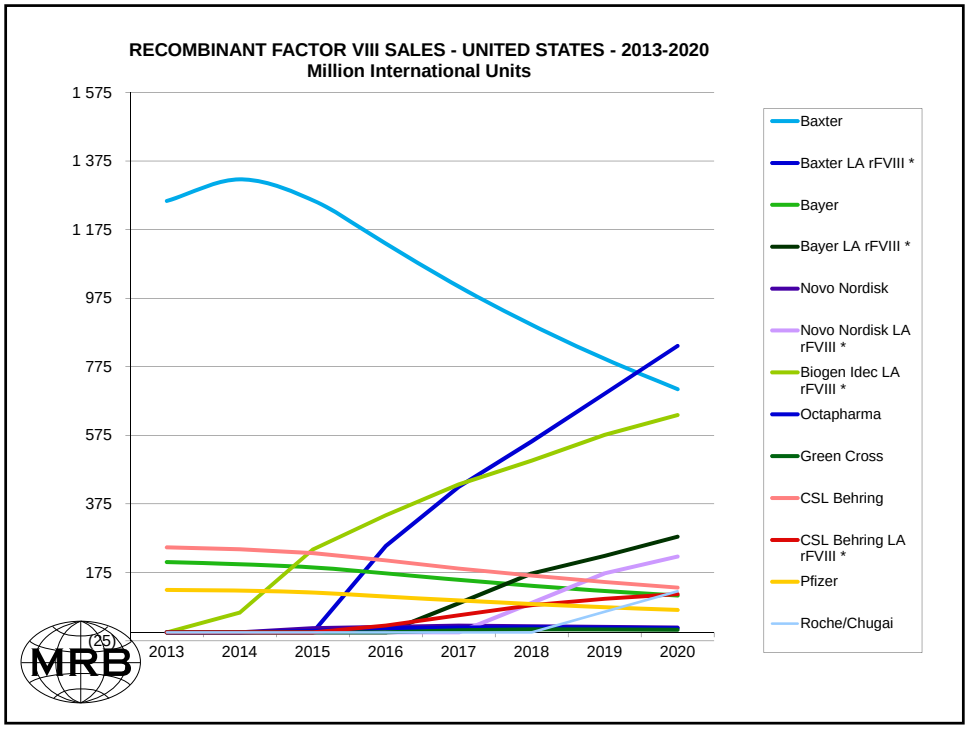


The gradual market penetration of the extended half-life (EHL) recombinant factors VIII and IX products are expected to have the following consequences:

- 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


RECOMBINANT FACTOR VIII SALES - EUROPE - 2013-2020
Million International Units
1 200
1 000
800
600
400
200
-
2013
2014
2015
2016
2017
2018
2019
2020
Baxter
Baxter LA rFVIII *
Bayer
Bayer LA rFVIII *
Novo Nordisk
Novo Nordisk LA rFVIII *
Biogen Idec LA rFVIII *
Octapharma
Green Cross
CSL Behring
CSL Behring LA rFVIII *
Pfizer
Roche/Chugai
MRB


RECOMBINANT FACTOR VIII SALES - UNITED STATES - 2013-2020
Million International Units
1 575
1 375
1 175
975
775
575
375
175
2013
2014
2015
2016
2017
2018
2019
2020
Baxter
Baxter LA rFVIII *
Bayer
Bayer LA rFVIII *
Novo Nordisk
Novo Nordisk LA rFVIII *
Biogen Idec LA rFVIII *
Octapharma
Green Cross
CSL Behring
CSL Behring LA rFVIII *
Pfizer
Roche/Chugai
(25)
MRB

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.**

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Thank you!

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GIESSEN

MEDICAL
FACULTY

EUROPEAN SYMPOSIUM
IV Wildbad Kreuth Initiative

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

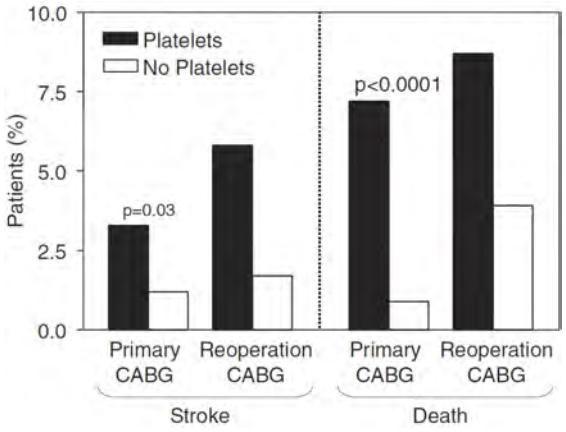
- Question: Association of blood (platelet) transfusion and survival?

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



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

Kremke M et al., Eur J Cardiothorac Surg 48:e102 (2015)

Observational studies in transfusion medicine

Confounding by Indication

Guidelines

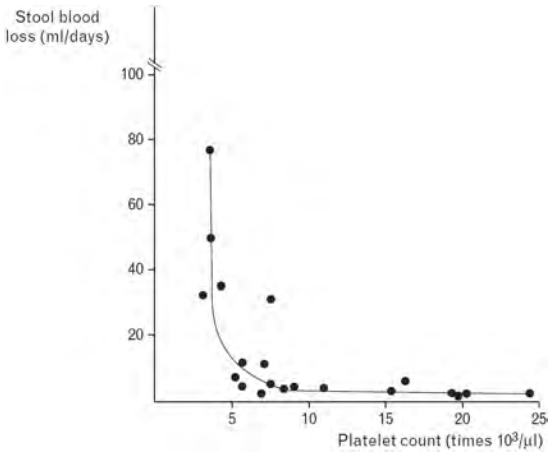
German Medical Association
Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives

http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/WB/QLL_Haemotherapie-englisch.pdf
See also: Kumar A et al., Transfusion 55:1116 (2015) and Kaufman RM et al., Ann Intern Med 162: 205 (2015) and Nahirniak S et al., Transfusion Med Rev 29: 3 (2015)

Hematology and Oncology patients

Hematology and Oncology patients
Prophylactic platelet transfusion - threshold

Fecal blood loss in thrombocytopenic patients



Slichter SJ, Harker LA Clin Haematol 7:523 (1978)

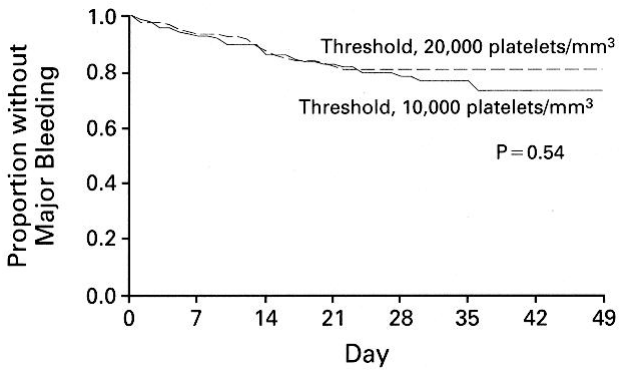
Hematology and Oncology patients
Prophylactic platelet transfusion - threshold

Patients with impaired platelet production (chemotherapy)
Prophylactic platelet transfusion: PLT count ≤ 10 x 10^9/L
Additional risk factors* for bleeding: PLT count ≤ 20 x 10^9/L

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

http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/WB/QLL_Haemotherapie-englisch.pdf

Hematology and Oncology patients
Prophylactic platelet transfusion - threshold



255 adult AML patients receiving induction chemotherapy

1. Standard arm: platelets given if count < 20 x 10^9/l
2. Low threshold arm: platelets given if counts < 10 x 10^9/l with a temperature of < 38°C, 10-20 x 10^9/l with temperature > 38°C, or if bleeding

Rebulla P et al., New Engl J Med 337:1870 (1997)

Hematology and Oncology patients
Prophylactic platelet transfusion - threshold

Cochrane review 3 RCTs

- Rebulla P et al., New Engl J Med 337:1870 (1997)
- Heckman KD et al., J Clin Oncol 15:1143 (1997)
- Diedrich B et al., Transfusion 45:1064 (2005)

Estcourt LJ et al., Cochrane Database Syst Rev 11:CD010983 (2015)

Hematology and Oncology patients
Prophylactic platelet transfusion - threshold

Outcomes up to 30 days	Illustrative comparative risks (95% CI)		Relative effect	Participants	Quality of evidence
	Higher trigger 20 / 30 x 10^9/L	Lower trigger 10 x 10^9/L			
Patients with bleedings	177 per 1000	239 per 1000 (168 to 336)	RR 1.35 (0.95 to 1.9)	499 (3 studies)	low
Patients with bleedings grade 3 or 4	82 per 1000	81 per 1000 (43 to 154)	RR 0.99 (0.52 to 1.88)	421 (2 studies)	low
No of platelet transfusions		2.09 lower (3.2 to 0.99)		333 (2 studies)	low
Mortality	75 per 1000	134 per 1000 (62 to 286)	RR 1.78 (0.83 to 3.81)	255 (1 study)	low

Estcourt LJ et al., Cochrane Database Syst Rev 11:CD010983 (2015)

Hematology and Oncology patients
Prophylactic platelet transfusion - threshold

Conclusion

Standard trigger (10 x 10^9/L) compared to a higher trigger

- No increase in the risk of bleeding (low-quality evidence)

Estcourt LJ et al., Cochrane Database Syst Rev 11:CD010983 (2015)

Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion

Cochrane review 5 RCTs

- Grossman L et al., ISBT Abstract Book (1980) n=100
- Murphy S et al., Am J Hematol 12:347 (1982) n=56
- Solomon J et al., Lancet I 8058:267 (1978) n=31
- Stanworth et al., New Engl J Med 368:1771 (2013) n=600
- Wandt et al., Lancet 380:1309 (2012) n=396

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

Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion

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

Hannes Wandt, Kerstin Schaefer-Eckart, Knut Wendelin, Bettina Pilz, Martin Wilhelm, Markus Thalheimer, Ulrich Mahlknecht, Anthony Ho, Markus Schaich, Michael Kramer, Martin Kaufmann, Lothar Leimer, Rainer Schwerdtfeger, Roland Conradi, Gottfried Dölken, Anne Klenner, Mathias Hänel, Regina Herbst, Christian Junghanss, Gerhard Ehninger, for the Study Alliance Leukemia

The NEW ENGLAND JOURNAL of MEDICINE

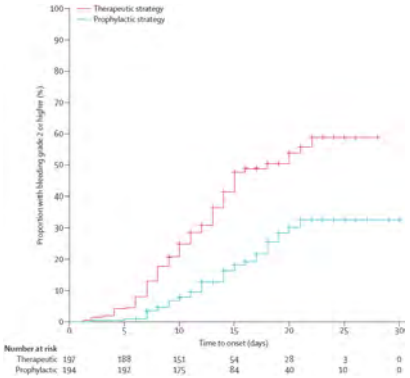
ESTABLISHED IN 1812 MAY 9, 2013 VOL. 368 NO. 19

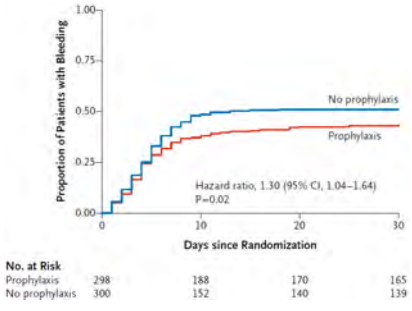
A No-Prophylaxis Platelet-Transfusion Strategy for Hematologic Cancers

Simon J. Stanworth, M.D., D.Phil., Lise J. Estcourt, M.B., B.Chir., Gillian Powter, B.A., Brennan C. Kahan, M.Sc., Claire Dyer, B.N., Louise Choo, Ph.D., Lekha Bakrania, B.Sc., Charlotte Llewelyn, Ph.D., Timothy Littlewood, M.B., B.Ch., M.D., Richard Soutar, M.B., Ch.B., M.D., Derek Norfolk, F.R.C.P., F.R.C.Path., Adrian Copplestone, M.B., B.S., Neil Smith, M.B., Ch.B., Paul Kerr, M.B., Ch.B., Ph.D., Gail Jones, M.D., Kavita Raj, M.D., Ph.D., David A. Westerman, M.B., B.S., Jeffrey Szer, M.B., B.S., Nicholas Jackson, M.B., B.S., M.D., Peter G. Bardy, M.B., B.S., Dianne Plews, M.B., Ch.B., Simon Lyons, M.B., Ch.B., Linley Bielby, B.N., M.H.A., Erica M. Wood, M.B., B.S., and Michael F. Murphy, M.B., B.S., M.D., for the TOPPS Investigators*

Wandt H et al., Lancet 380:1309 (2012)
Stanworth SJ et al., N Engl J Med 368:1771 (2013)

Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion





Wandt H et al., Lancet 380:1309 (2012)

Stanworth SJ et al., N Engl J Med 368:1771 (2013)

Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion

TABLE

Bleeding in two randomized controlled studies

WHO Bleeding Scale*1	Wandt et al. (12)		p-value	Stanworth et al. (13, 22)		p-value
	prophylactic	therapeutic		prophylactic	therapeutic	
All patients						
Grade 2 and higher	65/343 (19)*2	127/301 (42)	<0.001	128/299 (43)	151/301 (50)	0.04
Grade 3	3 (1)	7 (2)	ns	1 (<1)	4 (1)	ns
Grade 4	4 (1)	13 (5)	0.016	0	2 (1)	ns
Autologous HSCT						
Grade 2 and higher	8/98 (8)	29/103 (28)	0.0005	95/210 (45)	99/211 (47)	ns
Grade 3	0	1 (1)		0	1 (0.5)	
Grade 4	0	0		0	2 (1)	
Acute leukemia						
Grade 2 and higher	57/245 (24)	98/198 (51)	<0.0001	33/89 (37)	52/90 (58)	<0.05
Grade 3	3 (1)	6 (3)	ns	1 (1)	3 (3)	ns
Grade 4	4 (2)	13 (7)	0.0095	0	0	

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

*2 absolute numbers (%)

WHO, World Health Organization; ns, non-significant; HSCT, hematopoietic stem cell transplantation

Wandt et al., Dtsch Arztebl Int 111:809 (2014)

Hematology and Oncology patients
Therapeutic-only vs prophylactic platelet transfusion

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

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

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

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

Hematology and Oncology patients
Different doses of prophylactic platelet transfusion

Cochrane review 7 RCTs

Conclusion

Low dose platelet transfusion

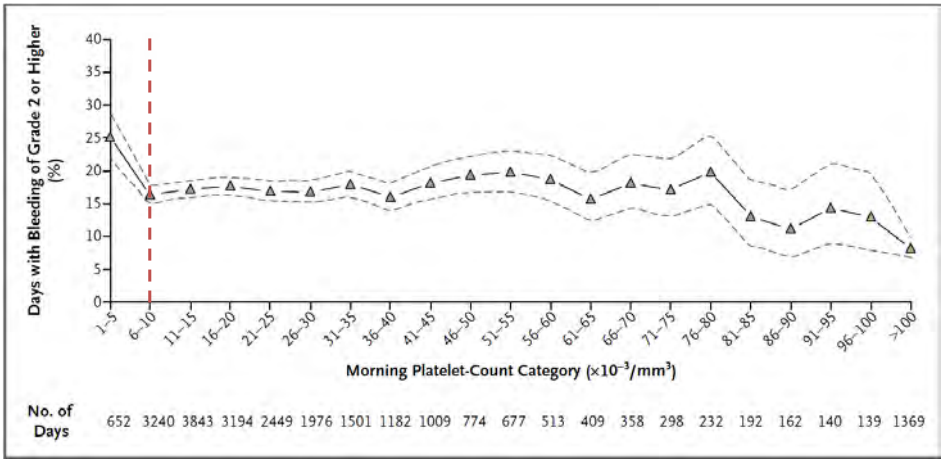
- requires more transfusions
- no increase in the risk of bleeding

High dose platelet transfusion

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

Estcourt LJ et al., Cochrane Database Syst Rev 10:CD010984 (2015)

Dose of Prophylactic Platelet Transfusions and Prevention of Hemorrhage (PLADO-Trial)



Days with bleeding of grade 2 or higher in all three treatment groups, according to morning platelet-count categories

Slichter SJ et al.; N Engl J Med 362:600 (2010)

Platelet transfusion for patients with hypoproliferative Thrombocytopenia - Summary

- Prophylactic platelet transfusions should be given (autologous HSCT?)
- Threshold: ≤ 10 x 10^9/L
- The standard dose of platelet concentrates is appropriate

Platelet transfusion thresholds prior to insertion of central lines

Cochrane review: No RCT

Estcourt LJ et al., Cochrane Database Syst Rev 12:CD011771 (2015)

Surgical patients

Platelet transfusion trigger in surgical patients

- Minor surgery ≤ 20 x 10^9/L
- Major surgery ≤ 50 x 10^9/L
- Neuraxial surgery ≤ 70 - 100 x 10^9/L
- Massive bleeding ≤ 100 x 10^9/L

Weak recommendations
low- to very-low-quality evidence

http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/WB/QLL_Haemotherapie-englisch.pdf

ICU patients

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

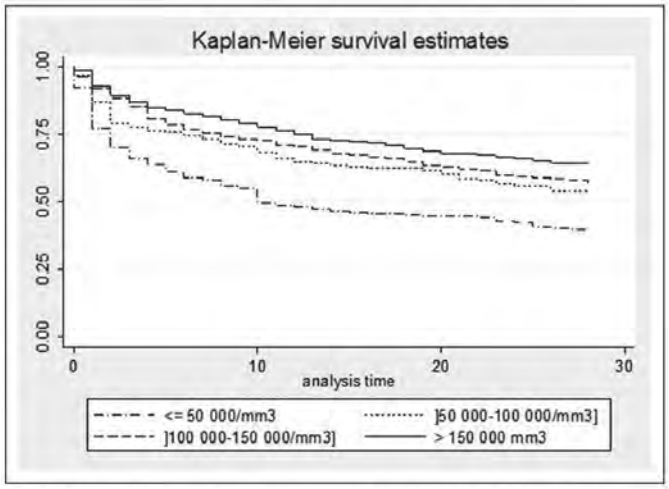


Figure 1. Kaplan-Meier survival estimates depending on the platelet count (EPIdemiology of Septic Shock Study, 2009–2011). *p* value from the log-rank test: less than 0.0001 for platelet count of more than 150,000/mm^3 versus less than or equal to 50,000/mm^3; $p = 0.0025$ versus 50–100,000/mm^3 and $p = 0.0427$ versus 100–150,000/mm^3.

Thiery-Antier N et al., Crit Care Med 44:764 (2016)

Evidence-Based Focused Review

CME Article

Platelet transfusions for critically ill patients with thrombocytopenia

Lani Lieberman,[1,2] Rachel S. Bercovitz,[3] Naushin S. Sholapur,[4] Nancy M. Heddle,[4,5] Simon J. Stanworth,[6,7] and Donald M. Arnold[4,5]

[1]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada; [2]Department of Clinical Pathology, University Health Network, Toronto, ON, Canada; [3]Blood Center of Wisconsin, Milwaukee, WI; [4]Department of Medicine, McMaster University, Hamilton, ON, Canada; [5]Canadian Blood Services, Hamilton, ON, Canada; [6]National Health Service Blood and Transplant/Oxford University Hospitals National Health Service Trust, John Radcliffe Hospital, Oxford, United Kingdom; and [7]Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Conclusion

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

Lieberman L et al., Blood 123:1146 (2014)

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)

Berséus O et al., Transfusion 53:114S (2013)

ABO-incompatible platelet (plasma) transfusion

Conclusion

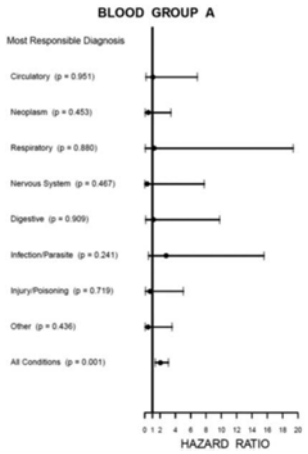
– A low titer of anti-A/B will minimize the risk of hemolytic transfusion reaction

Berséus O et al., Transfusion 53:114S (2013)

TRANSFUSION PRACTICE

Exposure to ABO-nonidentical blood associated with increased in-hospital mortality in patients with group A blood

Menaka Pai,[1,2] Richard Cook,[3] Rebecca Barty,[1] John Eikelboom,[2] Ker-Ai Lee,[3] and Nancy Heddle[1,2]



Further research is required

Pai M et al., Transfusion 56:550 (2016)
See also: Lozano M & Cid J Transfus Med Rev 17:57 (2003)

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

Cid J et al., Curr Opin Hematol 22:540 (2015)

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

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Clinical Efficacy of Platelet Transfusion

- Prophylactic transfusion:
  - Increase patient's platelet count
  - Prevent bleeding from occurring
- Therapeutic transfusion:
  - Stop bleeding

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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

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Corrected count increment calculation:

$$CCI = \frac{(\text{Post - transf. plt count - Pre - transf. plt count, } x10^9/L) \times \text{body surface area, } m^2}{\text{Platelets transfused, } x10^{11}}$$

$$24\text{-hours CCI} = \frac{(25-5) \times 1.5}{3.5} = \frac{20 \times 1.5}{3.5} = 8.5$$

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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.

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Definition of Successful Platelet Transfusion

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

Stanworth SJ, *et al*. Br J Haematol 2015; 171: 297-305

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Clinical Studies

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

TRANSFUSION PRACTICE

CME **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 MacLennan,[1] Kay Harding,[2] Charlotte Llewelyn,[3] Louise Choo,[4] Lekha Bakrania,[3] Edwin Massey,[2,5] Simon Stanworth,[6] Kate Pendry,[7,8] and Lorna M. Williamson[9]

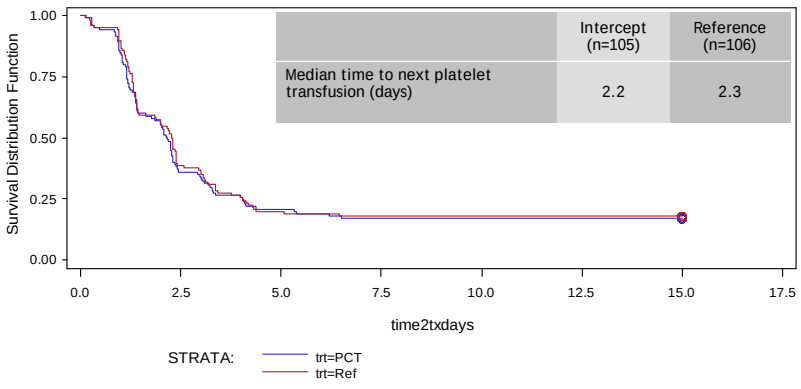
BACKGROUND: Bacterial screening offers the possibility of extending platelet (PLT) storage to Day 7. We conducted a noninferiority, crossover trial comparing PLTs stored for 6 or 7 days versus 2 to 5 days.
STUDY DESIGN AND METHODS: Stable hematology patients were allocated to receive blocks of 2- to 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.

TRANSFUSION 2015;55;1856–1865

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



	Intercept (n=105)	Reference (n=106)
Median time to next platelet transfusion (days)	2.2	2.3

Log-rank Test, p = 0.717

Lozano M, *et al*. Br J Haematol 2011; 153: 393-401

CME **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 MacLennan,[1] Kay Harding,[2] Charlotte Llewelyn,[3] Louise Choo,[4] Lekha Bakrania,[3] Edwin Massey,[2,5] Simon Stanworth,[6] Kate Pendry,[7,8] and Lorna M. Williamson[9]

TABLE 3. Summary of trial outcomes

	2- to 5-day PLTs	6- or 7-day PLTs	95% CI	p value
First evaluable blocks only (122 patients, 244 transfusions)				
Primary outcome				
Proportion of successful transfusions (CCI > 4.5 × 10^9/L) (%)	71.3 (87/122)	68.9 (84/122)	0.47 to 1.58	0.625
8- to 24-hour CCI, mean (SD)	9.4 (7.9)	7.7 (7.1)	−3.31 to 0.03	0.054
Interval to the next PLT transfusion,* median (IQR)				
Days	2 (1-4)	2 (1-3)	N/A	N/A
Hours	49.3, (27.5-85.9)	47.2, (27.2-69.3)	−10.5 to 5.4	0.531

TRANSFUSION 2015;55;1856–1865

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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

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WHO Hemostatic Assessment

	GRADING				
	0	1	2	3	4
MUCOCUTANEOUS					
Epistaxis	None	< 1 hour in duration	> 1 hour duration	See footnote 1	See footnote 2
Oropharyngeal	None	< 1 hour in duration	> 1 hour duration	See footnote 1	See footnote 2
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	None	Petechiae of skin or mucosa, purpura < 1 inch in diameter, confluent purpura	Purpura > 1 inch in diameter, generalized petechiae, purpura of skin	See footnote 1	See footnote 2
GASTROINTESTINAL					
Melena	None	N/A	Positive occult blood	See footnote 1	See footnote 2
Rectal bleeding / hematochezia (visible blood)	None	N/A	Positive occult blood	See footnote 1	See footnote 2
Covert GI bleeding (no visible blood; not black or tarry stools)	None	Positive occult blood	See melena / hematochezia	See footnote 1	See footnote 2
Hematemesis	None	N/A	Positive visual / occult blood	See footnote 1	See footnote 2
GENITOURINARY					
Hematuria	None	Up to 1+ (dl,trace,small)	2+ (moderate) or greater	See footnote 1	See footnote 2
Vaginal bleeding, abnormal	None	Spotting, <2 saturated pads/day	>2 saturated pads/day	See footnote 1	See footnote 2
BRONCHO - PULMONARY					
Hemoptysis	None	N/A	Positive	See footnote 1	See footnote 2
MUSCOLOSKELETAL & SOFT TISSUE	None	N/A	Spontaneous hematoma; joint bleeding	See footnote 1	Permanent debilitating change; See footnote 2
BODY CAVITY					
Pleural, peritoneal, pericardial, retroperitoneal	None	N/A	Red cell on microscopic exam	Grossly bloody	See footnote 2
CENTRAL NERVOUS SYSTEM					
CNS bleeding / hemorrhage	None	N/A	N/A	Bleeding on CT w/o clinical consequences	Non fatal bleeding with neurological signs and symptoms
Retinal bleeding	None	Retinal bleeding w/o visual impairment	N/A	N/A	Visual impairment, i.e. field deficit
INVASIVE SITES					
All	None	N/A	Any bleeding around catheter; bleeding at venipuncture sites	See footnote 1	See footnote 2

1. Requiring red cell transfusion specifically for support of bleeding within 24 hours of onset. If bleeding is continuous and the onset grading was grade 1 or 2 at onset, increase the severity grade when red cell support is needed
2. Bleeding associated with hemodynamic instability and/or fatal bleeding.

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Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	Short Name	1	2	3	4	5
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding requiring major non-elective intervention	Death
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

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% of Patients with Grade 2 or greater

Study	Grade ≥2	Score
SPRINT control[1]	63.6 %	WHO
SPRINT amatosalen[1]	62.6 %	WHO
SToP low dose[2]	51.7 %	WHO
SToP standard dose[2]	49.2 %	WHO
PLADO low dose[3]	70.0 %	WHO
PLADO medium dose[3]	68.0 %	WHO
PLADO high dose[3]	70.0 %	WHO
HOVON control[4]	19.0 %	CTCAE
HOVON PAS[4]	15.0 %	CTCAE
HOVON amotosalen[4]	32.0 %	CTCAE
IPTAS Intercept [5]	23.0 %	WHO
IPTAS Intercept control[5]	16.5 %	WHO

1. McCullough J, *et al*, Blood 2004;104:1534
2. Heddle NM, *et al*, Blood 2009;113:1564
3. Slichter SJ, *et al*. NEJM 2010;362:600
4. Kerkhoffs JLH, *et al*. Br J Haemat 2010;150:209
5. Rebulla P, *et al*. AABB Anaheim 2015

Asses Clinical Efficacy

- In clinical studies
- In routine practice

Transfusion and Apheresis Science 47 (2012) 271–276

Contents lists available at SciVerse ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Survey of current practice for monitoring and management of platelet refractoriness in Italy

Anna Quaglietta [a,1], Antonio Nicolucci [b,*,1], Patrizia Accorsi [a,1], Alessandra Pompa [a,1], Luca Pierelli [c,1], Antonio Iacone [a,1]

[a] Department of Transfusion Medicine, Pescara Civil Hospital, Pescara, Italy
[b] Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro (CH), Italy
[c] Immunohematology and Blood Transfusion Department Roma Ovest, S. Camillo Forlanini Hospital, Rome, Italy

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 61.8% 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 (over 1000 transfusions/year). In northern and central Italy, the majority of centers had a large volume of activity (51.9% 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 (95.3%) platelet transfusions were performed in both onco-hematological patients and thrombocytopenic patients undergoing surgical procedures, representing 70% and 30% of transfused patients, respectively. In 4.7% of the centers, only onco-hematological patients were transfused.

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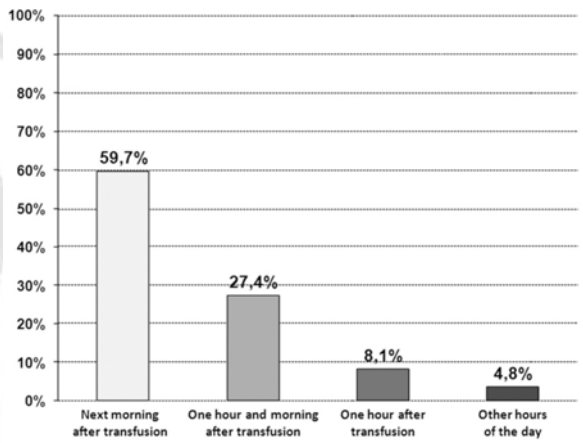
Time of evaluation of post-transfusion platelet values in hospitalized patients



Quaglietta A, et al. Transf Apher Sci 2012; 47:271-6

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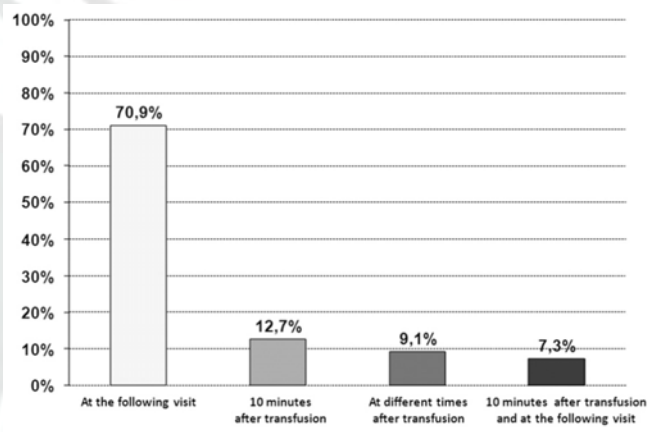
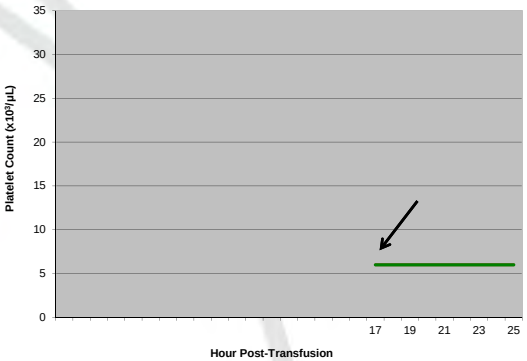
Time of evaluation of post-transfusion platelet values in outpatients



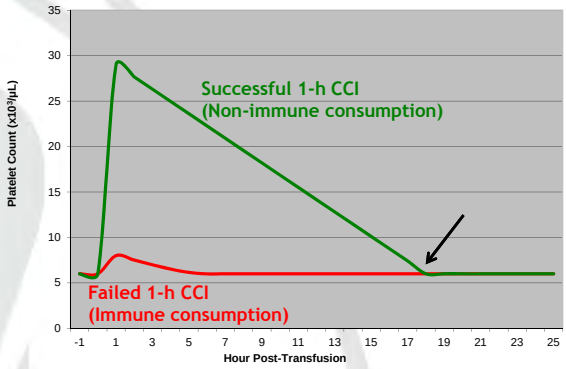
Quaglietta A, et al. Transf Apher Sci 2012; 47:271-6

Response to Platelet Transfusion



Vassallo R, Fung M. Management platelet transfusion refractory patient
In Sweeney JD, Lozano M (eds). Platelet Transfusion Therapy, AABB Press 2013.

Response to Platelet Transfusion



Vassallo R, Fung M. Management platelet transfusion refractory patient
In Sweeney JD, Lozano M (eds). Platelet Transfusion Therapy, AABB Press 2013.

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Failed 1-h CCI

- Product:
  - Poor quality
- Patient
  - Immune destruction of platelets due to antibodies against HLA or HPA
  - Massive splenomegaly
  - Active bleeding

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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

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NHS Blood and Transplant

Platelets: infectious risk, testing strategies, pathogen inactivation

Sheila MacLennan

NHS Blood and Transplant, UK

NHS Blood and Transplant

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

NHS Blood and Transplant

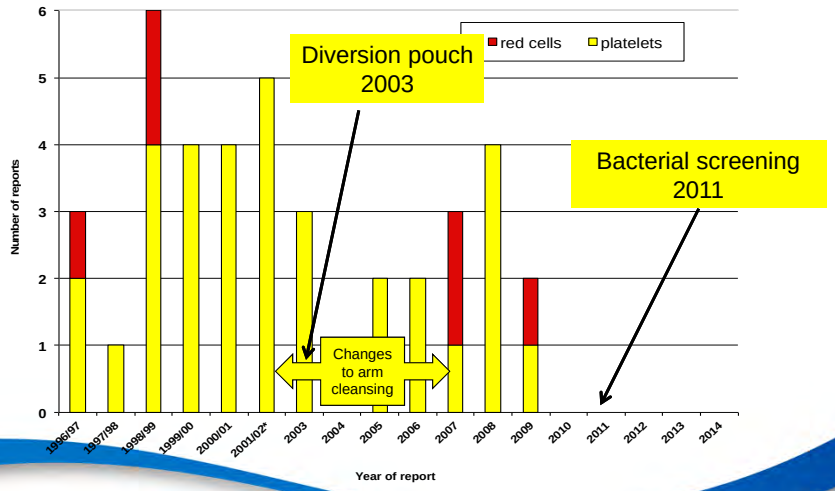
Calculated viral risk from blood transfusion in the UK

	HIV	HBV	HCV	HTLV
1 in x million donations released	6.47	1.32	28.0	17.74

http://www.transfusionguidelines.org.uk/index.aspx?Publication=DL&Section=12&pageid=7630

NHS Blood and Transplant

Bacterial transmissions reported to SHOT 1996-2014



NHS Blood and Transplant

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

NHS Blood and Transplant

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

Safe Supplies: Testing the Nation. Annual Review from the NHSBT/HPA Epidemiology Unit

Age of platelets (days)	1	2	3	4	5	6	NK	**total**
All species	**0**	**2**	**8**	**11**	**12**		**4**	**38**
Staph. epidermidis		1		2	7	1		**11**
Bacillus cereus				4			1	**5**
Escherichia coli		1	1				1	**3**
Group B Streptococcus			1	1			1	**3**
Group G Streptococcus				2	1			**3**
Klebsiella pneumoniae			2	1				**3**
Staph. aureus				1	1		1	**3**

NHS Blood and Transplant

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'

NHS Blood and Transplant

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

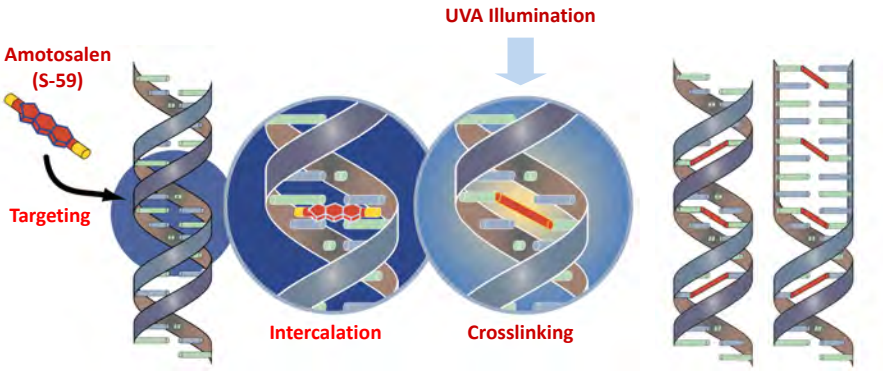
NHSBT process

- 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

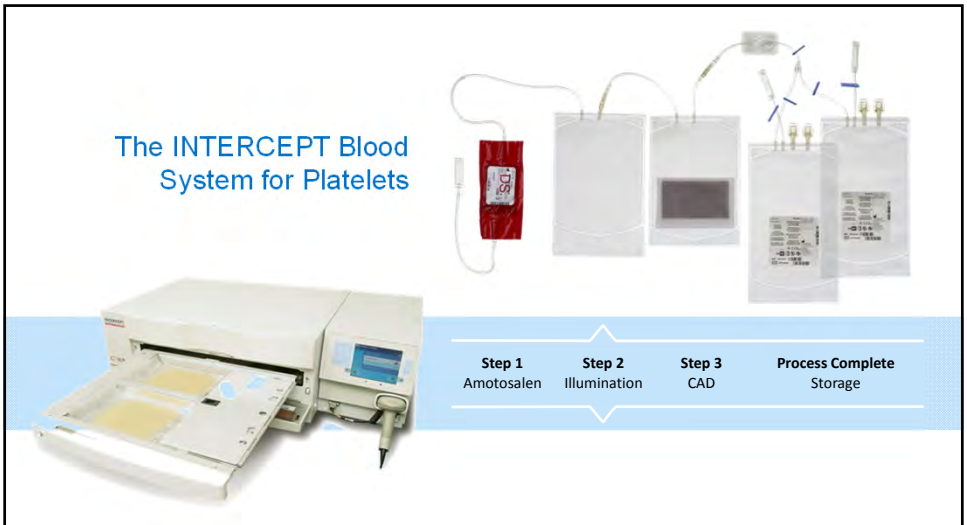
- Exploit the fact pathogens need nucleic acid to replicate but not necessary for platelet, plasma or red cells to function
- Act at the nucleic acid level
- Those in use are based on photodynamic methods: addition of photosensitising chemical followed by exposure to UV light
  - Intercept (UVA + Amotosalen)
  - 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



INTERCEPT Blood System for platelets & plasma

11

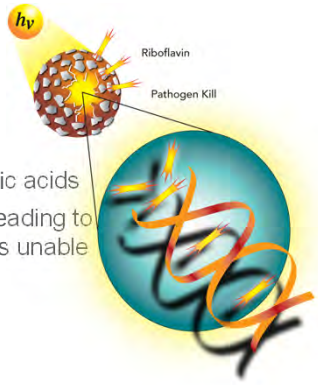


Can treat a single or double-dose in one go (double dose apheresis or pool of 7BC+)

Mechanism of Action - Mirasol

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

Can treat a single or double-dose in one go (double dose apheresis or pool of 7BC+)

Agents inactivated by Amotosalen/UVA

ROUTINELY TESTED AGENTS

ENVELOPED VIRUSES

HIV-1
HIV-2
HBV
HCV
HTVL-I
HTLV-II

SPIROCHETES

Treponema pallidum

ENVELOPED VIRUSES

HIV-1
HIV-2
HBV
HCV
HTVL-I
HTLV-II
BVDV
CMV
WNV
SARS
Vaccinia[1]
Chikungunya
Dengue[2]
Influenza A
DHBV

NON-ENVELOPED VIRUSES

Bluetongue virus, type 11
Simian Adenovirus-15
Feline calicivirus
Parvovirus B19
Human adenovirus 5

GRAM-NEGATIVE BACTERIA

Klebsiella pneumoniae
Yersinia enterocolitica
Escherichia coli
Pseudomonas aeruginosa
Salmonella choleraesuis
Enterobacter cloacae
Serratia marcescens
Anaplasma phogocytophilum
Orientia tsutsugamushi[3]

GRAM-POSITIVE BACTERIA

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

SPIROCHETES

Treponema pallidum
Borrelia burgdorferi

PROTOZOA

Trypanosoma cruzi
Plasmodium falciparum
Leishmania sp.
Babesia microti

LEUKOCYTES

T-cells

15

Mirasol System – Broadly Effective Against Clinically Relevant Pathogens

Effectiveness Demonstrated Against Broad Range of Pathogens

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

- Mirasol has been shown to be more effective than bacterial culture methods (98% vs. 50-70%) in preventing transfusion of contaminated platelet units at clinically relevant contamination levels (<20 CFU / product) Goodrich et al. 2009

NHS Blood and Transplant

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

NHS Blood and Transplant

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

NHS Blood and Transplant

Platelet claims for CE Mark in Europe

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

* contra-indicated in patients with allergy to photosensitiser

NHS Blood and Transplant

PI platelets clinical considerations

	Intercept	Mirasol	Theraflex
Recovery and survival	Reduced by 16-20% d5 plasma	Reduced by 25-27% d5 plasma	Reduced by 26-29% d5 SSP+
Clinical studies	Eurosprite d5 CI SPRINT d5 bleeding HOVON d7 CI TESSI d6-7 CI	MIRACLE d5 CI	None
Allergic reactions	↓Due to PAS?	?	Not known
HV data	Published, no issues raised	Limited	Not in use

NHS Blood and Transplant

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

NHS Blood and Transplant

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

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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 < 10^6 per PC
    - In France, mean efficiency is ~ 1.5 – 2.5 10^5
  - 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)

Foreword_2

- **<u>Antigens expressed on platelets</u>**
  - **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%)

Published Feb.2016

1.4 Critères de choix entre les différents types de produits plaquettaires

Voir aussi le chapitre « néonatologie »

Deux situations imposent le recours au CPA :	
A	Chez les patients porteurs d'anticorps anti-HLA et/ou HPA responsables d'un état réfractaire, il est recommandé de rechercher des donneurs de phénotype HLA et/ou HPA identiques ou proches de celui du patient, afin de transfuser des CPA les plus compatibles possibles. Ces donneurs sont prélevés par aphérèse pour préparer un CPA.
AE	Quand il y une nécessité d'adapter la dose à transfuser, plus particulièrement chez le petit enfant et en néonatalogie, la seule possibilité en accord avec la réglementation est de prendre une fraction d'un CPA.
B	En dehors de ces deux cas spécifiques, il faut considérer aujourd'hui qu'un patient chez qui une transfusion de CP est prescrite pourra recevoir indifféremment un MCP ou un CPA. Il n'y pas d'argument montrant que l'utilisation de MCP soit plus favorable au développement d'une immunisation dans le système HLA que l'utilisation des CPA depuis la généralisation de la déleucocytation. Plusieurs autres critères de choix de produits mentionnés ci-dessous sans hiérarchie seront déterminants pour une bonne efficacité clinique : • la quantité de plaquettes contenue dans le CP ; • la présence dans le CP d'anticorps immuns dirigés contre un antigène du système ABO ; • la compatibilité antigénique dans le groupe sanguin ABO ; • la durée de conservation du CP avant transfusion ; • la concentration en plaquettes du CP en particulier en néonatalogie.

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

<u>BC-PCs and SDA-PCs are considered equivalent</u>

REVIEW

Improving platelet transfusion safety: biomedical and technical considerations

Blood Transfus DOI 10.2450/2015.0042-15

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(Unofficial) 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

Tableau 3 : Cession des PSL en 2014 par type de produit

Type de PSL*		Quantité		Pourcentage
CGR		2 445 524		78,64 %
MCPS	BC-PCs	4 849	PAS	0,16 %
MCPS-SC		141 652		4,56 %
MCPS-IA		14 753	Amotosalen	0,47 %
CPA	SDA-PCs	7 085	PAS	0,23 %
CPA-SC		125 202		4,03 %
CPA-IA		11 923	Amotosalen	0,38 %
PFC-Se		107 850		3,47 %
PFC-IA		111 916		3,60 %
PFC-SD		135 336		4,36 %
PLYO		677		0,02 %
CGA		88		<0,01 %
CGR-AUTO		251		0,01 %
Total PSL		**3 107 106**		**100 %**

Source : EFS et CTSA

Tableau 9 : Nombre et incidence des EIR déclarés d'imputabilité 2 à 3, selon le type de PSL, 2014

Diagnostic	Nombre d'EIR	Taux de déclaration pour 100 000 PSL cédés			
		Tous PSL	CGR	Plasma	Plaquettes
Allo-immunisation isolée	2 368	76,21	87,21	0,84	75,62
Allergie	602	19,37	5,27	32,89	116,54
Réaction fébrile non hémolytique (RFNH)	595	19,15	19,91	0,84	34,37
Oedème pulmonaire de surcharge	185	5,95	7,11	1,12	2,29
Incompatibilité immunologique	184	5,92	3,64	0	31,10
Réaction hypertensive	161	5,18	6,21	0,28	2,62
Inefficacité transfusionnelle	37	1,19	0,12	0	11,13
Hémosidérose	25	0,80	1,02	0	0
Accidents métaboliques	1	0,03	0,04	0	0
Diagnostic non précisé	20	0,64	0,45	0	2,95
Réaction hypotensive	18	0,58	0,57	0	1,31
Diagnostic non listé	11	0,35	0,41	0	0,33
Oedème pulmonaire lésionnel	9	0,29	0,20	0,56	0,65
Hémolyse autre	8	0,26	0,29	0	0,33
Dyspnée non liée à un oedème pulmonaire	6	0,19	0,12	0	0,98
Infection virale	6	0,19	0,04	0	1,64
Hémolyse drépanocytaire	5	0,16	0,20	0	0
Infection bactérienne	5	0,16	0,12	0	0,65
Total	**4246**	**136,65**	**132,96**	**36,54**	**282,52**

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

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

Gravité	Famille de PSL			Total	
	CGR	Plaquettes	Plasma	Effectif	%
Grade 1	2 129	229	3	2 361	99,7 %
Grade 2	5	2	0	7	0,3 %
Total	**2 134**	**231**	**3**	**2 368**	**100 %**
Taux pour 100 000 unités cédées	**87,8**	**76**	**0,8**	**73,9**	

RBCCs PCs

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

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

Type d'anticorps	Effectif	%
Anti-érythrocytaire	2 341	98,86 %
Dont érythrocytaire – ABO	2	0,08 %
Dont érythrocytaire - non ABO	2 334	98,56 %
Dont érythrocytaire non précisé ou non listé	5	0,21 %
Anti-HLA	24	1,01 %
Anti-plaquettaires	1	0,04 %
Non renseigné	2	0,08 %
Total	**2 368**	**100 %**

anti-HLA/HPA → infrequent as opposed to RBC Ags

Tableau 14 : Répartition des anticorps anti-érythrocytaires non ABO dans l'allo-immunisation isolée déclarée d'imputabilité 2 à 3, 2014

Anticorps anti-érythrocytaire non ABO	Effectif	%
JK1	443	18,98 %
RH3	400	17,14 %
KEL1	355	15,21 %
FY1	257	11,01 %
RH1	139	5,96 %
LU1	113	4,84 %
MNS3	109	4,67 %
JK2	92	3,94 %
RH4	86	3,68 %
KEL3	82	3,51 %
RH2	80	3,43 %
RH8	43	1,84 %
MNS1	36	1,54 %
RH5	20	0,86 %
FY2	15	0,64 %
CH/RG1	10	0,43 %
LE1	10	0,43 %
MNS4	10	0,43 %
P1	6	0,26 %
YT2	5	0,21 %
KEL2	3	0,13 %
KN1	3	0,13 %
MNS2	3	0,13 %
YT1	3	0,13 %
DI3	2	0,09 %
FY3	2	0,09 %
LE2	2	0,09 %
RH6	2	0,09 %
CO1	1	0,04 %
LU2	1	0,04 %
Vel	1	0,04 %
Total	**2 334**	**100 %**

Classical distribution of Abs to RBC AgH:1 prevention policy in force

Tableau 15 : Répartition des anticorps non anti-érythrocytaires dans l'allo-immunisation isolée déclarée d'imputabilité 2 à 3, 2014

Anticorps non anti-érythrocytaire	Effectif	%
HLA classe I	17	68,00 %
HLA Cw1	2	8,00 %
HLA non précise	2	8,00 %
HLA A2	1	4,00 %
HLA classe II	1	4,00 %
HLA DR14(6)	1	4,00 %
Plaquettes non listé	1	4,00 %
Total	**25**	**100 %**

anti-class I → can originate from either Platelets or residual LKs

3_Mechanisms for allo-immunization and main hypotheses

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)

The bases in immunology

1) Introduction of foreign cells harbouring foreign antigens
2) Detection of danger by the recipient's innate immune system
3) Innate defense (inflammation)
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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*

1) Introduction of foreign cells harbouring foreign antigens

2) Detection of danger by the recipient's

3)

4) E
ar

5) Re

6)
lyr

7) B-

8) Memory initiation (T- B-cell)

Primary of secondary (treatment induced-) immune deficiency can interfere

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

RBCs:

1) Transfusion, pr

2) Functional innate im

3) Capacity in mounting an in

4) Dendritic cells or memory B-cells present (residual leukocytes); "good' presenters (HLA class II selected)

5) Selection in the T-cell reper

6) Functional T-cell adaptive im

7) Functional B-cell adaptive im

8) Same as 5,6,7

Table 1. Associations between HLA and the alloimmunization against various red cell antigens

RBC alloimmunization: anti-	Associated HLA	Population	Peptide binding prediction	Reference
D	DRB1*15	Caucasoid	yes	Quoted by Hall et al. 2005 [64]
D	DRB1*06	Caucasoid	no	Darke et al. 1983 [65]
D	DRB1*06	Caucasoid	no	Wojtulewicz-Kurkus et al. 1981 [66]
D – high titer	DQB1*02:01	Caucasoid	no	Hilden et al. 1995 [67]
D – high titer	DRB1*15	Caucasoid	no	Verhagen et al. 2013 [68]
D	Nil	Caucasoid	no	Hors et al. 1974 [69]
D	Nil	Caucasoid	no	Petranyi et al. 1975 [70]
D	Nil (with corrected p)	Indian	no	Kumar et al. 2002 [71]
E	DRB1*09	Oriental	no	Lin et al. 2014 [72]
K	DRB1*11, DRB1*13	Caucasoid	yes	Chiaroni et al. 2006 [73]
K	DRB1*13	Caucasoid	yes	Noizat-Pirenne et al. 2006 [74]
Fy^a	DRB1*04	Caucasoid	yes	Noizat-Pirenne et al. 2006 [74]
Fy^a	DRB1*04	Caucasoid	no	Raos et al. 2014 [75]
Jk^a	DRB1*01	Caucasoid	yes	Ansart-Pirenne et al. 2004 [76]
Jk^a	DRB1*07:01	Caucasoid	yes	Reviron et al. 2005 [77]
S	DRB1*07	Caucasoid	no	Schonewille et al. 2014 [33]
Mi^a	DRB1*09:01	Oriental	yes	Chu et al. 2009 [78]
Di^a	DRB1*07:01	Brazilian	yes	Balcotti Jr et al. 2014 [79]

Transfusion Medicine and Hemotherapy

Review Article

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Responder Individuality in Red Blood Cell Alloimmunization

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

A couple of recent reviews—among several—on the benefits of LKD, with focus on allo-immunization

REVIEW

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

Blood Transfus DOI 10.2450/2015.0154-15

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Netherlands The Journal of Medicine

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441

REVIEW

Clinical effects of leucoreduction of blood transfusions

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

Simancas-Racines D[1], Osorio D, Martí-Carvajal AJ, Arevalo-Rodriguez I.

Author information

Abstract

BACKGROUND: 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 infectious and non-infectious complications remain unclear.

OBJECTIVES: To determine the clinical effectiveness of leukoreduction of packed red blood cells for preventing adverse reactions following allogeneic blood transfusion.

SEARCH METHODS: 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.

SELECTION CRITERIA: 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.

DATA COLLECTION AND ANALYSIS: 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 I^2 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.

MAIN RESULTS: 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, I^2 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, I^2 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, I^2 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.

AUTHORS' CONCLUSIONS: 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]

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-idiotype antibodies that are tolerogenic

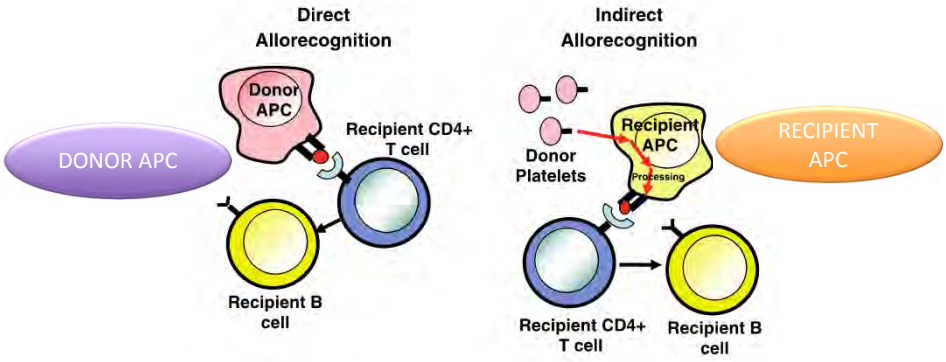

Figure 2 Models of direct and indirect allorecognition that can lead to platelet alloimmunization (25–27). Direct allorecognition occurs when the T-cell receptor (TcR) of recipient CD4+ T cells directly interact with major histocompatibility complex (MHC) class II molecules on donor antigen presenting cells (APC). This leads to T-cell activation and help for B cell differentiation into plasma cells and production of anti-MHC 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

Allo-Immunization to HLA (± HPA) moieties

→ *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.*)

TISSUE ANTIGENS
IMMUNE RESPONSE GENETICS
Tissue Antigens ISSN 0001-2815

REVIEW ARTICLE

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

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Tissue Antigens, 2012, **79**, 237–245

Figure 1 Etiology of refractoriness to platelet transfusions.

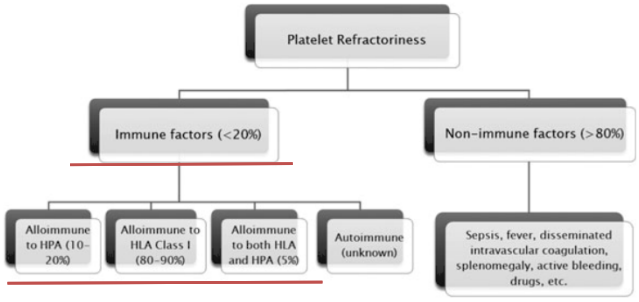

Table 2 Summary of results of the TRAP)

Non Leukoreduced →	Controls: untreated pooled random donor platelets	Leukoreduced pooled random donor platelets	Leukoreduced single-donor apheresis platelets
Number of patients	131	137	132
Alloimmunization	45%	18% ($P < 0.001$)*	17% ($P < 0.001$)*
Refractoriness	16%	7% ($P = 0.03$)*	8% ($P = 0.06$)*
Alloimmunization and refractoriness	13%	3% ($P = 0.004$)*	4% ($P = 0.01$)*

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

The Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *N Engl J Med* 1997: **337**: 1861–9.

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

Aurélien Daurat,[1] Claire Roger,[1] JeanChristophe Gris,[2] Gérald Daurat,[3] Michel Feissel,[4] Yannick Le Manach,[5] JeanYves Lefrant,[1] and Laurent Muller[1]

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TRANSFUSION 2016;00;00–00

TABLE 3. Comparison of recipient adverse reactions after PLT transfusion between APCs and PPCs

	APCs (n = 477,747)		PPCs (n = 313,107)		
Adverse reactions	Number of adverse reactions	Rate/10^6	Number of adverse reactions	Rate/10^6	p value
Overall reported	2983	6244	773	2469	<0.001
Severity grade*					
Grade 1 (mild)	2774	5806	692	2210	<0.001
Serious reactions	209	437	81	259	<0.001
Grade 2	115	241	41	131	<0.001
Grade 3	87	182	38	121	0.04
Grade 4 (death)	7	15	2	6	0.50
Imputability level					
Possible (1)	1059	2217	376	1201	<0.001
Probable (2) or c	1924	4027	397	3127	<0.001
Type of adverse rea					
Allergic transfusion reaction	1917	4013	310	990	<0.001
FNHTR	453	948	207	661	<0.001
Transfusion reaction with alloantibody (HLA or HPA)	230	481	110	351	0.007
PLT transfusion refractoriness	80	167	29	93	0.006
TACO	34	71	13	42	0.1
TRALI	25	52	9	29	0.16
Transfusion-transr	13	27	8	26	0.99
Hypotensive	7	15	10	32	0.14
Posttransfusion p	4	8	0	0	0.16
Miscellaneous	220	460	77	246	<0.001

* Severity grades: G … e 3, immediate life threat; Grade 4, death; serious adverse reaction, adverse reaction from Gra…
FNHTR = febrile nc… sfusion acute circulatory overload.

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

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

- Hypothesis: Pre-storage??
  - SDA-PCs are sometimes LKD “in process” by the cell separator → no need to re-filter the component, not with the TRIMA™ 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

4_Published works (allo-immunization to RBC antigens)

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

Gravité	Famille de PSL			Total	
	CGR	Plaquettes	Plasma	Effectif	%
Grade 1	2 129	229	3	2 361	99,7 %
Grade 2	5	2	0	7	0,3 %
Total	**2 134**	**231**	**3**	**2 368**	**100 %**
Taux pour 100 000 unités cédées	**87,8**	**76**	**0,8**	**73,9**	

RBCCs PCs

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

bjh research paper

Low frequency of anti-D alloimmunization following D+ platelet transfusion: the Anti-D Alloimmunization after D-incompatible Platelet Transfusions (ADAPT) study

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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 d 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 d (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, RhIG.

British Journal of Haematology, 2015, 168, 598–603

Table III. Demographic and clinical information of the primary allo-immunized recipients *versus* all other recipients in this study.

Parameter	Primary anti-D formers	All other recipients	*P* value
Number of recipients (%)	7 (1·4)	478 (98·6)	NC
Gender (Male/Female)	4/3	299/179	0·2
Median age (range), years	60 (2–100)	65 (39–85)	0·2
ABO group (O/A/B/AB)	3/3/1/0	206/212/43/17	0·9
Main diagnosis (haematology-oncology/others)	3/4	264/214	0·5
Iatrogenic immunosuppression (yes/no/unknown)	3/3/1	197/177/104	0·9
History of pregnancy (yes/no)*	2/0	55/12	0·5
Patient location: Europe/Americas	2/5	222/256	0·6
Previous RBC transfusion (yes/no)	6/1	217/261	0·08
Previous PC transfusion (yes/no)	2/5	94/384	0·9
Transfused PCs (whole blood/apheresis/both)	2/4/1	179/288/71	0·8
Median length of serological follow-up (range), days	216 (32–368)	75 (28–2111)	0·09

RBC, red blood cell; PC, platelet concentrate; NC, Not calculated.
*For those whose pregnancy history was known.

Table II. Type and quantity of the platelets transfused to the 485 recipients in this study.

Platelet product type	D+ (*n*)	D− (*n*)	Total (*n*)
Whole blood-derived platelets	1180	1505	2685
Apheresis platelets	1970	694	2664
Total number	3150	2199	5349

Table IV. 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.

Parameter	Primary anti-D formers	All other recipients	*P* value
Recipients, *n* (% of total)	7 (1·4)	478 (98·6)	NC
D+ PC	2 (1–31)	2 (1–115)	0·9
D− PC	0 (0–14)	0 (0–127)	0·5
Total PC	2 (1–37)	3 (1–157)	0·5

PC, platelet concentrate; NC, Not calculated.

Disponible en ligne sur ScienceDirect www.sciencedirect.com
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Mise au point

Transfusion plaquettaire et iso-immunisation anti-Rh1 : intérêt de la séroprévention

Platelet transfusion and immunization anti-Rh1: Implication for immunoprophylaxis

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Disponible sur Internet le 2 octobre 2014

Tableau 1
Risque d'allo-immunisation plaquettaire anti-D en l'absence de séroprévention selon le terrain et la durée de suivi. La durée de suivi correspond au temps écoulé entre la première exposition transfusionnelle à des plaquettes Rh1 et le dernier dépistage sérologique à la recherche d'anticorps anti-Rhésus.

Référence	Taux d'anti-D Cas/patients (%)	Terrain, contexte	*n* semaines de suivi Médiane (extrêmes)
Goldfinger et al., 1971 [23]	8/102 (7,8)	Traitement immunosuppresseur	36 (2–174)
Baldwin et al., 1988 [24]	9/49 (18,4)	Immunodépression, oncologie	27 (2–182)
McLeod et al., 1990 [16]	3/16 (18,7)	Immunodépression	3 (2–12)
Heim et al., 1992 [30][a]	0/37 (0)	Immunodépression	27 (4–104)
Atoyebi et al., 2000 [15]	0/24 (0)	Hématologie	8 (2–76)
	8/59 (13,6)	Maladies non hématologiques	38 (2–133)
Molnar et al., 2002 [19]	0/35 (0) (490 transfusions)	Onco-hématologie pédiatrique hors greffe	27 (2–223)
	0/7 (0) (255 transfusions)	Greffes de CSH pédiatriques	8 (6–11)
Cid et al., 2002 [21]	0/22 (0)	Hématologie (chimiothérapie +++)	8 (1–37)
Cid et al., 2011 [17]	6/177 (3,4)	Hématologie	24 (4–351)
	4/31 (12,9)	Oncologie	54 (5–375)
	2/107 (1,9)	Pas d'immunodépression	59 (4–718)
O'Brian et al., 2014 [25]	0/62 (0)	Immunodépression	? (4–?)
	0/68 (0)	Pas d'immunodépression	

CSH : cellules souches hématopoïétiques.
[a] Dans cette étude, les patients ont reçu des immunoglobulines anti-Rhésus.

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LETTER TO THE EDITOR

Red blood cell alloimmunisation after platelet transfusion: a 5-year study

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

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

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 five 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.

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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 that 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

BC-PC ↘

	Whole Blood Buffy Coat derived Platelet Components				Single Donor Apheresis Platelet Components			
Period	# of PCs issued	# of anti-erythrocyte antigen allo-immunisations recorded	Incriminated antigens		# of PCs issued	# of anti-erythrocyte antigen allo-immunisations recorded	Incriminated antigens	Cell separators used
2010	4494	6	RH:1 (x2); RH:3 (x3); LU:1		5418	0		
2011	4747	5	RH:3 (x3); MNS:3		5010	0		
2012	5501	8	RH:1 (x4); RH:3; RH:1+RH:3; KEL:3; LU:1		5298	2	RH:3 (x2)	TRIMA* (x2)
2013	6257	4	RH:1; RH:3; RH:1+KEL:1; JK:1		5596	4	RH:1 (x2); RH:3 (x2)	TRIMA** (x4)
2014	6200	2	RH:4; RH:3+RH:4		5681	4	RH:1; RH:2; RH:3; RH:4	TRIMA*** (x2); AMICUS (x2).
Total	27,199				27,003			

SDA-PC ↗

P=0.015

*: TRIMA was the only one cell separator used in 2012

**: >90% of APCs were collected with TRIMA separators in 2013 (and none with AMICUS)

***: >80% 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)??
- ??

mise normal hemostasis in the recipient.[1] In centers that have adopted the policy of only issuing ABO-identical PLTs and cryoprecipitate, statistically and clinically significant reductions in febrile and allergic reactions and RBC alloimmunization have been reported.[7,8] In contrast, in a secondary analysis of the PLT dose (PLADO) trial, a large randomized, prospective study in hematology-oncology patients, the clinical complications including risk of severe bleeding as well as febrile and allergic reactions were not increased in recipients of ABO major-mismatched PLT units despite lower PLT count increments in this patient group compared to those who had received ABO-identical units or ABO minor-mismatched PLT transfusions.[9,10] Despite these conflicting data regarding the detrimental effects of ABO-mismatched PLT transfusions, this study would have further benefited if receipt of PLT transfusions as well as their ABO status was also included as a confounder in the analysis.

Red blood cell non–ABO-identical transfusions are harmful: *really*?

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ABO identity vs compatibility may reduce allo-immunization (along to the increase of platelet recovery) → this information should be examined in more detail

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 te 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
  - Marschner S, Fast LD, Baldwin WM III, Slichter SJ, Goodrich RP. White blood cell inactivation after treatment with riboflavin and ultraviolet light. *Transfusion* 2010: **50**: 2489–98
  - What about actual reduction of allo-immunization in patients receiving PRT PCs (difficut to ascertain as those events are quite infrequent)
    - But?

Any question?

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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

Availability of platelet concentrates in Europe

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, CD-P-TS 2015: The collection, testing and use of Blood and Blood Components in Europe, 2012
- 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

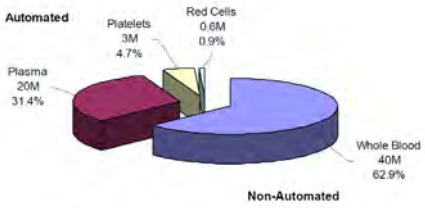
EDQM Guide Blood Components – Platelet component monographs

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



Worldwide annual blood collection by component

Automated versus Non-automated collection processes

Region	Units of RBCs (in millions)
United States	15
Europe	22
Japan	12
ROW	36
Total	85

Geographical distribution of RBC demand by region, 2007

Blood loss segment	Units RBCs (in millions)
Acute Blood loss	50
Chronic Blood loss	35
Total	85

Worldwide demand for RBC for acute and chronic conditions, 2007

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			Utilization for transfusion			
	Total Donors	Donors/1000 inhabitants	WB donations (U)	Use of WB (U)	Use of RBC (U)	Use of Plasma (U)	Use of Platelets (U)
Austria	334,066	28.17	472,206	301	425,537	74,420	37,245
Belgium	365,813	33.7	549,266	0	516,035	92,761	69,328
Bulgaria	119,110	16.2	162,658[a]	1,654	183,120	93,666	6,606
Cyprus*	48,544	63.3	49,294	0	44,283	15,735	11,167
Czech Republic	376,176	36.4	440,700	393	389,521	201,220	31,866
Denmark	255,231	45.9	337,000	0	316,733	66,110	33,907
Estonia	44,805	33.4	58,729	19	51,586	27,196	6,086
Finland	154,602	28.6	265,592	314	249,922	53,512	43,023
France	2,125,786	32.7	2,483,577	0	2,378,241	382,449	278,097
Germany	3,074,037	37.6	4,940,257	5,657	4,694,567	1,216,153	496,281
Greece	533,015	50.8	613,275	49	615,692	201,909	133,375
Hungary	322,735	32.3	418,794	0[b]	361,151[b]	93,987[b]	14,259[b]
Ireland	96,737	21.1	151,894	0	140,037	23,612	24,431
Italy	1,722,503	28.5	2,694,871	3,025	2,522,355	395,602	205,791
Latvia	50,361	25.2	55,702	0	52,017	36,758	6,131
Lithuania	72,663	22.1	68,324	25	79,012	29,682	11,020
Luxembourg*	10,367	21	22,105	0	20,272	4,410	2,315
Malta	12,339	29.5	14,548	0	14,051	6,161	1,609
Poland	203,461	18.4	1,179,668[a]	610[a]	1,095,838[a]	369,474[a]	93,184[a]
Portugal	293,571	27.8	414,268	116	336,421	10,990	66,428
Romania	480,150	25.3	400,285	109,597	396,490	249,245	22,664
Slovakia	120,319	22.2	205,246	957	186,978	87,690	16,023
Slovenia	110,497[a]	53.9[a]	95,601[a]	0	87,451[a]	29,879[a]	10,944[a]
Spain	1,133,040	24.7	1,740,091	140	1,618,419	200,583	192,332
Sweden	245,289	26.1	493,439	0	488,373	89,064	42,817
The Netherlands	352,083	21.1	542,160	619	548,793	81,742	56,165
United Kingdom	1,566,463	25.1	2,305,482	16	2,182,950	303,377	287,027
Total	14,664,952	29.38	21,175,032	123,492	19,995,845	4,437,387	2,200,121

*Austria and Luxembourg: data are for 2009; Cyprus data are for 2008

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

adapted from EDQM reports

[a] Data provided by Competent Authority

[b] 2009 data

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

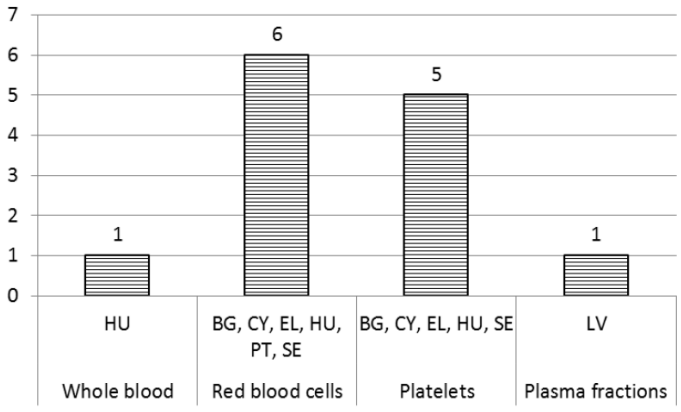
Collection of blood components across the EU (2012)

adapted from Implementation Survey 2013

	Number of Whole blood donations	WB collections/1000 inh	Number of Platelets Donations by Apheresis	Platelets apheresis Donations/1000 inh	Other donations by apheresis
Austria	-	-	-	-	-
Belgium	538.336	48,5	13.471	1,2	6.078
Bulgaria	167.851	22,9	2.714	0,4	
Croatia	179.305	41,9	2.646	0,6	118
Cyprus	57.847	67,1	272	0,3	261
Czech Republic	418.954	39,8	18.271(a)	1,7	
Denmark	293.765	52,6	1.232	0,2	
Estonia	5.812	4,4	105	0,1	804
Finland	246.434	45,6	483	0,1	
France	2.641.930	40,5	131.875	2,0	32.643(i)
Germany	4.785.048	59,6	196.106	2,4	35.245(b)
Greece	400.002(c)	35,9	18.123	1,6	
Hungary	425.637	42,9	3.573	0,4	825
Ireland	138.099	30,1	12.023	2,6	
Italy	2.683.127	45,2	80.051	1,3	26.147
Liechtenstein	5	0,1	0	0,0	
Latvia	5.559	2,7	3.461	1,7	
Lithuania	79.367	26,4	1.049	0,3	2.221(d)
Luxembourg	20.631	39,3	679	1,3	
Malta	16.995	40,7	469	1,1	
The Netherlands	498.117	29,8	4.723	0,3	
Norway	198.584	39,8	51.000	10,2	4.654
Poland	1.173.050	30,4	34.133	0,9	600(e)
Portugal	387.222	36,7	4.568	0,4	346
Romania	399.848	19,9	6.830	0,3	1.037(f)
Slovakia	203.825	37,7	6.257	1,2	
Slovenia	93.099	45,3	2.343	1,1	125(g)
Spain	1.702.768	36,4	7.880	0,2	24.728(f)
Sweden	484.755	50,7	0	0,0	
United Kingdom	2.256.736	35,3	148.012	2,3	0
Total	**20.502.708**	-	**752.349**	-	**135.832**

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

Creative Ceutical Report 2015 // European Commission Implementation report 2016



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 3
Survey 2012

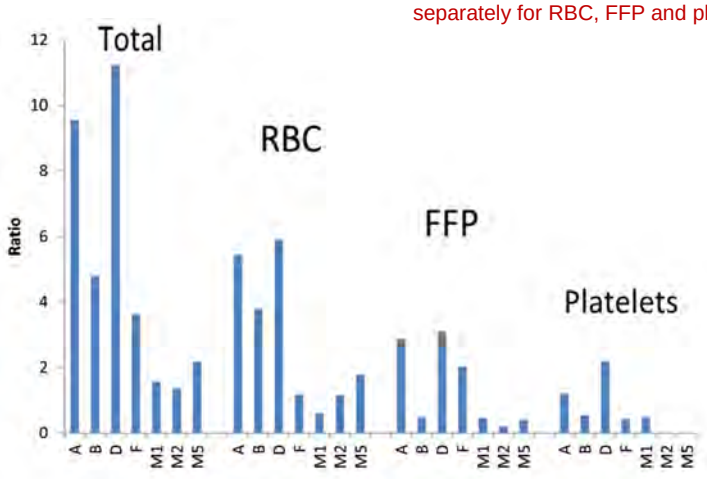
Use of blood and blood components for transfusion

Country	Transfused or distributed	whole blood (U)	% whole blood of total RBCs	red blood cell concentrates (U)	r.b.c. (U) per 1,000 inhabitants	plasma for transfusion (U)	platelets total (U)	platelets recovered (U)	platelets apheresis (U)	% platelets by apheresis	cryoprecipitate 10^4 IU FVIII)
Albania											
Andorra											
Armenia	Trans.	0	0,0	11 294	3,8	11 087	2 159	2 127	32	1,5	710
Austria											
Azerbaijan											
Belgium	Trans.	0	0,0	491 774	44,3	89 053	68 668	33 064	35 604	51,8	0
Bosnia / Herzegovina											
Bulgaria											
Croatia	Distr.	321	0,2	177 061	41,3	91 593	21 969	19 169	2 800	12,7	1
Cyprus											
Czech Republic	Trans.	654	0,2	393 804	37,4	187 000	37 100	9 200	27 900	75,2	
Denmark	Trans.	0	0,0	277 960	49,6	60 692	33 631	32 001	1 630	4,8	1
Estonia	Trans.	46	0,1	55 162	41,7	25 993	6 985	5 712	1 273	18,2	873
Finland	Distr.	0	0,0	229 090	42,2	49 429	41 565	41 085	480	1,2	0
France	Distr.	0	0,0	2 517 097	38,4	387 976	300 683	154 955	145 728	48,5	0
FYR Macedonia											
Georgia	Trans.										
Germany	Distr.	3 590	0,1	4 633 911	57,5	1 571 068	589 179	226 457	362 722	61,6	0
Greece	Distr.	0	0,0	413 568	39,4	193 872	129 807	115 897	13 910	10,7	0
Hungary	Distr.	0	0,0	414 755	43,1	97 219	47 695	44 645	3 050	6,4	0
Iceland	Distr.	0	0,0	11 538	35,8	3 284	2 330	732	1 598	68,6	0
Ireland	Distr.	0	0,0	135 357	29,4	21 240	24 971	5 117	19 854	79,5	197
Italy	Trans.	1 469	0,1	2 564 093	43,2	432 884	219 785	146 334	73 451	33,4	2 950
Latvia	Distr.	0	0,0	51	0,0	35	7 681	7 677	4	0,1	7
Liechtenstein											
Lithuania	Trans.	0	0,0	87 402	29,3	31 154	19 002	8 586	10 416	54,8	
Luxembourg	Distr.	0	0,0	19 889	37,0	4 100	2 765	1 904	861	31,1	0
Malta											
Moldova	Distr.	160	0,4	39 100	11,5	63 041	8 399				13 160
Montenegro	Trans.	3 990	26,2	15 250	24,4	10 298	509	509	0	0,0	544
Netherlands	Distr.	363	0,1	453 623	27,1	67 907	57 720	52 416	5 302	9,2	0
Norway	Trans.	132	0,1	191 431	37,8	49 732	24 508	16 911	7 597	31,0	
Poland											
Portugal	Trans.	133	0,0	341 976	32,6	6 578	39 942				
Romania											
Russian Federation	Distr.	1 335	0,1	1 669 907	11,7	1 907 368	148 684				
San Marino											
Serbia											
Slovakia	Distr.	420	0,2	189 865	35,1	86 679	15 033	2 748	12 285	81,7	0
Slovenia											
Spain	Trans.	95	0,0	1 553 720	33,8	198 521	188 510	158 356	30 154	16,0	1 557
Sweden	Trans.			460 837	48,2	182 093	46 523	40 788	7 735	15,9	
Switzerland	Distr.			297 588	37,2	49 832	34 265	11 526	22 739	66,4	
Turkey											
Ukraine											
United Kingdom	Distr.	2	0,0	2 102 521	33,0	286 402	310 426	43 333	267 093	86,0	196 559

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

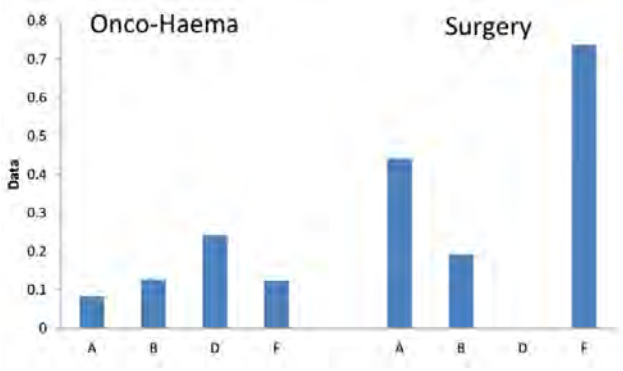


EDQM, Richardson C, 2014

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

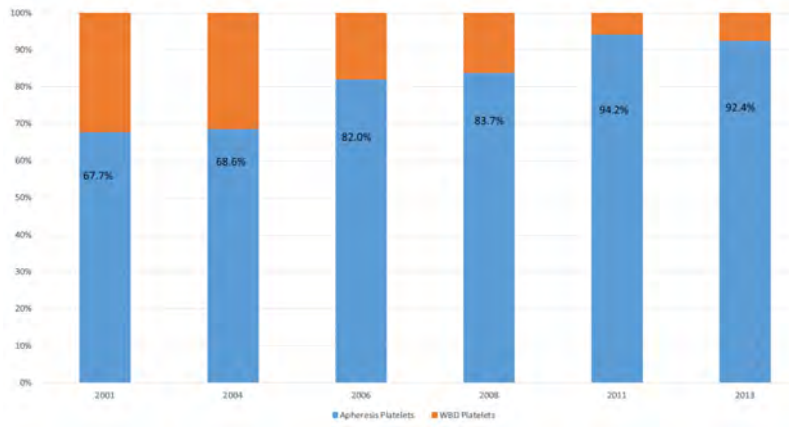
Estimated 2013 Collection and Transfusion by AABB US Member Blood Centers and Hospitals for Non-RBC-Components (expressed in thousands of units)

	Blood Centers	Hospitals	2013 Combined Total	±95% CI	2011 Total	% Change 2011-2013	p-value
Collection/Production							
Apheresis Platelets Collected and Produced	2,112	114	2,226	55	2,283	–2.5	0.078
Apheresis Platelets Distributed for Transfusion	1,908	94	2,002*	50	2,090	–4.2	0.015
WB-Derived Platelets Concentrates Distributed†	154	9	164(819)*	9	129(643)	27.1	<0.0001
Total Platelets Distributed for Transfusion	2,062	103	2,166	51	2,219	–2.4	0.249
Plasma Collected or Produced	3,995	283	4,278*	118	5,784	–26.0	<0.0001
Plasma Distributed for Transfusion	3,286	201	3,488*	76	4,495	–22.4	<0.0001
Cryoprecipitate Distributed for Transfusion‡	1,218	117	1,335*	70	867	54.0	<0.0001
Transfusions							
Apheresis Platelets	0	1,143	1,143	104	1,019	12.2	0.112
WB-Derived Platelets Concentrates†	0	167	167(835)	53	116 (581)	30.7	0.142
Total Platelets Transfused	0	1,310	1,310*	121	1,135	15.4	0.0423
Plasma	1	1,796	1,797*	129	1,995	–9.9	0.036
Cryoprecipitate‡	0	1,054	1,054*	132	634	66.2	<0.0001

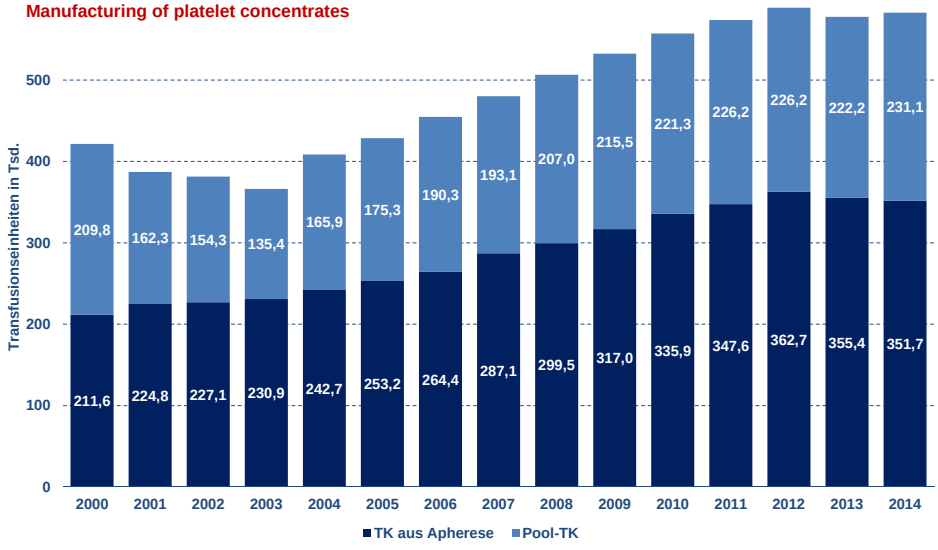
*Significantly different from 2011 data.
†Apheresis equivalent units; numbers in parenthesis represent individual platelet concentrates produced from whole blood donations.
‡Includes individual units and pools expressed as individual units using weighted average units per pool as reported by the responding facilities.

AABB Blood survey report 2013

Apheresis platelets as percent of total platelets produced.

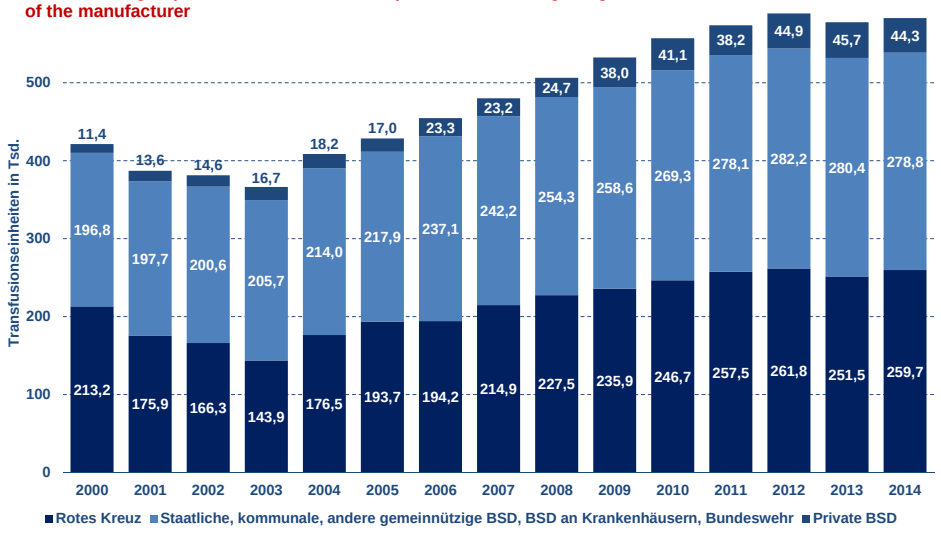


German data according to Transfusion Law §21, 2014



German data according to Transfusion Law §21, 2014

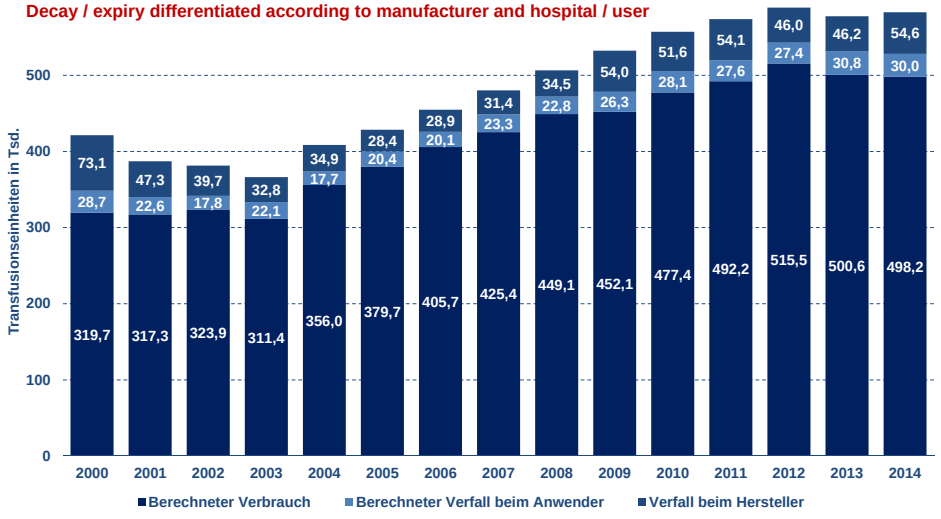
Manufacturing of platelet concentrates in dependence of the legal organizational status of the manufacturer



German data according to Transfusion Law §21, 2014

Use and decay / expiry of platelet concentrates

Decay / expiry differentiated according to manufacturer and hospital / user



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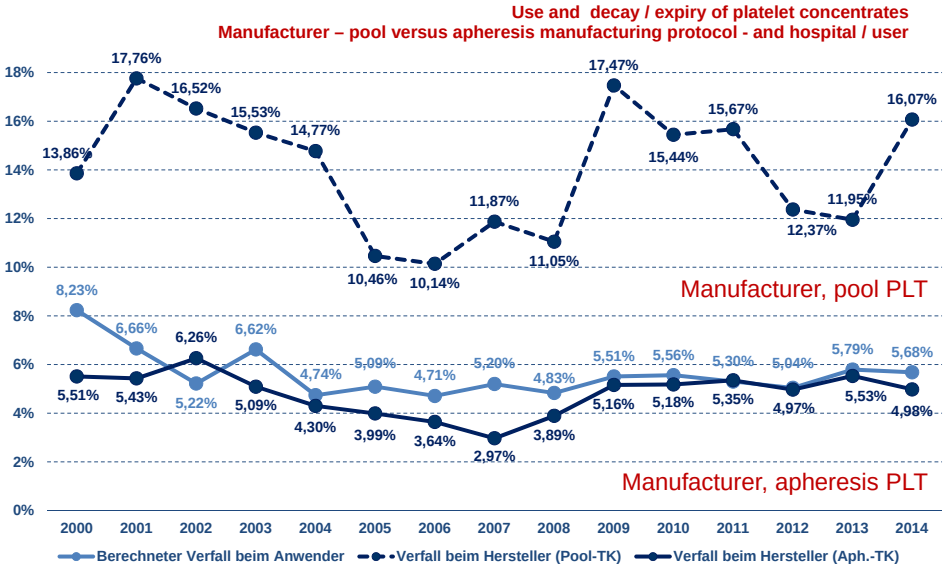

Availability of platelet concentrates in Europe – Summary.1

- Platelets“ - Do we exactly know what we are talking about?
  - Wide variety of manufacturing processes.
- Data on manufacturing and use of patelets 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 maufacturing 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 interdependenies 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 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, …).
- ….

Knowledge gaps as evident from consideration of available data

Platelet manufacturing processes

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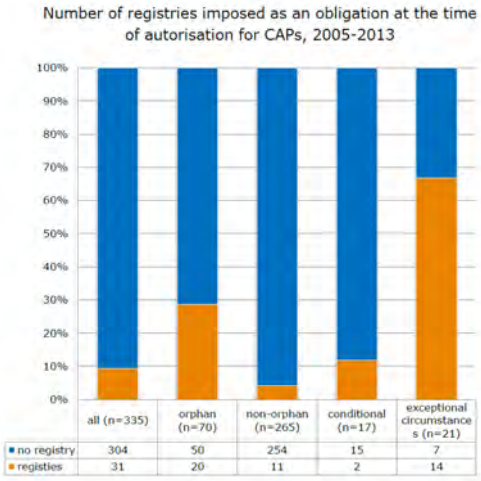
- ….

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



Registries characteristics	N	%
Disease registry	11	35%
Product registry	20	65%
New registry	24	77%
Existing registry	6	19%
Both (combination of new and existing)	1	3%

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

Daurat A et al., Transfusion. 2016 Jan 26. doi: 10.1111/trf.13475 [Epub ahead of print]

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, $p < 0.001$).

Linking data with a broader scientific context

Systems biology approach, systems medicine approach

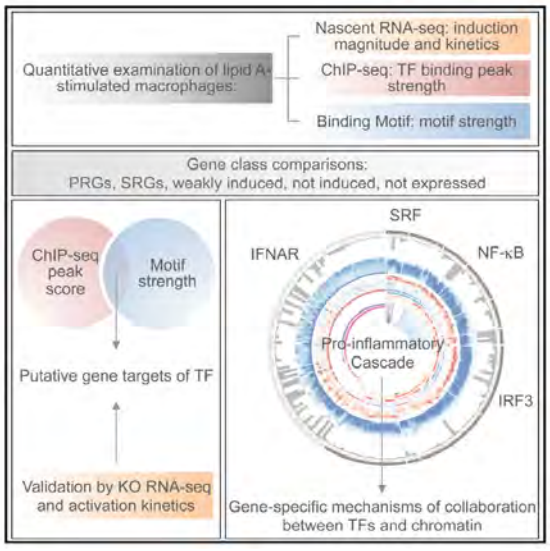
Blocking neutrophil diapedesis prevents hemorrhag during thrombocytopenia

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 $G\alpha_i$ 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.

Linking data with a broader scientific context

Systems biology approach, systems medicine approach – The proinflammatory context



A stringent systems approach uncovers gene-specific mecanisms 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 6121 citations identified by our literature search, 59 studies met our eligibility criteria (50 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 that 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 alloimmunization, n = 9), presence of antileukocyte antibodies (OR 5.84 [1.66, 20.59] for risk of transfusion-related acute lung injury, n = 4), and donor RBC antigens selection (OR 0.20 [0.08, 0.52] for risk of alloimmunization, n = 4). Based on poor quality evidence, positive antileukocyte 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 vein-to-vein data infrastructure to allow for large robust evaluations. PROSPERO registration number: CRD42013006726.

Linking data with infrastructural data of healthcare provision

Micro- / macroenvironment – Health analytics

Hematopoietic stem cell transplantation

Gratwohl A et al., JAMA 2010; 303 : 1617 – 1624; Niederwieser D et al., Bone Marrow Transplant 2016, 1–8; Gratwohl 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, systematic, 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

		Haematology / Oncology Unit	Internal Medicine Emergency Care	Clinic for General Surgery
Number of cases / patients		**150**	**356**	**179**
Allocation at blood bank	RBC	357	124	386
	Plasma	61	4	63
	Platelets	240	8	2
	Total	**658**	**136**	**451**
Use of components	RBC	258	38	72
	Plasma	61	4	63
	Platelets	237	8	2
	Total	**556**	**50**	**137**
Allocation at blood bank	**RBC / 100 cases**	**238,00**	**34,83**	**215,64**
	Plasma / 100 cases	40,67	1,12	35,20
	Platelets / 100 cases	**160,00**	**2,25**	**1,12**
	Total / 100 cases	**438,67**	**38,20**	**251,96**
Use of components	**RBC / 100 cases**	**172,00**	**10,67**	**40,22**
	Plasma / 100 cases	40,67	1,12	35,20
	Platelets / 100 cases	**158,00**	**2,25**	**1,12**
	Total / 100 cases	**370,67**	**14,04**	**76,54**
Allocation / Use (RBC)		**72,30%**	**30,60%**	**18,70%**
Allocation / Use (Platelets)		**99 %**	**100 %**	**100%**

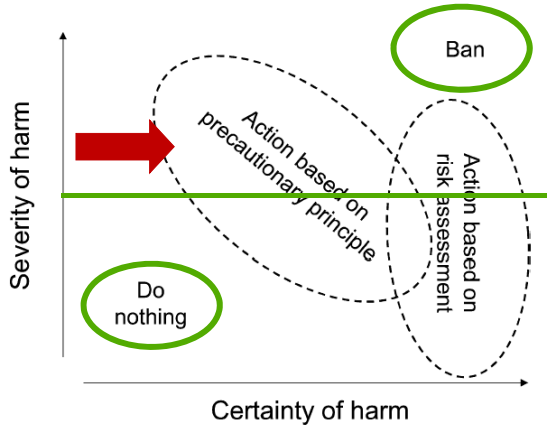
Availability of platelet concentrates in Europe – Summary.2

- Platelets“ - Do we exactly know what we are talking about?
  - Wide variety of manufacturing processes.
- Data on manufacturing and use of patelets 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 maufacturing 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
  - Clinicals 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

Abbildung modifiziert nach Grandjean P, Annu Rev Public Health 2004;25:199-223

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*

RBC transfusion category	Diagnosis or procedure	Number of transfusion episodes	Total RBC unit exposure† (time)	Immune suppressed	Use of irradiated blood
Acute	Cardiac surgery[6,7]	Single	3‡	No	No
Acute	Trauma[8]	Single	5‡	Suppressed cell immunity	No
Intermittent	ICU[9]	Variable	3.5‡	No	No
Intermittent	Cardiovascular disease[10]	Variable	3‡	No	No
Sustained over limited time frame	HSCT[11,12]	Multiple	10-20 (3-6 months)	Yes	Yes
Chronic but time-limited	MDS[13]	Multiple	13/year (3 years)	Immunosuppressed in many cases	No§
Chronic, lifelong	SCD[14]	Multiple	24‡/year (30 years[15,16])	Asplenic	No§
	Thalassemia[17]		15/year (50 years[18,19])	No	

* 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 median, mean, or range thereof.
† The data include only the patients who received transfusions.
‡ Median.
§ Not routinely; may be irradiated if hospital-wide policies for hematology-oncology patients or for pediatric patients require.

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

Pathogen	Risk	Method of estimation
Higher-risk pathogens		
B. microti[27]	0.076% (1 in 1316)	Antibody and PCR data in endemic areas*under IND screening†
CMV[1,46]	0.1% (1 in 1000)*	Detection of infection in transfused recipients and PCR data in donors
EIA		
Acute-type agent[4]	0.025% (1 in 4000)	Mathematical modeling‡
Chronic-type agent[4]	0.045% (1 in 2222)	Mathematical modeling‡
Lower-risk pathogens		
Plasmodia—all species	Rare	Clinical case reporting (<1 TT case per year in United States)
Bacteria[33]	0.00005% (1 in 2 million)	Based on French and German Data
	Clinical Sepsis	No documented clinical cases in the United States in past 5 years; May be more common for subclinical cases
A. phagocytophilum[50,51]	Rare	Clinical case reporting (<1 TT case per year in United States); May be more common for subclinical cases
HIV[63]	0.00007% (1 in 1.5 million)	Mathematical modeling§
HCV[63]	0.00009% (1 in 1.1 million)	Mathematical modeling§
HBV[64]	0.0001% (1 in 1 million)	Mathematical modeling§
WNV[65]	Rare	Clinical case reporting (<1 TT case per year in United States)

* Rare in nonendemic areas.
† Assumes that all PCR-positive donations, regardless of antibody status, would be infectious.
‡ Using data from previously detected EIAs.
§ Using NAT donor screening data and a window period model.
IND = investigational new drug.

Risk assessment models – Aggregated risk assessment

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TABLE 5. Aggregate single-unit risks in transfused RBC under current donor testing protocols in the United States

Aggregate risk category	Risk elements*	Risk
Minimum	• HIV + HCV + HBV • Bacteria • *Babesia*-nonendemic area	0.00031% (1 in 322,600)
Minimum + CMV†	• HIV + HCV + HBV • Bacteria • CMV risk for immunocompromised patients • *Babesia*-nonendemic area	0.10031% (1 in 996)
Maximum	• HIV + HCV + HBV • Bacteria • *Babesia*-endemic area • New chronic EIA	0.12031% (1 in 831)
Maximum CMV†	• HIV + HCV + HBV • Bacteria • CMV risk for immunocompromised patients • *Babesia*-endemic area • New chronic EIA	0.22031% (1 in 454)

* 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).

Risk assessment models – Aggregated risk assessment

Kleinman S et al., Transfusion 2015

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

Diagnosis	RBC unit exposure	Aggregate risk per patient (%)	
		Minimum*[1]	Maximum†[2]
Cardiac surgery	3	0.0009 (1/107,000)	0.36 (1/277)
Trauma	5	0.0016 (1/65,000)	0.60 (1/167)
ICU	3.5	0.0011 (1/91,000)	0.42 (1/238)
Cardiovascular disease	3	0.0009 (1/107,000)	0.36 (1/277)
HSCT	15	1.49 (1/67)	3.25 (1/31)
MDS	39	0.012 (1/8,000)	3.76 (1/27)
SCD	720	0.22 (1/450)	43.17 (1/2)
Thalassemia	750	0.23 (1/430)	45.13 (1/2)

* The method of calculating risk when large numbers of units are transfused as described by Kleinman et al.[66]
† 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.[1] Minimum per-unit risk is 0.00031% for all patient groups except for HSCT patients, where minimum risk is 0.10031% based on potential sequelae from TT-CMV infection.[2] Maximum per-unit risk is 0.12031% for the first four patient groups and 0.22031% for HSCT patients. For patients with MDS, SCD, and thalassemia, risk is 0.12031% for a 1.5-year period (when a new acute EIA is in the blood supply) and 0.07631% (due to *Babesia*) when transfused during other time intervals.

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EUROPEAN SYMPOSIUM

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Optimal use of platelets

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Platelets: transfusion efficacy and effectiveness (outcome)

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Session Summaries
&
Recommendations

SESSION 1 (Plenary): Clinical use of clotting factors and platelets – Challenges

Moderators & Rapporteurs: Pier Mannucci, Rainer Seitz, Michael Wierer

In his welcome address, **Karl-Walter Jauch**, Medical Director of the clinical centres, introduced the co-organising University of Munich as a major contributor to healthcare and research. He pointed out that blood products were not only essential elements of patient care, but also had a high economic impact. The cost for blood and blood products represented a very significant share of the university hospitals´ budget for medicines. The trends in indications and number of transfusions were closely followed. He underlined that optimal use of blood and blood products was necessary in ethical, moral and social respects.

Michael Wierer, representing the main sponsor of the symposium, the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe, also welcomed the participants on behalf of the co-organising Ludwig-Maximilian-University (LMU) Munich, and Paul-Ehrlich-Institut (PEI), Langen (Germany). He highlighted the important role of the EDQM in regulating the blood transfusion sector in Europe. The EDQM Committee (Partial Agreement) on Blood transfusion (CD-P-TS) was responsible for 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, and for proposing ethical, safety and quality standards for professional practices and blood component specifications.
He reiterated that EDQM had been the main sponsor for the 2009 and 2013 symposia, and pointed to the achievements of those meetings, particularly the two Council of Europe Resolutions adopted by the Committee of Ministers on 15 April 2015 on principles concerning haemophilia therapies CM/Res(2015)3, and on principles concerning normal human immunoglobulin therapies for immunodeficiency and other diseases CM/Res(2015)2. He introduced the members of the Scientific Committee and acknowledged their contribution to preparing, once again, a very attractive programme. Finally, he expressed his gratitude to the EDQM Technical Organisation team for their excellent support.

The rationale for the meeting was presented by **Wolfgang Schramm**, University of Munich, Germany, who recalled the merits of the original venue in Wildbad Kreuth and explained the unavoidable move to the premises in Freising. He reminded the audience of two essential statements setting the scene for the Wildbad Kreuth Initiative:
1) Optimal use is to avoid overuse, underuse, and inappropriate use.
2) Optimal use requires 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.
He highlighted important recommendations from the previous meetings, and their major impact on health policy and patient care, particularly the recommendations of the 2013

symposium forming the basis for Council of Europe resolutions.
In the field of haemophilia, the main objectives of the symposium were: critical appraisal of the status quo and identification of gaps in clinical and outcomes research in haemophilia; discussion of perspectives on "innovative products"; and identification of best practice and future needs in haemophilia care. Several developments needed to be discussed: how had the recommendations of the previous meeting been translated into actions; what were best practices in Europe, e.g. in prophylaxis in children and adults, treatment of elderly haemophilia patients, immune tolerance induction, perioperative care; how much factor was needed for adequate treatment; was the access to products equitable? Another much-debated topic was the question of relative immunogenicity of products.
There were a number of reasons to revisit the topic of platelets. The rationale for many aspects of current practices needed further consideration as did the impact of different manufacturing processes for concentrates, and measures, such as testing strategies and pathogen inactivation methods, for minimisation of infectious risks – particularly bacterial contamination. A further very important theme was that of ensuring an adequate supply if the current high level of use continued. Up-to-date, representative real-world data (demographic and epidemiological data, blood usage) would be required to predict future needs in the face of changes ahead with more elderly patients and fewer young donors. Also infectious risks, with newly spreading and emerging pathogens, would remain on the agenda.

As pointed out by previous speakers, the earlier Kreuth symposia had brought about very important and useful recommendations, but there were still controversies in clinical use of blood components which warranted the exchange of views, experiences and priorities in this forum comprising the Council of Europe area and beyond. **Rainer Seitz**, Paul-Ehrilich-Institut, pointed out that the two main topics of the present symposium were different in several respects. In the area of clotting factors we had well-defined indications, a broad spectrum of authorised products, treatment specialists, and a notably well-informed and active patient community. Very exciting aspects of haemophilia treatment were forthcoming implementation and evaluation of novel therapies. In the clinical use of platelets, transfusion triggers were debated, there were diverse producers and methods, and there was no organised patient community.
Besides the clinical issues already indicated in Wolfgang Schramm´s speech, there were also some challenges for industry and regulators, particularly the question of how to evaluate the efficacy and safety of those new therapies in the pipeline given only a limited number of patients. The guidelines for clinical evaluation of factor VIII and IX products had been recently updated but met some criticism because of increased requirements, especially towards including more children, and resuming the need for previously untreated patients (PUP) studies for novel products. Evaluating efficacy and safety would be demanding for new products with increased half-life – and even more so for novel approaches such as the bispecific antibody mimicking factor VIII, or therapies which interfere with coagulation inhibitors.
Blood components for transfusion had been discussed at the 2009 symposium. During recent years the trend curves of consumption showed a considerable decline for red cells, but an increased and steady high demand for platelets. The declining use of red cells could be partly

explained by an improvement of surgical techniques, implementation of transfusion guidelines, and propagation of patient blood management. However, there were still some controversies in the area of red cells, particularly an ongoing debate on "liberal versus restrictive" transfusion triggers. Recent studies suggested that a restrictive trigger was safe, but the underlying disorder (e.g. cardiac or central nervous system disorders) may be relevant. Further attention and research was also warranted into concerns about a potential immunosuppression which might increase the risk of infection or cancer, relating to storage of red cells for a longer period.
However, for the present symposium, platelets had been chosen as the main topic for several reasons. For platelets, availability and clinical use appeared to be quite diverse across Europe. There were various methods to collect and process platelets, but their impact on platelet integrity and functionality was still incompletely explored. Platelets, more than red cells, carried an infectious risk, particularly of bacterial contamination. And, according to current guidelines for clinical application, the trigger for transfusion and the parameter for monitoring was platelet count (increment). It would be an attractive goal to develop methods suitable for routine use to assess the intended haemostatic platelet functionality *in vitro* and *ex vivo*.
Generally, in order to enable broad and comprehensive evaluation of efficacy and safety of therapies, it would be desirable to continuously collect clinical data of complete patient groups. In haemophilia, patient registries were available but needed to be expanded and interrelated. Clinical registries would also be valuable in the area of blood components for transfusion.

Quality indicators for monitoring the clinical use of blood were addressed in her presentation by **Constantina Politis**, Coordinating Haemovigilance Centre, Athens, Greece. The importance of a quality management system (QMS) in transfusion medicine was now well established; however the development of appropriate quality indicators (QIs) as a tool for quality monitoring and improvement had only recently begun to receive attention in this field. QIs were measurable, objective indicators of the efficiency of the key segments of a system. Constantina Politis was the leader of an EDQM initiated project from 2010 to 2014 that performed an enquiry into QIs for monitoring the clinical use of blood. One of the objectives was to identify and develop a set of commonly accepted performance QIs for monitoring the clinical use of blood and blood components in Europe. The enquiry yielded interesting and encouraging results.

The intriguing question of how novel drugs would change the treatment of haemophilia was addressed by **Flora Peyvandi**, University of Milan, Italy. Novel factor VIII and IX products with extended half-life were entering the market. The prospect of reducing the frequency of injections was attractive – not only as an improvement of quality of life. One of the limitations of haemophilia treatment was the necessity for venous access over a prolonged period; concomitant risks such as infection, sepsis, and thrombosis – particularly in children – may be decreased by reduced frequency of venepuncture. The new factor VIII products showed a 1.4 to 1.6 fold extension of half-life; the optimal dosage schedules and actual clinical benefit needed to be further substantiated. The new factor IX products were shown to extend the half-

life 3 to 5 fold. There were also new factor VIIa products showing a half-life extension in a similar range. Long-term assessment of safety of novel, extended half-life products and an accurate post-registration surveillance was required.
A further option was the development of non-replacement products. One approach was the interference with physiological inhibitors of coagulation, i.e. the inhibition of tissue factor pathway inhibitor (TFPI) by a monoclonal antibody, or the down-regulation of antithrombin III by small interference RNA (ribonucleic acid) (siRNA). Another interesting approach was the chimeric, bi-specific humanised antibody ACE910 directed against FIXa and FX, which mimicked the cofactor function of FVIII by binding FIXa with one arm and FX with the other, placing them in spatially appropriate positions and promoting FIXa-catalysed FX activation.

In recent decades, platelet concentrates had been used as an essential part of treatment of e.g. cancer, haematological malignancies, bone marrow failure and stem cell transplantation. Current challenges using platelet concentrates were discussed by **Jean-Pierre Cazenave**, ARMESA, Strasbourg, France. There was an increasing use of platelets in medicine, paediatrics and neonatology, surgery and obstetrics. While clinical bleeding was a therapeutic indication, the transfusion threshold in prophylactic use should be modulated according to risk factors. Regarding the type of platelet concentrate there were numerous variables needing further evaluation, such as donor profile, processing (e.g. aphaeresis or buffy coat derived) and modifications (e.g. additive solutions, pathogen inactivation (PI)) and storage conditions. For assessment of clinical efficacy, surrogate markers and/or bleeding grade were currently used; the relationship between corrected count increment (CCI) and bleeding was however unclear. Clinical trials aimed at further exploring indications and adequate posology faced complexity in transfusion medicine due to many diverse underlying disorders and concomitant treatment modalities. A cornerstone of estimating safety was a robust haemovigilance system. Referencing the 2007 Toronto Consensus Conference, Jean-Pierre Cazenave made a strong case for PI of blood components. He presented favourable clinical experiences and haemovigilance records with amotosalen-treated platelets and plasma in Alsace from 2006-2015. Finally, he pointed to the significance of this technology in relation to chikungunya and dengue virus infections in France and overseas *departements*, and emerging pathogens such as Zika virus.

The related requirements for regulatory mechanisms, such as marketing authorisation (MA) and health technology assessment (HTA) were reviewed by **Jan Müller-Berghaus**, Paul-Ehrlich-Institut. He illustrated the development of scientific committees and working parties at the European Medicines Agency (EMA), and the criteria for MA, the core of which was a favourable benefit/risk balance, without taking into account costs. An important and increasingly used element in the forefront of MA was providing scientific advice to developers. The perspective of HTA bodies was somewhat different from that for MA. The HTA bodies aimed to ensure an advantage over existing therapies in terms of patient-relevant endpoints (e.g. mortality, morbidity, health-related quality of life), demonstrated according to criteria of evidence-based medicine (EBM). As an example, Jan Müller-Berghaus described the system in Germany involving the "Gemeinsamer Bundesausschuss (G-BA)" (Federal Joint Committee), the highest decision-making body of joint self-governance of physicians,

dentists, psychotherapists, hospitals and statutory health insurance funds. The GB-A was supported by the independent Institute for Quality and Efficiency in Health Care (IQWiG) which performed, upon request, systematic assessments of existing scientific clinical literature. A key element of these assessments was evaluating the amount, content and particularly the "quality" of studies (evidence grade), which were the basis for grading the benefit relative to existing therapies. Since clinical trials with new medicinal products would have to cover both sets of requirements, for MA and for HTA, a promising and necessary way forward was to arrange parallel scientific advice, as already initiated in an EMA pilot project.

Current challenges of benefit, effectiveness and risk assessment in coagulation factor and platelet usage were presented by **Karin Berger**, University Hospital of Munich, Germany. In the face of increasingly cost-constrained healthcare systems, resources needed to be allocated to interventions with both proven benefit and safety. It was estimated that adverse drug reactions (ADR) killed 197,000 EU citizens annually, at a cost of 79 billion euros. The direct hospital costs of managing ADR were already substantial. The role of payers had become more prominent, and the influence of HTA bodies was increasing. Payers have a strong focus on relative effectiveness, i.e. the added benefit or incremental safety relative to existing therapies. While pre-authorisation studies assessed the efficacy ("how things work"), for access to the market the effectiveness ("doing the right thing") needed to be assessed in a large sample size, looking at comprehensive patient-relevant endpoints and over a relatively long-term. The European Network for HTA (EUnetHTA) and the EMA had initiated co-operation with the objective of identifying and undertaking specific steps to improve the efficiency of the processes and conditions for patients' timely access to an effective medicine.
Considerations of patient-relevant endpoints and patient-reported outcomes in haemophilia treatment and platelet transfusion should be substantiated. In haemophilia treatment they included mortality and symptoms and complications such as bleeds, arthropathy, osteoporosis, patient-reported endpoints such as health-related quality of life, activity and participation, patient preferences, as well as risks such as inhibitor development. In platelet transfusion they included mortality and bleeding as for haemophilia, and also a different spectrum of risks with immunological and non-immunological adverse reactions and an ever-present infectious risk, particularly due to bacterial contamination. To measure and assess these endpoints was challenging, since collecting "real life data" was not the same as conducting formal clinical studies. An important tool could be patient registries; already 27 European countries had established national registries in the haemophilia area though these needed to be further developed and interrelated. In the field of platelet transfusion the definition of appropriate endpoints for effectiveness research and methodological approaches needed further elaboration, and access to clinical data needed to be improved.

Brian O'Mahony, president of the European Haemophilia Consortium (EHC), gave the views of a patient organisation. EHC had conducted a survey on the 'State of Haemophilia Care in Europe' based on 2014 data from 37 countries. The recommended implementation of Comprehensive Care Centres (CCC) had been achieved in 6 more countries since the previous survey in 2011; however, there were still countries without CCC. 18 countries (three more than previously) had a National Co-ordinating group. Levels of access to home

treatment were above 75% in most countries, but in some countries it was below 50% or even absent. There was a clear increase of access to prophylaxis, both for children and adults. The availability of specialist treatment in paediatrics, emergency care and orthopaedics was good; access to social and psychological support and pain management was much lower, and there were some improvements regarding genetics and physiotherapy. The specific problems of ageing haemophilia patients were apparently not a priority in most countries. The 2013 Kreuth recommendations had been implemented in many cases: for instance prophylaxis for children in 33 countries, and prophylaxis for adults in 31. On the other hand, the recommendation of a minimum factor VIII supply of 3 IU per capita has been implemented in 18 countries and not implemented in 8, with no data provided from 19 countries. All in all, Brian O'Mahony considered the previous Kreuth recommendations, particularly their adoption in official Council of Europe resolutions, as very important in advocating patient needs. Current priorities of EHC were: continued efforts to achieve a supply of > 3, or better > 4 IU per capita; implementation of a national co-ordinating body; improved access to immune tolerance induction; hepatitis C treatment; access to new extended half-life factors at sustainable cost and with individualisation of therapy; and agreed protocols on ageing-patient care.

SESSION 2: Clotting Factors: Impulse Presentations (parallel session)

Moderators & Rapporteurs: Paul Giangrande, Pier Mannucci, Brian O'Mahony, Flora Peyvandi

Coagulation factors had been discussed during previous Wildbad Kreuth Symposia and at this latest meeting in Freising. Many questions continued to be raised about optimal use of coagulation factors, particularly in the context of ongoing therapeutic developments focussed on products with extended half-life.
The wide variations both in availability of coagulation factors and in practices in their clinical use throughout Europe had long been recognised leading, further to the 1999 and 2009 sets of recommendations and as a follow-up to the Kreuth III symposium in 2013, to the drafting of the Council of Europe Resolution 2015(3) on principles concerning haemophilia therapies. Further open questions identified by the specialists attending the 2016 symposium related to: the critical appraisal of the *status quo* for research in haemophilia and identification of gaps; identification of best practices and future demands in haemophilia care; and perspectives on innovative therapeutic products.
It was believed necessary to tackle current issues such as the need for procurement of therapeutic products through national tenders, for the certification of treatment centres, for genotype analysis of patients and carrier detection as well as for centralised collection of treatment-outcome data. Other points raised were: the ageing of the haemophiliac population; the need for treatment of iatrogenic infection with the hepatitis C virus; the management and treatment of patients with inhibitors; and the impact of using factors with extended half-life – notably in relation to trough levels.

An overview of the regulatory aspects in clinical trials for clotting factors was given by **Anneliese Hilger** of the Paul-Ehrlich-Institut, Langen, Germany. The role of regulators and the European approach for approving clinical trials, granting marketing authorisation to new products and organising pharmacovigilance and market surveillance were presented.
A focus on recent changes in the European regulatory framework addressed Article 45 of the Paediatric Regulation [1] (notably the Paediatric Investigation Plan) as well as requirements for clinical trials of clotting factor VIII products[2] including the current requirements for determination of inhibitors in previously untreated patients (PUP) and in post-marketing investigations. Over recent decades a constant upward trend could be observed in the number of FVIII and FIX concentrates receiving marketing authorisation. Several innovative therapeutic products to treat haemophilia patients were in development.

[1] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use

[2] 21 July 2011 EMA/CHMP/BPWP/144533/2009 Committee for medicinal products for human use (CHMP) Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products replaced by EMA/CHMP/BPWP/144533/2009 rev. 1

In order to get the best capture of data from patients suffering from a rare disease like haemophilia, several options were presented. These included clinical trials, registries, pharmacovigilance measures and scientific research options, which should complement each other to clarify unresolved issues (e.g. inhibitor development), in order to identify best practices in haemophilia care.

The latter statement nicely linked in with the next presentation entitled "Inhibitor development in PUP – a comparison of previous studies and the Sippet study" by **Frits Rosendaal**, Leids Universitair Medisch Centrum, the Netherlands.
An introduction to the impact on caregiver burden therapeutic management and costs of handling patients with haemophilia and inhibitors was given. Risk factors for the development of inhibitors were presented with a focus on FVIII product-type linked frequency in PUP and Previously Treated Patients (PTP). It was reported that observational studies and reviews suggested that inhibitor development frequency might be higher for recombinant Factor VIII (rFVIII) than for plasma-derived FVIII concentrate (pdFVIII). In order to confirm this assumption, a randomised trial, the SIPPET study had been conducted. Details on the hypothesis, the design and the analysis of the study were given. Data from 251 patients from 14 countries were analysed for baseline characteristics and inhibitor occurrence leading to the conclusion that patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant factor VIII.[3] It was concluded that relevant strategies to minimise inhibitor development in patients needed to be developed.

The next presentation entitled "Inhibitors in Haemophilia, prophylaxis-immune tolerance induction" was given by **Hervé Chambost**, Faculté de Médecine Aix Marseilles, France. He set the scene by presenting the consequences for the patient, for society and for future therapies of inhibitor development – the major haemophilia treatment-related complication. Solutions should comprise both prevention of inhibitor development and treatment after its occurrence. The nationwide experience of prophylaxis and immune tolerance in France was chosen to illustrate real-life practices. Inhibitor development rates in the French cohort for haemophilia A and B patients and treatment options for bleeding in patients with inhibitors were shown. The rationale for immune tolerance induction (ITI) was presented, as were international registries and a randomised trial[4] which contributed valuable data toward evidence-based ITI practice. Recent studies on prophylaxis by bypassing agents were also discussed. Finally, prophylaxis and ITI in the life of patients were illustrated by 2 case studies showing that large case-to-case variations in clinical response to these interventions occurred both in adults and infants. It was concluded that treatment of bleeds by bypassing agents was not optimal for many patients with inhibitors and was also a controversial subject for health insurance/reimbursement organisms, and that ITI should be undertaken at least once in each patient in good conditions. It was also reminded that ITI and bypassing agents' prophylaxis represent challenging treatments with rare indications in a rare disease; hence clinical trials

[3] http://www.nejm.org/doi/full/10.1056/NEJMoa1516437
[4] http://www.bloodjournal.org/content/bloodjournal/119/6/1335.full.pdf

and data collection via registries were encouraged to allow the expansion of knowledge in this field.

Paul Giangrande and **Brian O'Mahony** representing the European Haemophilia Consortium (EHC), Brussels, Belgium then addressed the topic of "Access, supply, procurement and tenders".
After recalling the recommendations arising from the previous "Kreuth" meetings in relation to access, supply and procurement of clotting factors, an international survey on tender and procurement procedures in European countries[5] was presented. Procurement methods, products subjected to tendering procedures and product selection criteria as well as the main representatives involved in tender and procurement boards, were reported for 38 countries. The involvement of clinicians and patient organisations in the tender and procurement processes was reported in only a limited number of countries.
Important outcomes in relation to pricing were that lower prices were obtained for most clotting factor products (except in monopoly situations) when using a tender system rather than an alternative procurement process, and when clinicians and patients organisations were involved in the procurement process (to illustrate these findings, the impact on availability of all products and on price of recombinant products from the UK national procurement and tender processes were presented). Nevertheless, the importance of using the most effective and safe product rather than the cheapest one was emphasised. The usefulness of patient registries to allow forecasting of demand was also noted.

The final impulse presentation entitled "Hemophilia care in Europe and in the USA, current data and future trends" was contributed by **Patrick Robert** of the Marketing Research Bureau Inc, Orange, United States of America. The data from surveys conducted in 70 countries were used to evaluate the current market and future trends in both Europe and the United States of America.
As of 1992, growth of the European market for factor FVIII was mainly driven by the use of rFVIII but since 2008, the rise in consumption of pdFVIII had also contributed significantly to the total annual consumption rate. In 2014 (as had already been the case in previous years, e.g. 2011) a large variation in terms of consumption per capita, ranging from 0.1 to 9.6 International Unit (IU)/capita) was observed between countries in Europe. Changes in Factor VIII consumption between 2011 and 2014 showed a clear upward trend for all countries and particularly in some Central and Eastern European countries[6].Growth of the European market for factor FIX was also reported and, as of 1998, this was mainly linked to the introduction and expanding use of recombinant FXI (rFIX).
In North America, upward trends in total consumption were also observed for rFVIII (as of 1992) and rFIX products (as of 1996) but market share changes had also been observed in recent years. In the USA, accelerated adoption of prophylaxis occurred from 2002 to 2012 (from 20% to 50% of haemophilia A and B patients treated), but the introduction of the

[5] Haemophilia. 2015 Jul;21(4):436-43. doi: 10.1111/hae.12720
[6] where consumption per capita is below the threshold of 3 IU/capita set as a minimum by the Council of Europe Resolution 2015(3) on principles concerning haemophilia therapies

extended half-life recombinant products in 2015 did not elicit many conversions of new patients to prophylaxis. However this may change in the future.
As regards future trends, the gradual market penetration of the extended half-life rFVII and rFIX products was expected to allow stabilisation, if not a drop, in consumption (in terms of total IU number) in Europe and the USA, and a rise in expenditure (price per unit). Meanwhile, on the global market, consumption of recombinant and plasma-derived factors would continue to grow.

The discussions following the impulse presentations centred on the follow-up of previous recommendations, notably those of Kreuth III, and there was broad consensus that experience demonstrated that well-founded consensus recommendations describing essential elements of accepted state-of-the-art could be helpful for developing and raising standards for optimal clinical use at the national and regional levels. The Kreuth III recommendations[7] were reviewed and it was felt necessary to reconsider the recommended minimum utilisation level of factor VIII in terms of IU per capita. In the light of the progress achieved for haemophilia diagnosis and of the extended indications for prophylaxis, the value of 3 IU per capita required by Res(2015)3 was challenged. The introduction of a similar recommendation for minimum utilisation level of factor IX in terms of IU per capita was proposed. Finally, an agreement was reached on the need to raise the recommended minimum utilisation level of factor VIII to 4 IU per capita and to introduce a recommended minimum utilisation level of factor XI of 0.5 IU per capita of the general population.

Discussions then focussed on new areas for improvement of haemophilia therapy and notably on the desired features of treatments with extended half-life factors. The impact on the sustainability of healthcare systems of robust tendering processes involving both clinicians and patient organisations was widely recognised.
Formal designation of hospitals providing clinical care as European Haemophilia Centres (European Haemophilia Treatment Centres (EHTCs) for local routine care or European Haemophilia Comprehensive Care Centres (EHCCCs), which provide the highest level of care and function as tertiary referral centres)[8] and equitable access to comprehensive care and replacement therapy in all parts of a country, were recognised to be prerequisites for improvement.
The priority of the access to treatment of iatrogenic infection with the hepatitis C virus for haemophiliacs was also discussed in the context of the recent marketing of new, very active combination medicinal products (e.g. Sofobusvir/Velpatasvir) in Europe. The ageing of the haemophilia population, being a consequence of the broader access to replacement therapy, and access to ITI and to elective surgery patients with inhibitors, were also deemed of primary importance.
Other subjects that were addressed related to choice of products – notably in relation to inhibitors' incidence. In order to gather relevant information and expand current knowledge e.g. regarding treatment outcome, health-related quality of life and genotype analysis for

[7]https://www.edqm.eu/sites/default/files/resolution_cm_res_2015_3_on_principles_concerning_haemophilia_therapies.pdf
[8] http://www.euhanet.org/docs/Euhanet-European_guidelines_for_the_certification_of_Haemophilia_Centres_2013.pdf

patients with severe haemophilia, options of different data sources like clinical trials, registries and cohort studies were discussed.
After extensive and fruitful discussions in open sessions (with industry representatives) and closed sessions, consensus recommendations addressing those issues were produced.
The overarching objective of the Kreuth initiative, to promote optimal use of blood products, was felt to be particularly valid and many participants expressed their interest and willingness to continue the work in further upcoming meetings in the tradition of the Kreuth initiative.

Recommendations

1. Hospitals providing clinical care for people with haemophilia and related disorders are strongly recommended to seek formal designation as either European Haemophilia Comprehensive Care Centre (EHCCC) or European Haemophilia Treatment Centre (EHTC). (Access to comprehensive care and replacement therapy should be equitable in all parts of a country.)

2. There should be agreed national protocols or guidelines on management of the ageing patient with haemophilia. Treatment centres are encouraged to include an appropriate general physician in the comprehensive care team.

3. The minimum consumption of Factor VIII concentrate in any country should be 4 IU per capita of general population. (Data expressed as units per severe patient should also be collected in parallel in future.)

4. The minimum consumption of Factor IX concentrate in a country should be 0.5 IU per capita of general population.

5. Treatment for hepatitis C with direct-acting antiviral agents should be provided to all people with haemophilia on a high priority basis.

6. Genotype analysis should be offered to all patients with severe haemophilia. Patients shall be free to decide whether or not to take up this possibility. Genetic counselling of the affected person, when given, should encompass the recommendation that genetic relatives of the affected person be advised to seek genetic counselling.

7. People with inhibitors should have access to immune tolerance.

8. People with inhibitors should also have access to elective surgery at a specialist centre with relevant experience.

9. National or regional tenders for factor concentrates are encouraged and should always include both haemophilia clinicians and national haemophilia patient representatives.

10. Outcome data including health related quality of life should be collected with appropriate study design, e.g. annualised bleed rates (ABR), mortality, joint score and time off from education or employment.

11. Treatment with extended half-life factors should be individualised and protection against bleeding should be improved by increasing trough levels.

12. There is increasing evidence that the incidence of inhibitors amongst previously-untreated patients (PUPs) varies between products. Steps should be taken to understand and minimise this risk. (Patients, or their parents, should be involved in discussions related to product choice.)

SESSION 3: Platelets: Impulse Presentations (parallel session)

Moderators & Rapporteurs: Karin Berger, Jean-Pierre Cazenave, Sheila MacLennan, Dorothea Stahl

While coagulation factors had been a topic of all Wildbad Kreuth Symposia, blood components for transfusion had not been on the agenda since 2009. However, as had already been pointed out in Plenary Session 1, since in recent years important questions had been raised about their optimal use, platelets had been included as a main topic of this latest meeting in Freising.

The wide variation in availability and clinical use of platelets throughout the European Community suggested that it was difficult to identify which patients actually needed platelets, particularly those who should receive prophylactic platelet transfusion. A further open question was the impact of the many different aspects of manufacture (e.g. donor profile; pool vs aphaeresis platelet concentrates; pathogen inactivation). It would be difficult, but necessary, to define better criteria as to which platelet component was the right one for the individual patient from a clinical and economic perspective. Thus, whereas platelets had been available for transfusion for decades, many aspects needed further clarification from laboratory and clinical studies. To this end, it was important to define efficacy and effectiveness of platelet transfusions, and to develop better methods and tools to assess the outcome. The scene for the Workshop was set by several expert presentations.

An overview of the current practice in platelet transfusion was given by **Gregor Bein**, University Hospital of Giessen & Marburg, Germany. In principle, the purpose of platelet transfusion was treatment or prevention of bleeding, but there may be pitfalls in assessing efficacy and safety. For instance, observational studies in coronary artery bypass surgery showed, at first glance, an association between platelet transfusion and serious adverse events and decreased survival, but this was resolved by full adjustment for confounding factors. Experts formulating recommendations such as the Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives of the German Medical Association, needed to carefully scrutinise the level of scientific evidence. For haematology and oncology patients receiving frequent prophylactic transfusions current evidence suggested that, compared to higher platelet counts, a standard threshold of 10 x 10^9/L did not increase the risk of bleeding; however the quality of evidence was low. Also the value of prophylactic versus therapeutic-only platelet transfusion was debatable; studies showed that bleeding episodes were reduced, but there was insufficient evidence for reduction of severe (World Health Organisation (WHO) grade 3 or 4) bleeding and mortality. For surgical patients there were only weak data supporting thresholds and, in the area of intensive care unit patients, high-quality data to support or refute the need for prophylactic platelet transfusion were lacking. Another question warranting further research was whether ABO- or Rh-compatible or identical platelet transfusions were necessary. The overview showed that, for many aspects of platelet

transfusion, current evidence from observational studies needed to be augmented by well-designed clinical trials with meaningful assessment of outcomes.

The latter statement nicely linked in with the next presentation entitled "How do we assess clinical efficacy of platelet transfusion?" by **Miguel Lozano**, Department of Haemotherapy and Haemostasis, University Clinic Hospital of Barcelona, Spain. Clinical efficacy of platelet transfusion could be defined for prophylactic transfusion as increasing a patient's platelet count and/or preventing bleeding, and for therapeutic transfusion as stopping bleeding. However, assessing efficacy of platelet concentrates in routine practice as well as in clinical studies was challenging. Tools for platelet concentrates evaluation were *in vitro* studies including studies under flow conditions, *in vivo* studies with radio labelled platelets, clinical studies, and haemovigilance. Typical end points of clinical studies were: corrected count increment (after 1 hour or 24 hours), interval between consecutive platelet transfusions, and application of bleeding scores, e.g. WHO grades of bleeding. In routine practice, monitoring post-transfusion platelet counts was recommended, but there was a considerable variation in the time points. Low corrected count increment could be due to poor quality of the concentrate, but also to patient characteristics such as immune destruction of platelets, massive splenomegaly, or rapid turnover due to active bleeding.

The next presentation entitled "Platelets: infectious risk, testing strategies, pathogen inactivation" was given by **Sheila MacLennan**, NHS Blood and Transplant, UK. She presented data on transfusion-transmitted infections in the UK 1996 – 2014, as collected by the haemovigilance scheme serious hazards of transfusion (SHOT). The calculated viral risk from blood transfusion in the UK was remarkably low (e.g. for HIV, 1 in 6.47 million donations released). However, there were 43 transmissions of bacterial infections, including 9 deaths from contaminated platelets. Preventive measures, i.e. use of diversion pouches, improved skin cleansing and bacterial screening, implemented by NHSBT in 2011, were effective in reducing the cases of bacterial transmission. The NHSBT process involved samples from 'daughter packs' with a volume of 2 x 8 mL (aerobic and anaerobic), a minimum pre-sample time of 36 hours, and 6 hours quarantine post-loading of samples. Units were released as 'negative to date' with culture to beyond end of shelf life of component (7 days); index component and associated packs were recalled if an initial reactive result triggered further investigation. Another option was pathogen inactivation (PI) with one of several available methods, which were briefly described. Dr MacLennan concluded that, depending on the process used, bacterial screening and PI could be considered of equivalent efficacy, with pros and cons for both. There was increasing use of PI in Europe, though questions remained regarding toxicity and cost-effectiveness of PI; no methods were yet licensed for red cell PI.

A frequent complication of platelet transfusion was allo-immunisation; **Olivier Garraud**, representing the Institut National de la Transfusion Sanguine, Paris, and the Faculty of Medicine of Saint-Etienne, University of Lyon, France, addressed the potential impact of the manufacture of platelet concentrates (PC), i.e. whole blood (buffy coat; (BCPC)) versus single donor ((aphaeresis);(SDAPC)). In France, leukoreduction/leukodepletion (LKD) was mandatory with residual leucocytes < 10^6 per PC and implemented with a mean efficiency of ~

1.5 – 2.5 x 10^5 per PC; the residual content of red cells was not specified. Relevant antigens expressed on platelets included A, B (ABO/ABH system), HLA class I with an intense polymorphism, and nearly 30 HPA antigens. Apart from situations where recipients presented with (allo) anti-HLA/HPA antibodies (Abs), there was no specific preference in France of SDAPC over BCPC. Dr Garraud reviewed the known mechanisms and main hypotheses for allo-immunisation, involving an intact innate immune system, antigen-presenting cells, as well as functional T-cell and B-cell adaptive immunity pathways. The picture may be modified by primary or secondary immunodeficiency. There are several mechanisms which may modify allo-immunisation including: CD8+ T-cell suppression; regulatory T- and B-cells; soluble HLA antigens; cytokine pattern due to pre-LKD storage; transfusion related immune-modulation (TRIM); direct versus indirect recognition of antigens, and in the case of frequent transfusion generation of anti-idiotype, tolerogenic antibodies. Allo-immunisation to HLA (± HPA) moieties was recognised more than 5 decades ago, was clearly associated with leucocytes, and boosted after previous transfusions, pregnancies or transplantations. LKD apparently reduced allo-immunisation, though a recent Cochrane meta-analysis did not find substantial strong evidence. In a recent study, Daurat et al. [Transfusion 2016] had found that BCPC immunised significantly less than SDAPC regarding HPA or HLA antigenic specificities; a hypothesis was that this difference might be due to the pre-storage of 15-16 hours before LKD, while LDK of SDAPC occurred "in process". Also allo-immunisation to red cell antigens may occur, and a recent study including a total of 54.202 PC found more allo-immunisations with BCPC (25 cases) than with SDAPC (10 cases). The role of ABO-identical versus ABO-compatible PC transfusion should be further elucidated. Furthermore, the impact of PI, which also inactivates leucocytes, on allo-immunisation should be further studied.

The final presentation entitled "Availability of platelet concentrates in Europe" was contributed by **Dorothea Stahl**, Section Head Transfusion Medicine, Paul-Ehrlich-Institut, Germany. She used several data sources from market analyses, EDQM and AABB (American Association of Blood Banks) surveys and the German national data base. The definition of PC, with 12 platelet component monographs in the EDQM Guide, highlighted diversity. The Creative Ceutical Report 2015 revealed a wide variation in collection and use of blood components across the EU, and identified 5 countries which reported a relative deficiency in the supply of PC. EDQM data (Richardson C, Quality indicators for monitoring the clinical use of blood in Europe, 2014) showed large differences in the numbers of units per transfused patient for all blood components including PC, and also in the relative share of onco-haematology and surgery in blood component use. In the USA, according to AABB data, SDAPC with 92.4% had become the dominant PC over a period from 2001 to 2013. In Germany, the numbers of manufactured PC had been increasing since 2004 (with ca. 60% SDAPC). For SDAPC, a lower rate of wastage at manufacture was found than for BCPC. Dr Stahl concluded that data on manufacturing and use of PC in Europe existed, but collecting further data for decision-making would be desirable, particularly data on the use of the different manufacturing protocols which might help in the understanding of the interdependencies of the manufacturing protocol with quality, safety, and efficacy of the PC. Currently there was insufficient linking of data on the amounts of PC transfusion with

epidemiological data and the underlying transfusion protocols and clinical and haemovigilance data in order to evaluate different practices of platelet use. Clinical studies and "real world data" from patient registries might provide tools to enhance the information needed. Linking data with a broader scientific context, using a systems biology approach or systems medicine approach may be a way forward, as illustrated by several examples.

The discussions following the presentations centred on the areas of safety, efficacy and appropriate use of PC. It became evident that there were profound differences in resources available among the participating member states. However experience with previous Kreuth statements, e.g. for haemophilia treatment, suggested that well-founded recommendations describing essential elements of accepted state-of-the-art could be helpful for developing and raising standards.

There was broad consensus that pre-storage leukodepletion should be implemented. Of the transfusion-transmitted infections, bacterial contamination was currently the most frequent, and the participants agreed on the necessity for measures to be taken to reduce this risk. Since contaminating bacteria needed some time to multiply in stored components, limiting storage time may reduce the risk although significant contamination, leading to severe morbidity, had been reported in components stored for as short a time as 2 days. A measure with proven efficacy was PI, with several approved methods being available. Another successful approach was bacterial screening, where different strategies may be followed. As had already been pointed out in the presentation by Sheila MacLennan, bacterial screening and PI could be considered of equivalent efficacy, with pros and cons for both. As a further element to increase safety, particularly to reduce immune-mediated reactions, the use of platelet additive solutions (PAS) was proposed.

The participants unanimously agreed that, in order to improve the scientific evidence concerning efficacy of PC, more relevant clinical endpoints for prophylactic and therapeutic use needed to be defined. The clinical evaluation should focus specifically on aspects of manufacture such as different types of products e.g. BCPC versus SDAPC, or the impact of using PAS. Also the significance of ABO-compatibility should be further explored. A particular issue necessitating further research was refractoriness to PC transfusion. In the face of many open questions concerning clinical evaluation of PC, more European public funding for clinical studies was advocated.

The overarching objective of the Kreuth initiative, to promote optimal use of blood products, was felt to be particularly valid with respect to PC transfusion. Comprehensive documentation of transfusion episodes was identified as a basic but essential step. Documentation of patient characteristics, indication and outcome were indispensable for both monitoring therapy and haemovigilance. Elements of quality assurance, particularly a system of audits and feedback, should be implemented in each hospital. In order to enable cross-sectional evaluation, and with a view to augmenting the evidence concerning efficacy and safety of PC, the use of patient registries and/or pragmatic trials should be considered. In order to support meaningful evaluation and monitoring optimal use, key performance indicators were needed.

Further to fruitful and extensive discussions in open sessions (with industry representatives) and closed sessions, the platelet working group produced consensus recommendations.

The optimal use of platelets was a "new" or at least "re-emerging" topic of the Kreuth symposia. The general impression at the end of the platelet workshop was that it was not an easy topic, given the multitude of open issues and the lack of data concerning many of them. It was also felt that the "platelet group" would need more time for in-depth discussion of many remaining questions. To this end, many participants expressed their interest and willingness to continue the work in further upcoming meetings in the tradition of the Kreuth initiative.

Recommendations

1. Pre-storage leucodepletion should be implemented to reduce platelet refractoriness and immunisation, and the risk of certain infections.

2. Of the transfusion-transmitted infections, bacterial contamination is currently the most frequent; it is strongly recommended that measures be taken to reduce this risk. Effective measures include limiting storage time, pathogen inactivation, and bacterial screening.

3. Consideration of the use of platelet additive solutions (PAS) is recommended to reduce immune mediated reactions.

4. More data need to be generated on the impact on platelet concentrates (PC) efficacy and safety of different methods of manufacture (e.g. aphaeresis versus whole blood derived; use of platelet additive solutions).

5. Comprehensive documentation of transfusion episodes (e.g. relevant patient characteristics, indication, outcome) is essential.

6. Key performance indicators are needed to monitor PC use.

7. For quality assurance of PC transfusions, clinical audit and feedback in each hospital are recommended.

8. More relevant clinical endpoints for prophylactic and therapeutic use of PC should be defined.

9. Strategies for management of refractoriness should be further evaluated.

10. The clinical significance of ABO compatibility of PC transfusion should be further studied.

11. The use of patient registries and/or pragmatic trials to improve information on outcomes should be explored.

12. In order to promote the implementation of these recommendations, more European public funding for clinical studies is advocated.

Optimal use of clotting factors and platelets

The Council of Europe is the continent's leading human rights organisation. It comprises 47 member states, 28 of which are members of the European Union. The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a directorate of the Council of Europe. Its mission is to contribute to the basic human right of access to good quality medicines and healthcare and to promote and protect public health.

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