European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

24-25 April 2009

Optimal Clinical Use of Blood Components

PROCEEDINGS

International Symposium co-organised by
the EDQM & HealthCare/DBO - Transfusion Medicine, Council of Europe
PEI, the German Official National Agency for Biologicals
The Transfusionsmedizin und Haemostaseologie, Klinikum der Universitaet Muenchen

***Wildbad Kreuth**, Bavaria, Germany*

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Paul-Ehrlich-Institut

Bibliografische Information der Deutschen Nationalbibliothek
Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über
http://dnb.d-nb.de abrufbar.

ISBN 978-3-86853-674-4

Herausgegeben von Prof. W. Schramm,
LMU im Nov. 2010
in Vertretung von Dr. J-M. Spieser, EDQM und Prof. R. Seitz, PEI

Sternstr. 18, 80538 München
Tel.: 089/66060798
www.dr.hut-verlag.de

1. Auflage 2010

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Introduction to Kreuth Proceedings:

About 8 years after having organised a meeting of specialists from the, at that time 15 EU member states in Wildbad Kreuth (Bavaria) to exchange view points on possible ways to optimise the use of blood components, the organizers approached the EDQM to seek the possibility of getting experts together on a larger international scale. This continuation of the Kreuth initiative aimed at exchanging view points and gathering information in the field of therapeutical application of transfusion medicine, in order to make recommendations on how to optimise the clinical use of blood and blood components based on clinical evidence. The challenge was taken up by the LMU Munich and relevant Health Authorities, namely PEI and the EDQM who accepted to pool together their resources and experience to foster a successful meeting, and the basis for a new symposium in April 2009 was launched.

In order to prepare the participants for a fruitful discussion, a survey was launched prior to the Conference on the basis of the recommendations set up in the 1999 Kreuth meeting to query whether they were still acceptable, and which adaptation they might need in view of the changing environment.

We would wish to thank the Deutsche Ärztekammer (German Medical Association) who agreed to have their just finalised Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives translated into English; this document was used as a useful model for further elaborating on optimal clinical use of blood components and plasma derivatives, and access to these life saving products to all patients in need.

Finally, 110 experts from 38 countries accepted the invitation to meet in Kreuth again on 25-26 April 2009, to exchange their experiences with the aim to develop a consensus largely accepted internationally on the clinical use of blood components and to revisit the 1999 recommendations. The discussions were centred around four topics:

1. Blood products: red cells, platelets, fresh frozen plasma, albumin
2. Clotting factor concentrates and haemophilia treatment
3. Quality management in clinical use
4. Efficacy in terms of outcome including Health Technology Assessment and cost-effectiveness.

The present book represents the proceedings of the scientific presentations and the debates held during the workshops, their consensual conclusion and the final recommendations. The outcome is an updated appraisal of the state of the art, in view of an optimal clinical use of blood components and albumin and clotting factors which can be presented as an international reference, and will largely be distributed to relevant stakeholders including scientific and professional societies.

These proceedings will hopefully form the basis of further discussions at the level of the relevant National Authorities, but mainly European Institutions such as the EU Commission DG Sanco, and the Council of Europe/EDQM relevant scientific committees, and also beyond Europe, notably WHO.



Prof W. Schramm | Prof R. Seitz | Dr J-M. Spieser

Programme

European Symposium on "Optimal Clinical Use of Blood Components"
April 24th-25th 2009, Wildbad Kreuth, Germany

Friday 24 April 2009

8.00 – 10.00	**Welcome**	EDQM- 5mn BMG F. v. Auer- 5 mn University of Munich B. Göke- 5 mn
	Challenges in Haemotherapy **Key elements and Rationale for the meeting**	W. Schramm- 10 mn J.-M. Spieser- 10 mn
	Status quo: Safety, supply vs. demand, regulations	R. Seitz- 15-20 mn
	Report on the EUOBUP project	B. McClelland (tbc)- 10 mn
	Guidelines for Haemotherapy: The German Approach	P. Scriba- 5 mn H. Klüter- 15 mn
10.00 – 10.30	Coffee Break	
10.30 – 13.00	**Different perspectives on optimal clinical use of blood components**	
	1. Blood products: red cells, platelets, FFP, albumin	
	• Transfusion services • Clinicians	E. Seifried- 15 mn H. Gombotz- 20 mn
	2. Clotting factor concentrates and haemophilia treatment	
	• Clinicians • Patient organisations (WFH/EHC) • Rare disorders	P. Giangrande - 15 mn B. O'Mahony- 15 mn F. Peyvandi- 15 mn

3. Quality management in clinical use

- Transfusion services — E. Briet- 15 mn
- Clinicians: management of bleeding — M. Spannagl- 10 mn; M. Samama- 10 mn
- Education in Haemostasis — J. Astermark- 15 mn

13.00 – 14.00 Lunch

14.00 – 15.10 ***4. Efficacy in terms of outcome***

- Transfusion services — C. van der Poel (tbc)- 15 mn; C. Politis (tbc)- 15 mn
- Clinicians:
  Health Technology Assessment; — A. Nimmo - 10 mn
  Clotting factor concentrates / Haemophilia — G. Minno - 10 mn

15.10 – 15.30 Coffee break

15.30 – 18.45 ***Discussion in working groups***

- Working group 1 Blood products (Red blood cells, platelets, fresh frozen plasma and albumin)
- Working group 2 Clotting factor concentrates and haemophilia treatment
- Working group 3 Quality management in clinical use
- Working group 4 Efficacy in terms of outcome (including economical aspects)

20.00 ***Dinner***

Saturday 25 April 2009

08.00 – 09.00 ***Plenary session: Interim reports from working groups***

09.00 – 10.45 ***Discussion in working groups***

10.45 –11.00 Coffee break

11.00 – 13.00 ***Plenary session: Final reports from working groups***

- Working group 1 Blood products (Red blood cells, platelets, fresh frozen plasma and albumin)
- Working group 2 Clotting factor concentrates and haemophilia treatment
- Working group 3 Quality management in clinical use
- Working group 4 Efficacy in terms of outcome (including economical aspects)

13:00 – 14:00 Lunch

14:00 – 17:00 ***Plenary session: Conclusions and Recommendations***

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Department of Biological Standardisation, OMCL-Network & HealthCare (DBO)

SYMPOSIUM ON "OPTIMAL CLINICAL USE OF BLOOD COMPONENTS; QUALITY AND BEST PRACTICES IN HAEMOTHERAPY"

VENUE: Wildbad Kreuth – Bavaria – Germany - 24-25 April 2009

Participants list

24 – 25 April 2009

Participant	Laboratory/Institute	Country
ABU AMIN Noryati	World Health Organisation (WHO)	Switzerland
AGAFONOVA Zoya	Burnazyan Federeal Medical Biophysical Center	Russian Federation
AKESON Jonas	Malmö University Hospital	Sweden
ANDREEV Andrey Angelov	National Center of Transfusion Haematology	Bulgaria
AUVINEN Marja-Kaisa	Finnish Red Cross – Blood Service	Finland
AVALISHVILI Levan	The Jo Ann Medical Centre	Georgia
BAELE Philippe	Cliniques Universitaires Saint Luc	Belgium
BAGDATEVA Marina	Clinical Hospital 119 of Federal Medico-biological Agency	Russian Federation
BAROTINE TOTH Klara	Hungarian National Blood Transfusion Service-Ministry of Health	Hungary
BASTIDA Eva	Plasma Proteins Therapeutics Association (PPTA)	Spain
BEHR-GROSS Marie-Emmanuelle	EDQM	
BEIN Gregor	Institut für Klin. Immunologie und Transfusionsmedizin	Germany
BENSON Kaaron	H. Lee Moffitt Cancer Center	USA
BERGER Karin	University Hospital of Munich	Germany

BOGDANOVA Vera	Federal Medico Biological Agency	Russian Federation
BRIËT Ernest	Sanquin Blood Supply Foundation	Netherlands
BUCHHEIT Karl Heinz	EDQM	
BURGER Reinhard	Robert Koch-Institut	Germany
CEBOTARI Svetlana	National Blood Transfusion Centre	Moldova
CHRONIDES Antonis	Nicosia General Hospital	Cyprus
CID Joan	Hospital Universitario de Tarragona Juan XXIII	Spain
CORDOBA Raul	Hospital Infanta Sofia	Spain
COURRIER Paul	Centre de Transfusion sanguine de la Croix-Rouge	Luxembourg
DAGBASHYAN Smbat	Center of Heamatology and Blood Transfusion - Ministry of Health	Armenia
DAVID Bernard	Etablissement français du sang	France
DE ANGELIS Vincenzo	Trieste University Hospital-Transfusion Medicines	Italy
DE WIT Jeroen	Sanquin Blood Supply Foundation	Netherlands
DHINGRA Neelam	World Health Organisation (WHO)-Blood Transfusion Safety	Switzerland
DI MINNO Giovanni	Centro di Coordinamento regionale per le emocoagulopatie	Italy
DOBROTA Alina Mirella	Regional Centre for Blood Transfusion	Romania
ERTUGRUL Nigar	European Union Coordination Dept- Ministry of Health	Turkey
ESPIRITO SANTO Deondile	Hospital D. Estefania	Portugal
FABBRIZZI Fabrizio	Plasma Proteins Therapeutics Association (PPTA)	Italy
FLESLAND Oystein	Asker and Baerum Hospital	Norway
GIANGRANDE Paul	Oxford Haemophilia & Thrombosis Center	United Kingdom
GOKE Burkhard	Klinikum der Universität München	Germany
GOMBOTZ Hans	Allgemeines Krankenhaus der stadt Linz GmbH	Austria
HARUTYUNYAN Hayk	Center of Heamatology - Ministry of Health	Armenia
HEIDEN Margarethe	Paul Ehrlich Institut	Germany
HEIN Marju	Haematology and Oncology Clinic of Tartu University	Estonia

HOINARESCU Mihaela	National Institute of Transfusion Haematology	Romania
JOHANSSON Pär	Blood Bank 2034 - Rigshsopiatlet	Denmark
JURSEVICA Evelina	Latvian State Blood Donor Centre	Latvia
KARAKOC Imdat	EU Coordination Dept - Ministry of Health	Turkey
KAVALLIEROU-SIONI Garyfalia	Blood Transfusion Centre, General Hospital Athens	Greece
KLEIN Harvey	National Institutes of Health – Clinical Center	USA
KLUTER Harald	Institut fur Transfusiosmedizin und Immunologie	Germany
KORSAK Jolanta	Military Institute of Medicine - Dept of Transfusiology	Poland
KORTE Wolfgang	Institut fur Klinische Chemie und Hamatologie	Switzerland
LASPINA Stephan	Mater Dei Hospital Blood Bank	Malta
LESICKA-GORECKA Joanna	Narodowe Centrum KRWI	Poland
LEVY Guy	Blood Transfusion Service of the Swiss Red Cross	Switzerland
LIUMBRUNO Giancarlo Maria	Italian National Blood Centre	Italy
LOREK Malgorzata	Narodowe Centrum KRWI	Poland
LOZANO Miguel	Hospital Clinic Provincial	Spain
MACLENNAN Sheila	NHS Blood and Transplant - Leeds Centre	United Kingdom
MANSOURI Behrouz	Inselspital Universitätsspital Bern	Switzerland
MARANTIDOU Olga	General Hospital Athens	Greece
MASHAROVA Natalia	National Institute of Haematology and Transfusiology	Bulgaria
MC CLELLAND Brian	Scottish National Blood Transfusion Service	United Kingdom
MENITOVE Jay	Community Blood Center of Greater Kansas City	USA
MESAR Peter	Klinika pediatrickej onkologie a hematoloogie - Children University	Slovak Republic
MISKOVITS Eszter	HNBTS	Hungary
NASCIMENTO Fatima	Instituto Portugues do Sangue	Portugal
NAUJOKAITE Alvyda	Steering Committee of the National Program - Ministry of Health	Lithuania
NIMMO Alastair	Royal Infirmary of Edinburgh	United Kingdom

NORDA Rut	Clinic Immunology and Transfusion Medicine	Sweden
NORGAARD Astrid	Blood Bank 2034, Rigshsopiatlet	Denmark
NUSSBAUMER Walter	Zentralinstitut fur Bluttransfusion Innsbruck	Austria
O'CONNELL Niamh	Hospital Consultant Haematologist	Ireland
O'MAHONY Brian	Irish Haemophilia Society	Ireland
OSTERMANN Helmut	Klinikum der Universitat Muenchen	Germany
OZIER Yves	Cochin University Hospital	France
PABINGER-FASCHING Ingrid	Medizinische Universtat Wien	Austria
PEERLINCK Kathelijne	UZ Leuven – Hemophilia Centre	Belgium
PETRINI Pia	Karolinska Institute – Hospital	Sweden
PEYVANDI Flora	Universita degli Studi di Milano	Italy
PLEYM Hilde	St Olav University Hospital	Norway
POLITIS Constantina	Ministry of Health and Social Solidarity	Greece
PROCHAZKOVA Renata	Krajska Nemocnice Liberec	Czech Republic
PUNAB Mari	Tartu University Hospital	Estonia
PUPELLA Simonetta	Italian National Blood Centre	Italy
RASOVIC Gordana	Blood Transfusion Center - Clinical Center of Montenegro	Montenegro
REBULLA Paolo	Fondazione Ospedale Maggiore Policlinico	Italy
REHACEK Vit	Fakultni Nemocnice Hradec Kralove	Czech Republic
REMEIKIENE Diana	Kaunas Medical University Clinics	Lithuania
RIVERA José	Centro de Transfusion de Murcia	Spain
ROSOCHOVA Jana	National Transfusion Service of Slovak Republic	Slovak Republic
SAMAMA Marc	Hotel-Dieu University Hospital	France
SAMARDZIJA Marina	Clinical Hospital Osijek – Dept of Transfusion Medicine	Croatia
SCHENNACH Harald	Zentralikinstitut für Bluttransfusion	Austria
SCHRAMM Wolfgang	Klinikum der Universitaet Muenchen	Germany

SCRIBA Peter	Medizinische Klinik – Innenstadt	Germany
SEIFRIED Erhard	DRK – Blutspendedienst Hessen	Germany
SEITZ Rainer	Paul Ehrlich Institut	Germany
SERBAN Margit	University of Medicine and Pharmacy Victor Babes	Romania
SONDAG-Thull Danielle	La Croix-Rouge de Belgique	Belgium
SPANNAGL Michael	University Hospital of Munich	Germany
SPIESER Jean-Marc	EDQM	
STEINERTE Anna	Latvian State Blood Donor Centre	Latvia
STRAUSS-PATKO Maja	Croatian Institute of Transfusion Medicine	Croatia
TRINKAUS Miha	Zavod Za Transfuzijsno Medicino	Slovenia
VAKKURI Anne	Helsinki University Central Hospital	Finland
VAN DER POEL Cees	Sanquin Blood Supply Foundation	Netherlands
VASILJEVIC Nada	National Coordinator of the National Blood Transfusion	Serbia
VELATI Claudio	General Hospital of Sondrio	Italy
VON AUER Friedger	Bundesministerium fur Gesundheit	Germany
VON HOEGEN Ilka	Plasma Proteins Therapeutics Association (PPTA)	Belgium
WALLER Charles	Plasma Proteins Therapeutics Association (PPTA)	
WALLVIK Jonas	Section for Hemaology – Dept of Medicine	Sweden
WALSH Tim	The Royal Infirmary of Edinburgh	United Kingdom
WELTE Martin	Institut fur Anaesthesiologie, Operative intensivmedisin und Schmerztherapie	Germany
ZWAGINGA Jaap Jan	Leids Universitair Meedisch Centrum	Netherlands

General enquiry in preparation of the European Symposium "Optimal Clinical Use of Blood Components"

General enquiry in preparation of the European Symposium "Optimal Clinical Use of Blood Components"

April 24th – 25th 2009, Wildbad Kreuth, Bavaria, Germany

Optimal use of blood and blood products is a postulate from clinical, ethical, moral, and social perspectives. 15 years after publication of the Sanguis study [1], apparently still large variations in blood usage exist despite the publication of numerous guidelines and reports on the optimal use of blood and its components.

Ten years ago a first milestone was set by the European Commission: The "Wildbad Kreuth Initiative" was a seminal meeting of experts from all member states of the European Union with the objective to explore existing practice, examine the literature, and provide recommendations for the implementation of optimal use of blood and blood products, as an element of a strategy for the European Union for blood safety and self-sufficiency. As major outcome of this initiative European recommendations have been published [2]. However since that time a tremendous number of new publications, new trends in treatment patterns and a growing focus on economic issues have changed the environment as compared to 1999.

As the World Health Organization stated, "Blood is an expensive and scarce resource. Unnecessary transfusion may cause a shortage of blood products for patients in real need." For the current century it can be anticipated that in most European countries the demand for blood and blood products will grow. The main reason for this is the demographic change towards ageing populations. Subsequently, the number of blood donations will decrease and the demand for blood products will grow with increasing morbidity and need for invasive procedures.

Discussing optimal use means talking about the right blood product for the right patient at the right moment, and to ensure appropriate documentation (Wildbad Kreuth Initiative 1999, of Conclusion No. 71). Transparency of treatment patterns, outcome and health economic data support the provision of optimal treatment and addresses also the economic concern from providers' and financial supports' perspective. Best practice in haemotherapy leads to avoidance of overuse, underuse, and inappropriate use.

[1] Use of blood products for elective surgery in 43 European hospitals. The Sanguis Study Group. Transfusion Medicine 1994; 4 (4): 251-268.

[2] Blood safety in the European Community: An initiative for optimal use.1999. Edt. W Schramm, R. Seitz, F. v. Auer. ISBN: 3-00-005705-6.

The second Symposium in Wildbad Kreuth will be largely sponsored by the European Directorate for the Quality of Medicines & Healthcare (EDQM) and will considerably broaden the scope beyond the EU member states of 1999, as members from almost all european countries are invited.
To prepare this meeting and ensure focused and fruitful discussions, it is deemed necessary to perform a survey on the actual status in the participating countries, in order to have a more precise idea about their supply situation, current practice and strategic needs are. The objective of the following questionnaire is to obtain country specific information on elements of the national health care structure and how they may influence best practice care/optimal use of blood.

The information gathered will remain confidential and any report or document worked out of this enquiry will be anonymised if so wished or required.

All data collected for the survey will be transferred securely to EDQM, will not be used for any other purpose whatsoever, and will be securely archived after the data has been successfully received and confirmed by EDQM.

We kindly ask you to answer the questions based on your individual national background and experiences in the area of blood usage.

We would greatly appreciate if you could complete the questionnaire either:

- directly online, using the following link http://www.wildbad-kreuth-2009.de (using the User Name & Password provided separately), or
- complete the questionnaire on your computer in PDF form on this document, and return it as an email attachment, or
- print out the questionnaire, complete it, and return it by fax.

Deadline April 8th: Completion of online questionnaire, or return by email, or send by fax.

EDQM – European Directorate for the Quality of Medicines & Healthcare
Jean-Marc SPIESER
Head of DBO, EDQM, Council of Europe

By Mail: Ahlem.Sanchez@edqm.eu (by preference)

or by Fax: +33 (0) 3 88 41 27 71

Thank you very much for your well appreciated contribution!
We look forward to welcoming you in Wildbad Kreuth on April 24th–25th 2009.

Prof. Dr. Wolfgang Schramm **Prof. Rainer Seitz** **Jean-Marc Spieser**

The information reported in this questionnaire will remain confidential and any report or document worked out of this enquiry will be anonymised if so wished or required.

If needed, please do not hesitate to add extra pages for your comments, if the space allowed is insufficient. Please then indicate in the relevant item that you have attached extra pages. (Please use .doc or .pdf format.)

For evaluation purposes we kindly ask you to give us the following background information:

Please indicate for what country the information is given _____

What is your professional background:

- ☐ Transfusion service
- ☐ Clinician in daily clinical routine care
- ☐ Governmental / Regulatory Authority

1. Guidelines

Do you use international recommendations or guidelines for the clinical use of blood products?

☐ Yes ☐ No

☐ Council of Europe

☐ Other (please indicate origin) _____

Do you use any specific national guidelines for clinical use of blood products?

☐ Yes ☐ No

Guidelines, Issuing Institution, Year: Please could you attach a copy of these guidelines to this questionnaire _____

Do these specific national guidelines cover:

Blood product (red blood cells, platelets, fresh frozen plasma, albumin	☐ Yes	☐ No
Clotting factor concentrates and haemophilia treatment	☐ Yes	☐ No
Quality management in clinical use	☐ Yes	☐ No

Are these specific national guidelines regularly updated? ☐ Yes ☐ No

Do you consider guidelines useful for the daily routine practice? ☐ Yes ☐ No

Comments: _____

2. Quality Management in clinical use of blood products

Clinical Decision making process: Who decides usually in clinical daily routine use on blood product usage?

Operating Theatre

- ☐ Anesthesiologist
- ☐ Surgeon
- ☐ Transfusion/Haemostasis specialists
- ☐ Other Specialist
- ☐ Others _____

Ward/Intensive care unit

- ☐ Anesthesiologist
- ☐ Surgeon
- ☐ Transfusion/Haemostasis specialists
- ☐ Other Specialist
- ☐ Specialist in internal medicine
- ☐ Others _____

Does your health care system collect quantitative information about the use of blood products?

☐ Yes ☐ No

Where is this information documented?

National registry ☐

National providers ☐

Others _____

Comments: _____

Do you have tracer operations like hip replacement or myocardial revascularization to control the use of blood products?

☐ Yes ☐ No

- ☐ Hip replacement
- ☐ Myocardial revascularization
- ☐ Others _____

Do you have any special regulation concerning for the use of blood products?

☐ Yes ☐ No

Do you have dedicated responsibilities for blood transfusion within the hospitals?

☐ Yes ☐ No

Do you operate a quality management systems for clinical blood usage?

☐ Yes ☐ No

Are the hospitals required to develop standard operating procedures?

☐ Yes ☐ No

Do you have a structured education for people involved in transfusion?

☐ Yes ☐ No

Do you consider it as important to assess efficacy / outcomes of transfusion?

☐ Yes ☐ No

What is the parameter of success?

- ☐ Laboratory parameters
- ☐ Outcomes in terms of morbidity
- ☐ Outcomes in term of mortality
- ☐ Others _____

3. Provision of blood products in your country

Who are the main providers of blood products in your country?

Provider	National	Private	Other	% of supply
_____	☐	☐	☐	_____
_____	☐	☐	☐	_____
_____	☐	☐	☐	_____

Do you encounter periods of shortage of blood products?

Red Cells	☐ Yes	☐ No
Platelets	☐ Yes	☐ No
Fresh Frozen Plasma	☐ Yes	☐ No
Albumin	☐ Yes	☐ No
Factor VIII		
Plasma-derived	☐ Yes	☐ No
Recombinants	☐ Yes	☐ No
Factor IX		
Plasma-derived	☐ Yes	☐ No
Recombinants	☐ Yes	☐ No

Analyzing the actual trends, how will these trends influence the supply and provision of blood products in the next years?

- ☐ Shortage
- ☐ Price increase
- ☐ Structural changes

What do you expect from health policy and regulatory institutions e.g. national authorities, EU/EDQM/WHO?

What are your priorities for the next years to achieve optimal provision of blood products?

How are blood products reimbursed in clinical care?

- ☐ Reimbursement is provided through a lump sum or DRG
- ☐ Blood products are separately reimbursed
  - ☐ fully reimbursed
  - ☐ partial reimbursed
  - ☐ special: _____
- ☐ Complete different modus of reimbursement, please specify:

8

Are there any patient co payments for blood products?

☐ Yes ☐ No

*What is the **average** price for blood products in your country? (indicate)*

Red Cells	_____	Euro per Unit
Platelets	_____	Euro per Unit
Fresh Frozen Plasma	_____	Euro per Unit
Albumin	_____	Euro per Unit
Factor VIII		
Plasma-derived	_____	Euro per Unit
Recombinants	_____	Euro per Unit
Factor IX		
Plasma-derived	_____	Euro per Unit
Recombinants	_____	Euro per Unit

BLOOD SAFETY IN THE EUROPEAN COMMUNITY: AN INITATIVE FOR OPTIMAL USE WILDBAD KREUTH, GERMANY

20–22 MAY 1999

Please find below the recommendations from the first Wildbad Kreuth Initiative, 1999.
We kindly ask you to give us feed back from your actual perspective if these earlier recommendations have been achieved, if they are still obsolete or if they have to be rediscussed and revised.
Further we are interested in the grade of priority of each of these earlier issued recommendations.

Chapter: Recommendations (No 97–150, p. 3–49)

3.1. RED BLOOD CELLS

3.1.1. Supply

97. Reduction of inappropriate blood use should help to minimise the incidence and severity of blood shortages. Consideration should be given to establishing a blood exchange programme in the European Community. Hospital inventory management should be optimised and should include the use of blood ordering schedules.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

98. An EC blood exchange programme could be envisaged as a single office serving as a central co-ordinating base matching shortages and available stock in different blood centres.
Such networks exist with varying success in several European centres. A pilot project would be necessary to assess whether the system would be useful or effective.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.1.2. Residual risk

99. Introduction of new strategies to improve transfusion safety should be prioritised on the basis of achievable safety gains. Optimising blood transfusion practices could be much more effective in terms of health gain and cost benefit than additional testing strategies.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

100. The administrative practices related to transfusion, including recipient identification and compatibility testing, vary widely in the Community. The basis for and the benefits of these differences need to be critically reviewed. Mortality and morbidity from ABO mismatch remains a very serious problem throughout the Community, and is probably far greater than any residual virus risk. Effective systems that reduce this risk to zero must be identified and adopted particularly at the hospital level.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

101. Certain definite indications for leucodepletion are generally agreed and implemented. Where leucodepletion is required it should be performed in a controlled fashion in a blood centre or facility, and in an optimum relation to the time of donation so as to minimise any risk of bacterial proliferation.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.1.3. Efficacy

102. Patients require a product that has maximum oxygen delivery capability and minimised risk. As optimum storage time and conditions as defined by clinical utility have never been determined they need to be urgently addressed.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.1.4. Inappropriate use

103. Every hospital undertaking blood transfusion must have a quality management system in place, that includes a designated and specially trained individual with responsibility for the quality of transfusion practice in the hospital and that includes a systematic programme of ongoing education and a documented and systematic approach to clinical audit. This system of clinical audit should use accepted specified audit measures uniformly adopted throughout the Community (to be specified) and a standardised, published audit report format, with published annual reports.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

104. Appropriate blood conservation programmes should be in use in every hospital.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

105. Attention should be given to the development of effective education programmes in transfusion at undergraduate and postgraduate level.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

106. There is an urgent need for well-designed large-scale studies in blood transfusion in surgical patients, both adult and paediatric, to provide even quite basic outcome data. These studies could be organised and funded on a Community level.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.2. PLATELETS

3.2.1. Products and their availability

107. Platelet products should be prepared and stored so as to maintain maximal therapeutic outcome and minimise untoward effects.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

108. Concerning availability, there is an urgent need to evaluate the impact of possible delays throughout the platelet transfusion chain as well as the cost-effectiveness of platelet transfusion therapy resulting from the introduction of NAT testing. Blood services should be organised in such a way so as to:

– minimise temporary and other possible shortages, e.g. rare phenotype platelets (collaboration between Member States may contribute to success in this respect); and

– minimise the wastage of products without compromising the quality of platelet concentrates.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

109. The implementation of NAT tests should enable the release of platelet concentrates preferably in less than 24 hours after donation.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.2.2. Indications and platelet transfusion threshold levels

110. The clinical decision to transfuse platelets should be based on careful evaluation of the individual patient's condition, including bleeding history, bleeding tendency, in addition to actual platelet count or any laboratory result reflecting platelet function.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

111. To support clinical decision making, it is strongly recommended that an algorithm for defining transfusion needs be developed. Such algorithms should be developed and implemented through the cooperative efforts of clinical and transfusion medicine specialists, and be subject to regular review.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.2.3. Dosage and efficacy

112. The outcome of platelet transfusion in terms of corrected platelet increment (CCI), for example, should be evaluated as a basis for improved transfusion practice. This involves assessing platelet recovery (or CI), actual increase in platelet count, and time (days) between two transfusions.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

113. It is recommended that research on developing better techniques to monitor the efficacy of platelet transfusion be supported.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.2.4. Refractoriness

114. Efforts should be made to prevent alloimmunisation in patients who are expected to be given repeated platelet transfusions by using products known to be less immunogenic such as leucocyte depleted cellular blood components.

Grade of priority of this recommendation
Please indicate from your opinion:

1	2	3	4	5
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.2.5. Quality aspects and haemovigilance

115. Development of algorithms in the appropriate use of platelet concentrates, in addition to the establishment of haemovigilance systems, is advocated as part of a quality system. The efficacy of platelet transfusion as well as the associated side effects should be assessed. Parameters on transfusion out-come should be registered and evaluated within an appropriate healthcare quality system.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.3. FRESH FROZEN PLASMA

116. For improved safety, FFP products that have been quarantined or virus attenuated should be used.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

117. The clinical and biological results of FFP infusion should be monitored since there are different FFP qualities available and the individual response of the patients with coagulation disorders may be variable.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

118. Since the intended benefit of FFP is the correction of coagulation disorders, tests that assess the haemostatic functions and provide results rapidly are essential for its optimal use. This implies the permanent availability of a laboratory to perform coagulation tests.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

119. The duration of therapy should be determined by clinical evaluation and serial determination of coagulation parameters.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

120. The numerous existing guidelines should be harmonised. Their dissemination and implementation should be strongly reinforced by quality assurance systems. As a possible way to improved application, summarised guidelines should be included on prescription forms and their impact should be measured.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

121. The education of medical personnel should be improved.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.4. ALBUMIN

122. The existing evidence from published clinical studies addressing albumin use is insufficient. A convincing elaboration of benefits of albumin with respect to measurable clinical endpoints in comparison to other colloids will need substantially augmented evidence by further well-designed clinical studies.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

123. Since a potential deleterious effect of albumin infusion has been highlighted in the Cochrane Injuries Group Albumin Reviewers meta-analysis, further studies on mortality are required.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

124. The impact of preparations with different albumin concentrations and their respective sodium content is unresolved and should be studied further with respect to clinical efficacy and economic consequences.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.5. CLOTTING FACTOR CONCENTRATES

125. In order that future requirements for expensive blood products within the European Community can be assessed, registers of patients with haemophilia and related disorders should be established and maintained in each Member State of the Community.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

126. A haemovigilance or pharmacovigilance programme should be established in the Community, in cooperation with each Member State, to gather information on such patient complications as inhibitor development, allergic reactions, viral transmission and other miscellaneous adverse events.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

127. A network of Comprehensive Care Centres should be established within each Member State, in accordance with common criteria, which would provide 24-hour clinical and laboratory service and be accessible to all patients.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

128. Adequate amounts of coagulation factor concentrates for the treatment of patients with haemophilia and related disorders should be available in each Member State. Quantities of both plasma--derived and recombinant products should be maintained, although it is recognised that recombinant products could gradually supplant plasma-derived ones. Individual patient preferences should be taken into consideration when choosing products.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

129. Particular attention needs to be taken by the European Community on the possible adverse consequences should a monopoly for the production of coagulation factor concentrates emerge. Research on the development of emerging recombinant technologies in the Community needs to be encouraged and funded.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

130. The numerous guidelines from medical bodies in the various Member States should be harmonised and expanded to include advice on dosages for the treatment of common spontaneous bleeding problems.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

131. As a general rule, prophylactic treatment for children with severe haemophilia is recommended.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

132. Immune tolerance should be offered to all patients with haemophilia who develop new inhibitory antibodies.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

133. The outcome of treatment, including parameters related to quality of life and economic aspects, still needs to be assessed, and further studies, which will require funding, should be initiated.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.6. QUALITY MANAGEMENT

134. There is an urgent need to foster the commitment of decision makers, both at national and local levels, to establish a Quality Management System within hospitals for the clinical use of blood products

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

135. There is the need to ensure that:
- A quality manager for clinical use of blood products is appointed and empowered to take appropriate actions to ensure and improve quality, in co-operation with the hospital transfusion committee; and
- The quality manager, along with the transfusion committee, should be responsible for defining and disseminating guidelines and SOPs for optimal use of blood products, and verifying their application by the healthcare professionals.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

136. There is the need to ensure that:
- Strategies are developed to maximise the cooperation of all healthcare professionals in the achievement of optimal use of blood products.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

137. There is an urgent need to:
- Carry out controlled studies to define the appropriate use for blood products and the parameters needed to evaluate their efficacy and outcome;
- Document the indications for the use of blood products on the request form; and
- Define a limited number of common indicators in order to allow comparison between different hospitals and increase awareness of inappropriate use.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

138. There is an urgent need to foster:
- A continuing education programme for healthcare professionals involved in the clinical use of blood products organised by the transfusion committee; and
- Inclusion of transfusion medicine in undergraduate and postgraduate training.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

139. In defining SOPs, particular attention should be given to preventing transfusion errors, re-engineering the process, and introducing, if possible, information instruments, such as portable barcode readers, to assess the identity of the patient, the blood samples and the assigned unit.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

140. The establishment of an integrated hospital information and documentation system is strongly recommended, since this could greatly facilitate the collection and analysis of data related to the use of blood products.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.7. ECONOMIC ASPECTS

3.7.1. Information needs

141. The epidemiology of blood and blood product use should be assessed in the European Community to determine the likely clinical need and assist in planning future provision.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

142. Blood and blood product use for the treatment of patients with index conditions should be recorded for each Member State on an annual basis, to provide baselines and indicators for comparison.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

143. Consideration should be made for a linkage between product usage and the clinical conditions for which they are being used. This might be best achieved through the use of automated databases, the use of electronic patient records and electronic prescribing.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

144. Reviews of blood and blood product use should be conducted using economic as well as clinical measures to determine the patterns of usage, to ascertain appropriateness of use, and to assess the effect of education programmes. Indicators should be developed to reflect optimum usage.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

145. Consideration should be given to sponsoring these kinds of studies across the European Community.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.7.2. Future demands

146. It is recognised that there are changes underway in the relative use of plasma-derived albumin, immunoglobulins, Factors VIII and IX. This will have important consequences on the costs and availability of these products in the future. A study of the future demand and need for blood and blood products should be undertaken with appropriate assessment of the economic factors to determine the viability of blood collection and fractionation centres.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

147. Consideration should be given to the rational distribution of these centres throughout the European Community, their commercial viability and national dependency in the context of self-sufficiency.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.7.3. Education requirements

148. Undergraduate and post-registration education and training of all clinicians who use blood and blood products should be promoted. Ways of increasing the impact of clinical recommendations and guidelines should be investigated.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

3.7.4. General recommendation

149. Economic evaluation should underpin the drive to improve the efficiency of resourcing and optimal use of blood and blood products, while maintaining the principle of voluntary non-remunerated blood donation.

Grade of priority of this recommendation
Please indicate from your opinion:

1 ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

150. The principle and the need for self-sufficiency should be re-assessed in the context of safety, availability, ethics and economics, in view of the continuing development of the European Community.

Grade of priority of this recommendation
Please indicate from your opinion:

1	*2*	*3*	*4*	*5*
☐	☐	☐	☐	☐

1 = lowest priority, 5 = highest priority

Actual perspective 2009

☐ Still valid ☐ Achieved and implemented ☐ Obsolete ☐ To be rediscussed and revised

Thank you very much!

Presentations

Challenges in Haemotherapy

Wolfgang Schramm

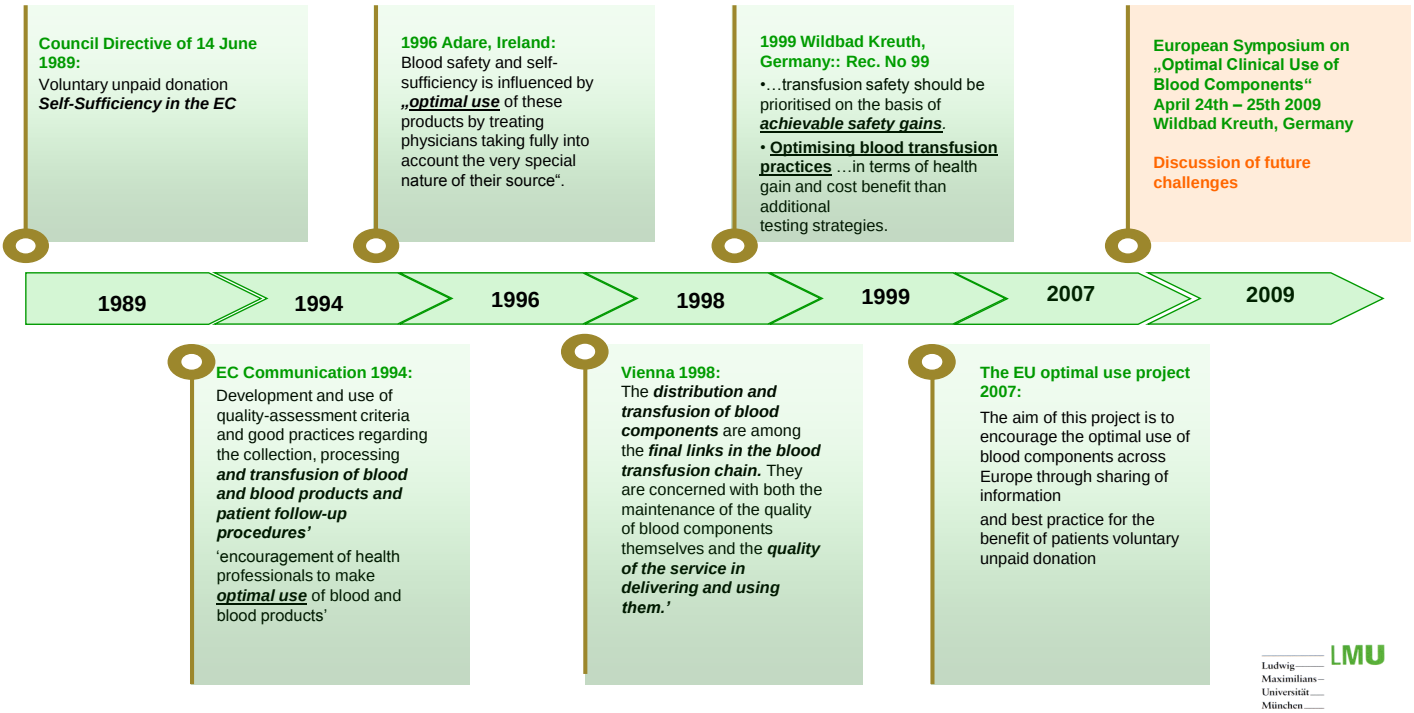
European Symposium on
“Optimal Clinical Use of Blood Components”
April 24th-25th 2009, Wildbad Kreuth, Germany

Challenges in Haemotherapy

Wolfgang Schramm
University Hospital of Munich
Dept. for Hemostasis and Transfusion Medicine
Germany

LMU Ludwig Maximilians Universität München

From Self- Sufficiency to Optimal Use of Blood and Blood Products in Europe



LMU Ludwig Maximilians Universität München

European Symposium on
"Optimal Clinical Use of Blood Components"
April 24th-25th 2009, Wildbad Kreuth, Germany

10 years after Wildbad Kreuth 1999

Since that time a tremendous number of new publications, new trends in treatment patterns, and a growing focus on economic issues have changed the environment as compared to 1999.

LMU Ludwig Maximilians Universität München

Haemophilia Care - European perspective

Wildbad Kreuth Initiative 1999

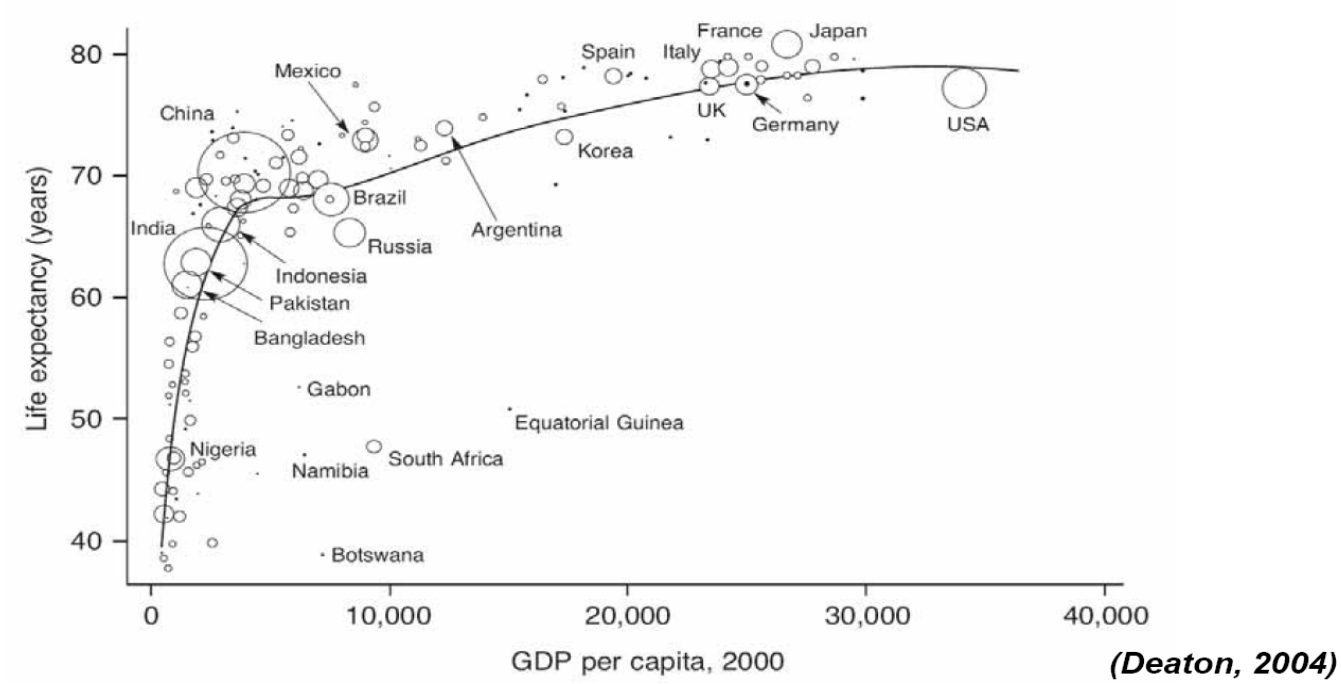
Recommendation 128

"Adequate amounts of coagulation factor concentrates for the treatment of patients with haemophilia and related disorders should be available in each Member State. Quantities of both plasma-derived and recombinant products should be maintained, although it is recognised that recombinant products could gradually supplant plasma-derived ones. Individual patient preferences should be taken into consideration when choosing products."

Schramm W.: Conference Proceedings ISBN 3-00-005705-6

LMU Ludwig Maximilians Universität München

Preston Curve in 2000

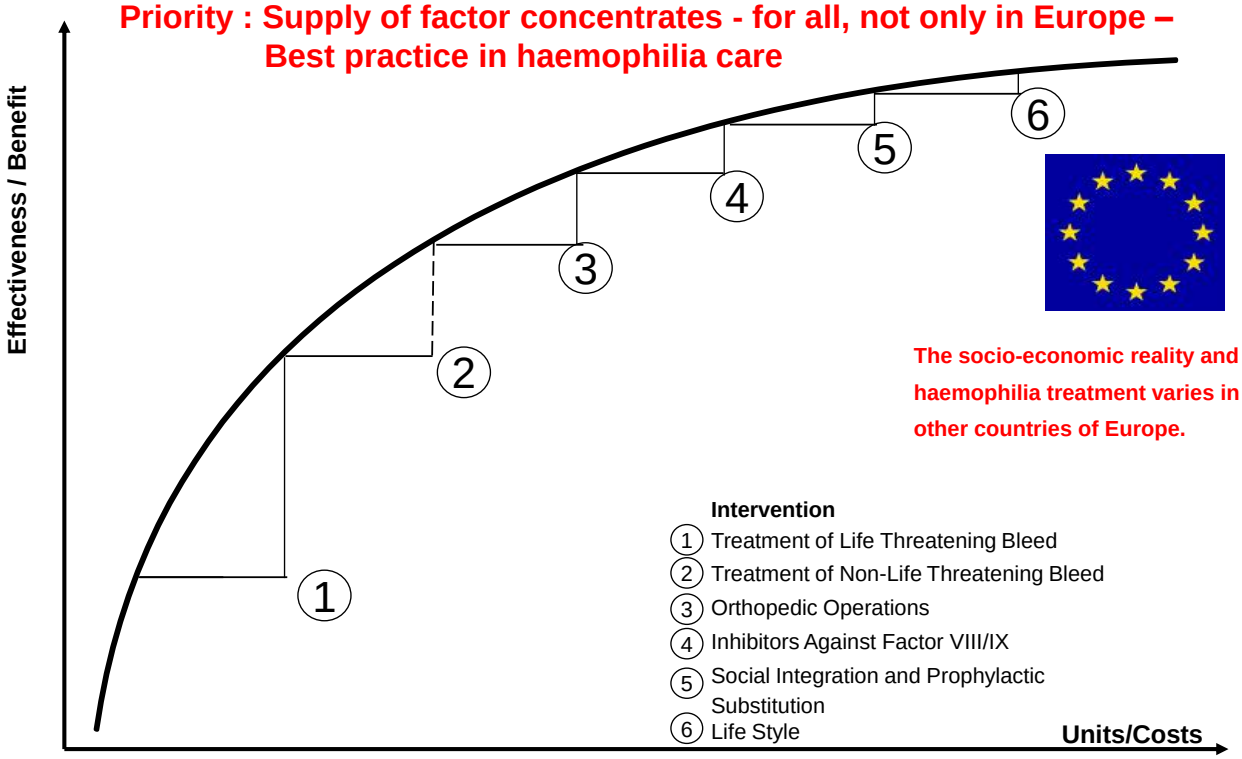


(Deaton, 2004)

LMU Ludwig Maximilians Universität München

Haemophilia Care in Europe

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



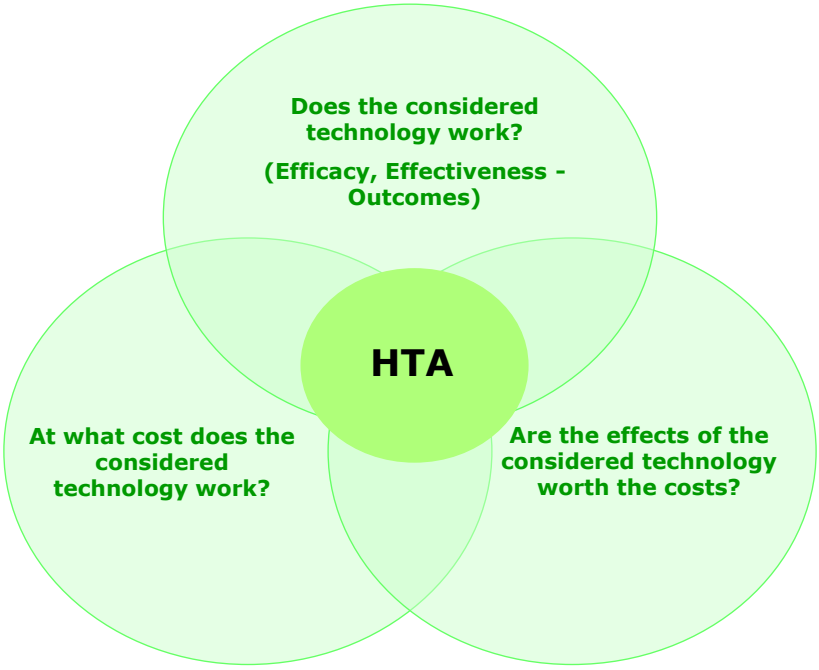
The socio-economic reality and haemophilia treatment varies in the EU & other countries of Europe.

Intervention

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

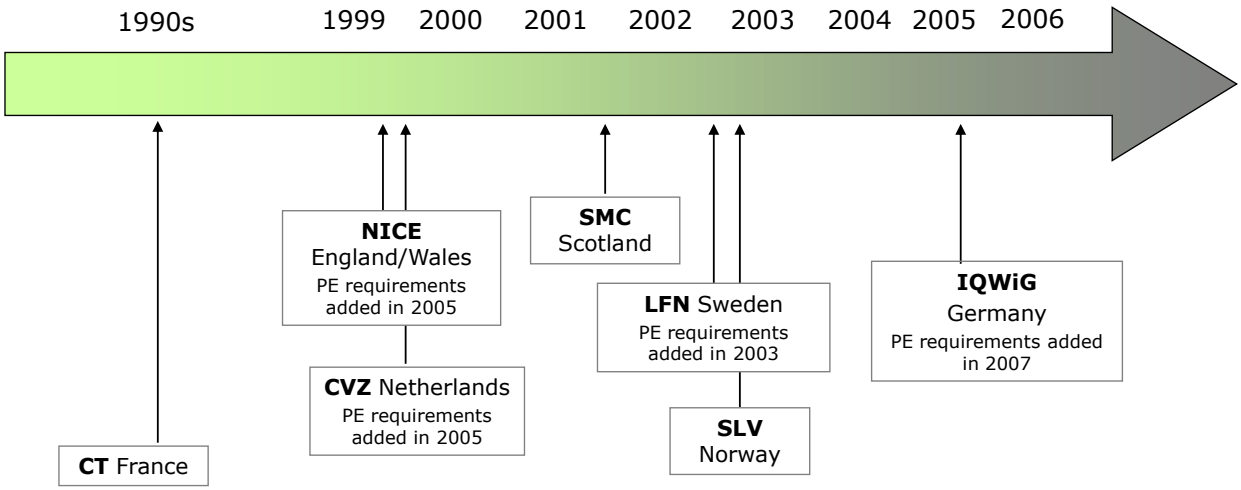
LMU Ludwig Maximilians Universität München

Health Technology Assessment (HTA) is a method to evaluate effectiveness, costs and impact of healthcare treatments to support decision-making under growing economic restrictions



LMU Ludwig Maximilians Universität München

Centers for Health Technology Assessment were founded in almost all health care systems with a growing influence on decision making processes



PE = Pharmacoeconomics

LMU Ludwig Maximilians Universität München

Optimal use of blood and blood products is also necessary from an ethical, moral and social point of view

The special case of blood:

„Blood is an expensive, scarce resource.

Unnecessary transfusion may cause a shortage

of blood products for patients in real need.“

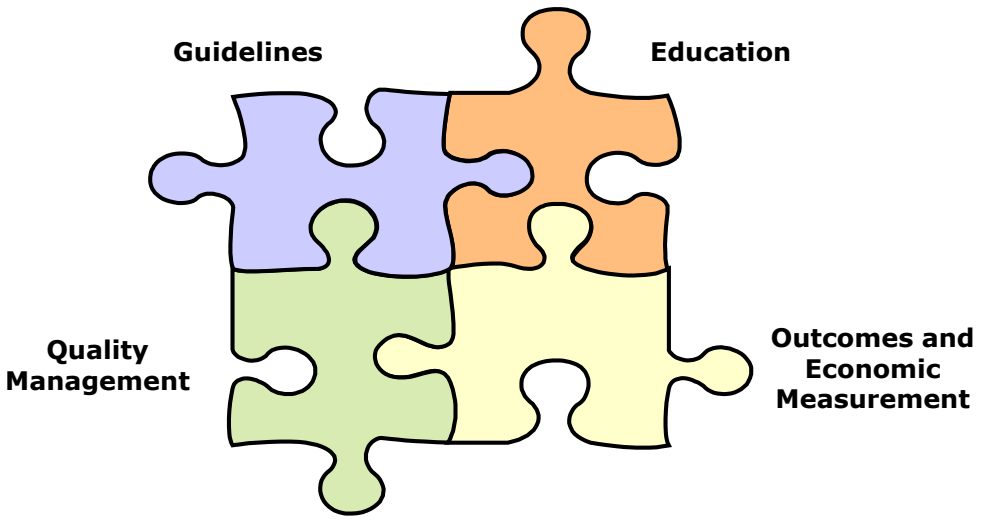
WHO (2001) - The clinical use of blood - Handbook

Synthetically substitution of blood is still not possible

Due to ageing populations it can be assumed that blood demand is increasing while blood supply is decreasing

Optimal Clinical Use of Blood Components

Four special challenges in Haemotherapy can be identified



Survey European Symposium „Optimal use of blood components“

The Survey targets the actual status of the blood supply situation, the current practice and strategic needs in the participating countries

Objectives of the survey:

- To obtain country specific information on the structure of national health care systems
- To find out how these structures influence best practice care and optimal use of blood and blood products
- To evaluate the recommendations of the first Wildbad Kreuth meeting; are these recommendations:
  - Still valid
  - Achieved and implemented
  - Obsolete
  - To be re-discussed and revised
- To assess how they are prioritized from an actual perspective

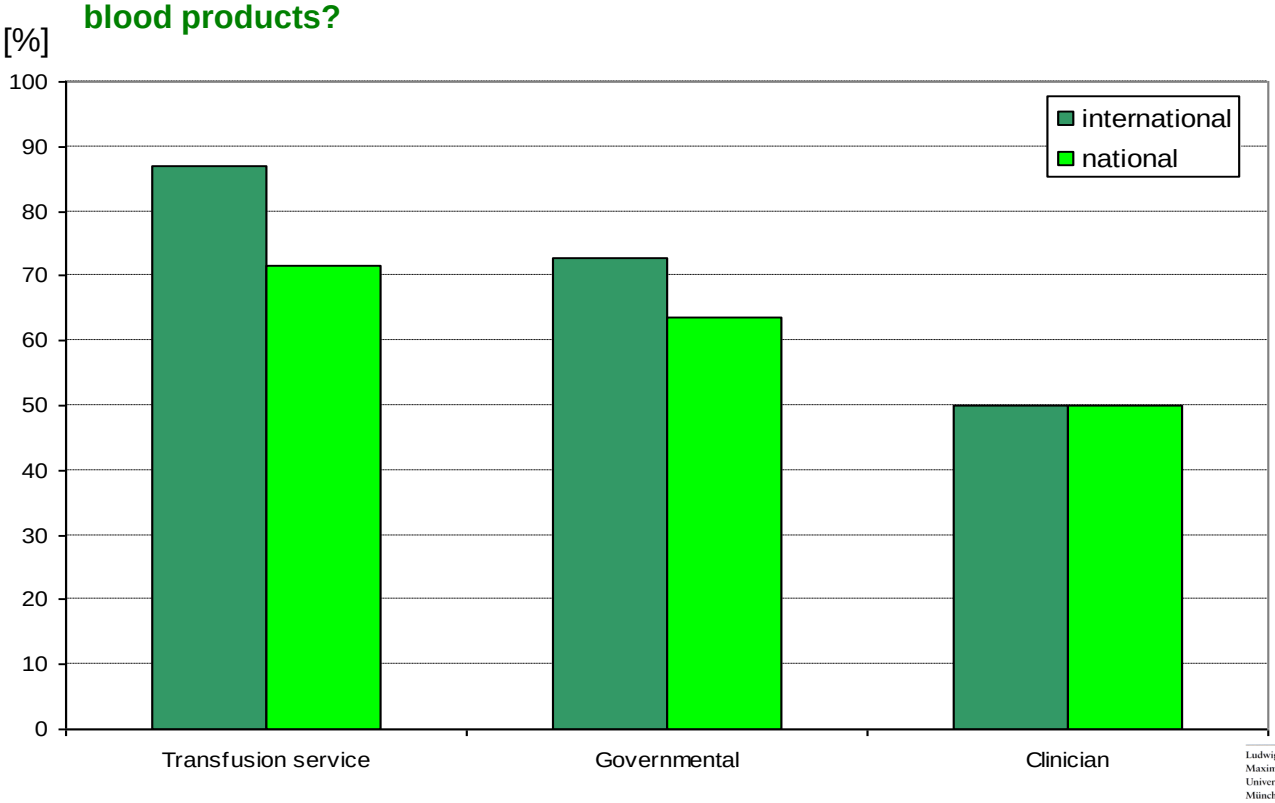
Survey design:

Addressees	All registered participants of the actual Wildbad Kreuth meeting
Questionnaire	e-CRF accessible over the Internet
Responders	N = 73
Time	March 2009

LMU Ludwig Maximilians Universität München

Evaluation of "LMU Questionnaire April 2009"

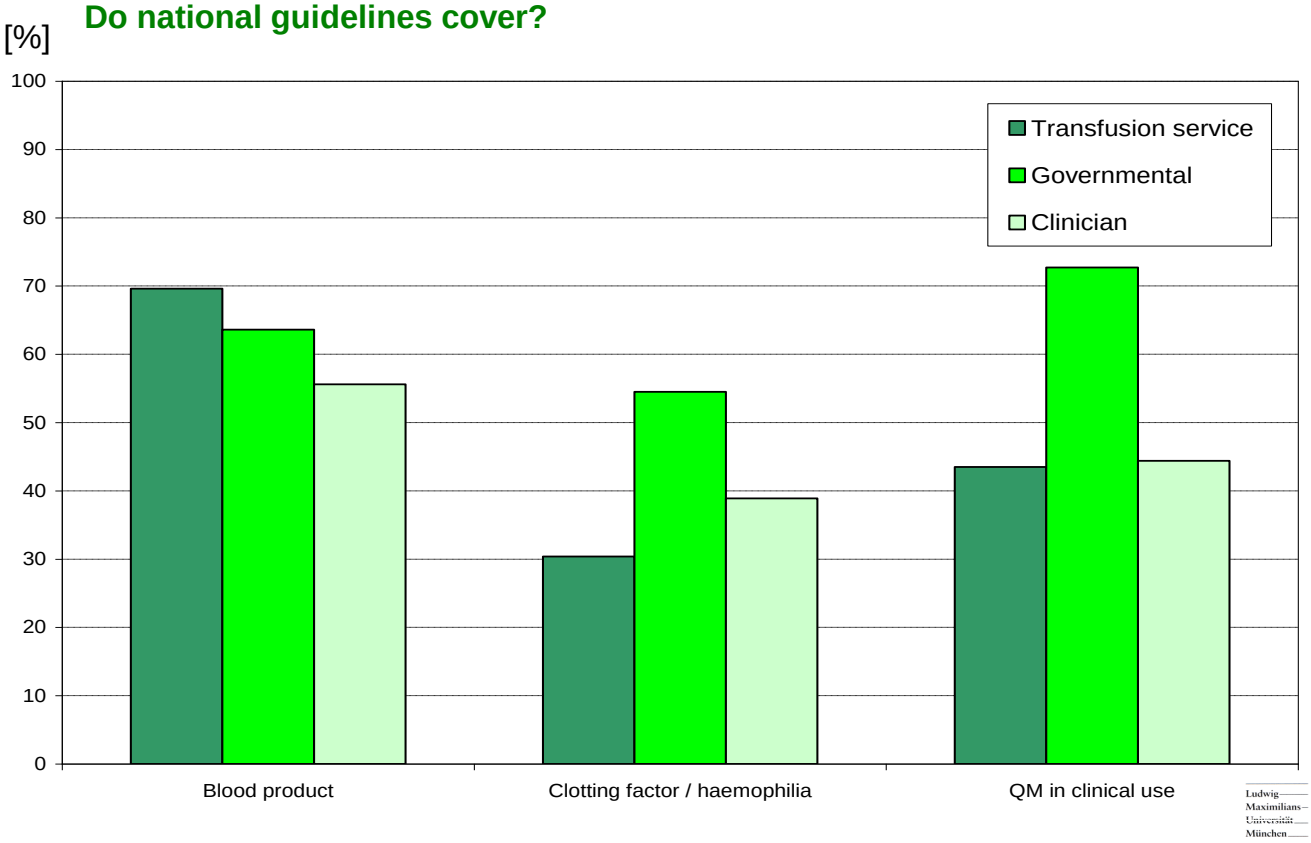
Do you use any specific international/national guidelines for clinical use of blood products?



LMU Ludwig Maximilians Universität München

Evaluation of "LMU Questionnaire April 2009"

Do national guidelines cover?



Survey European Symposium „Optimal use of blood components“

Results

73 participants completed the questionnaire, most of them working at transfusion services.

Transfusion service	**46 (63,89%)**
Clinician in daily clinical routine care	**21 (29.17%)**
Governmental / Regulatory Authority	**11 (15.28%)**
Other	**2 (2.78%)**

The majority of participants use guidelines (international and/or national) in daily practice and consider them useful.

	No (N (%)	**Yes (N / %)**
Do you use international recommendations or guidelines for the clinical use of blood products	**16 (23.53%)**	**51 (75%)**
Do you use any specific national guidelines for clinical use of blood products?	**21 (30.88%)**	**46 (67,65%)**
Are these national guidelines regularly updated	**20 (29.41%)**	**38 (55,88%)**
Do you consider guidelines useful for the daily routine practice	**4 (5.88%)**	**55 (80.88%)**

(multiple choices possible)

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Quality Management

	No (N (%)	Yes (N / %)
Does your health care system collect quantitative information about the use of blood products? Where is this information documented? National registry 30 (44.12%) National providers 15 (22.06%) Others 11(16.18%)	15 (20,83%)	56 (77.78%)
Do you have tracer operations like hip replacement or myocardial revascularization to control the use of blood products?	47 (65.28%)	19 (26.39%)
Do you have dedicated responsibilities for blood transfusion within the hospitals	11 (15.28)	58 (80.56%)
Do you operate a quality management system for blood usage?	7 (9.72%)	52 (72.22%)
Are the hospitals required to develop standard operating procedures?	9 (11.5%)	50 (69.44%)

A majority of responders have quantitative information on blood use, have clear responsibilities for blood transfusion, use a quality system and are working with SOPs

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Education

	No (N (%)	Yes (N / %)
Do you have a structured education for people involved in transfusion	22 (30,56%)	48 (66.67%)

A clear need for education in transfusion medicine was identified.
Over one third of the responders do not have a structured education programme.

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Efficacy in terms of outcomes and economics

	No (N (%)	Yes (N / %)
Do you consider it as important to assess efficacy / outcomes of transfusion?	1 (1.39%)	67 (93.06%)

What is the parameter of success?	
Laboratory parameters	47 (65.28%)
Outcomes in terms of morbidity	48 (66.67%)
Outcomes in term of mortality	46 (63.89%)
Others	16 (22.22%)

(multiple choices possible)

There is a clear committment to measure outcomes in transfusion medicine. However, only limited publications on outcomes show that possible study designs, study endpoints and statistical methods have to be discussed.

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Supply – Demand - Economics

Past

	No (N (%)	Yes (N / %)
Do you encounter periods of shortage of blood products?	21 (29.17%)	48 (66.67%)

Future

Analysing the actual trends, how will these trends influence the supply and provision of blood products in the next years?	
Shortage	34 (47.22%)
Price increase	31 (43.06%)
Structural changes	31 (43.06%)
Others	1 (1.39%)

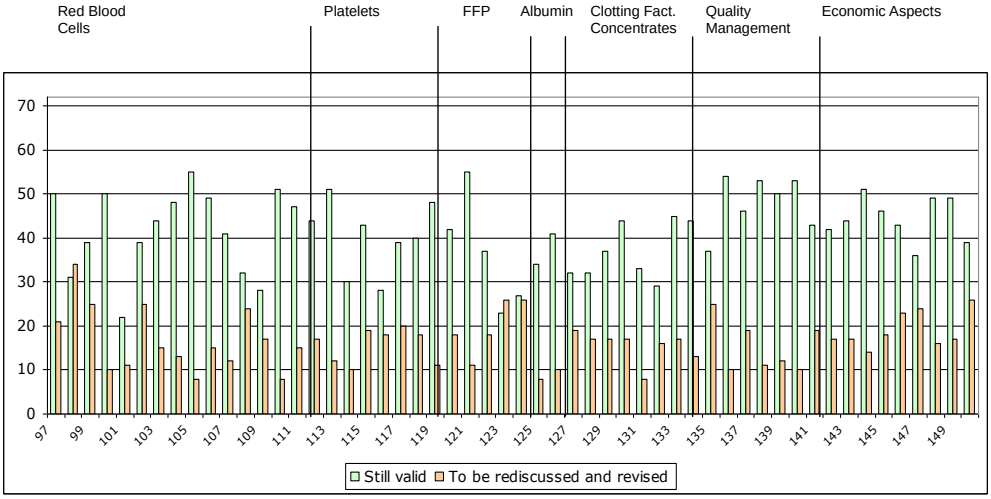
(multiple choices possible)

Supply and provision of blood components will be under pressure in the near future. Therefore strategies are expected to come from stakeholders (clinicians, porviders, authorities).

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999



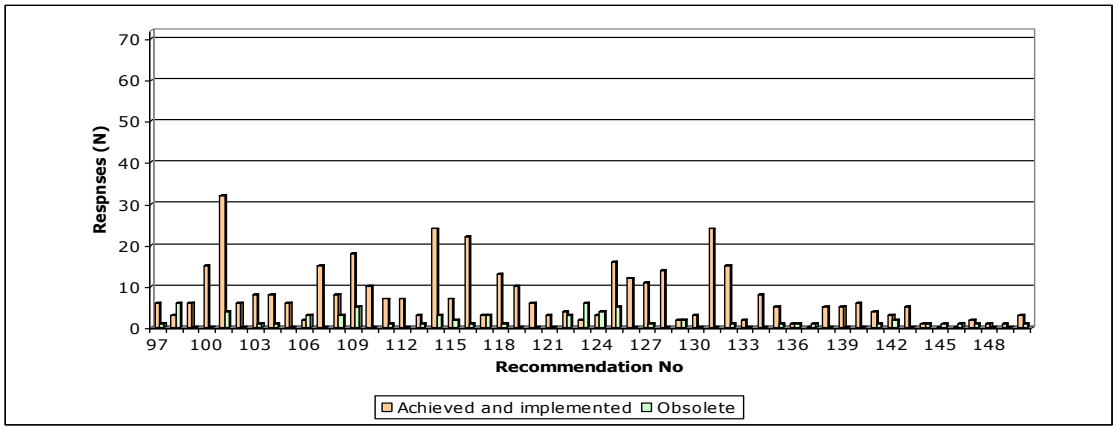
Total no. of questionnaires: 72. Multiple choice answers were possible

Most of the recommendations are assessed „still valid“ and / or that they should „be re-discussed and revised“.

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999



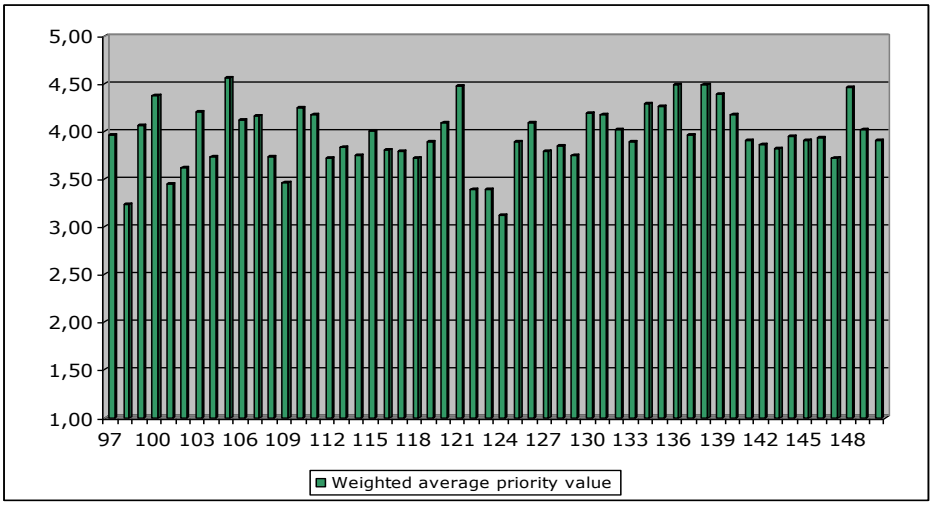
Total no. of questionnaires: 72. Multiple choice answers were possible

Until totay they rarely translated in daily routine transfusion practice. Critical discussions may identify reasons. Rediscussions and revisions may support to define actual implementation strategies.

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999

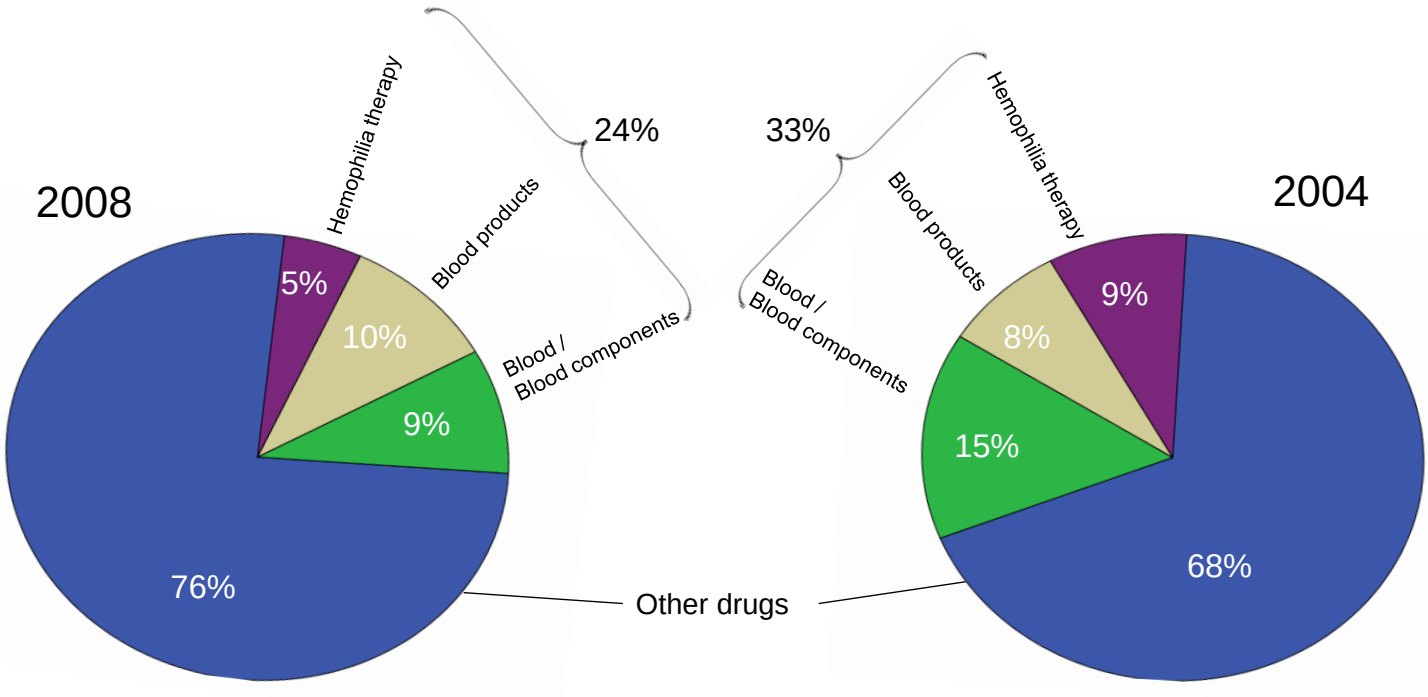


1 = Lowest priority; 5= highest priority

The priority for almost all recommendations has been valued high.

LMU Ludwig Maximilians Universität München

University hospitals Munich:
Annual expenses for drugs



~ 71,7 Mio €

~ 51,2 Mio €

LMU Ludwig Maximilians Universität München

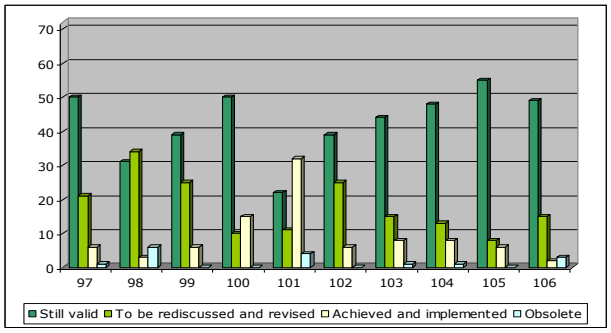
Challenges in Haemotherapy

LMU Ludwig Maximilians Universität München

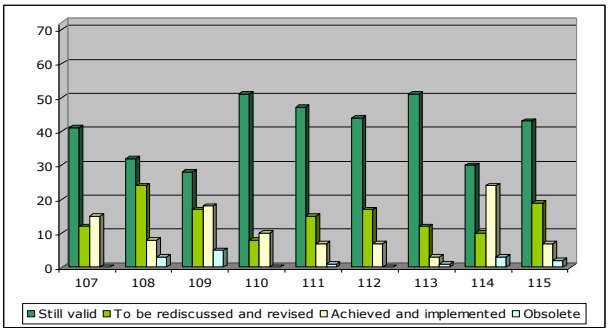
Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999

Red Blood Cells



Platelets



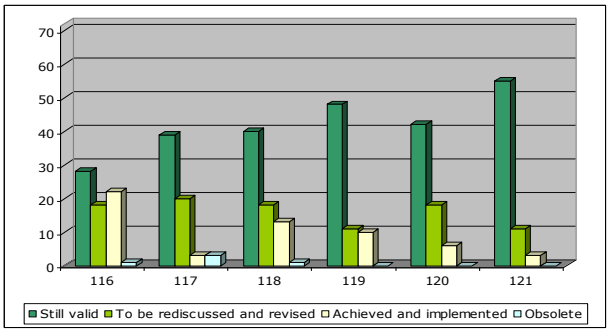
Total no. of questionnaires: 72. Multiple choice answers were possible

LMU Ludwig Maximilians Universität München

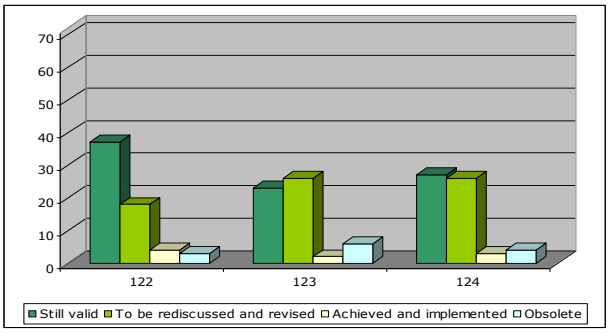
Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999

FFP



Albumin



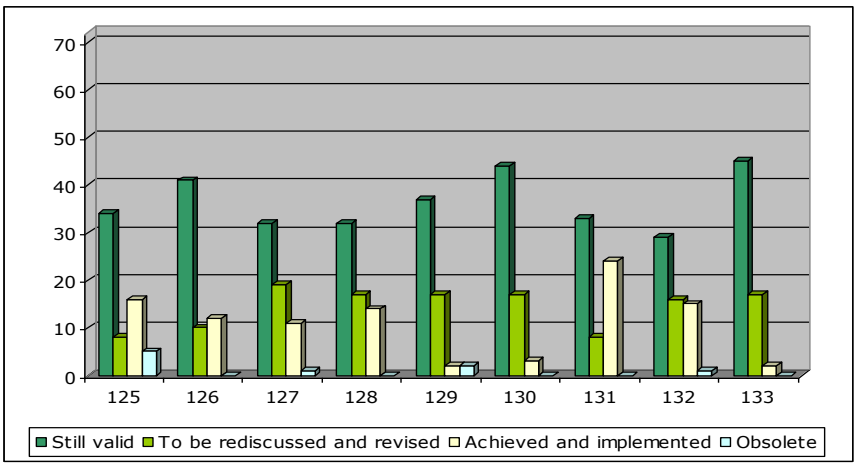
Total no. of questionnaires: 72. Multiple choice answers were possible

LMU Ludwig Maximilians Universität München

Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999

Clotting Factor Concentrates



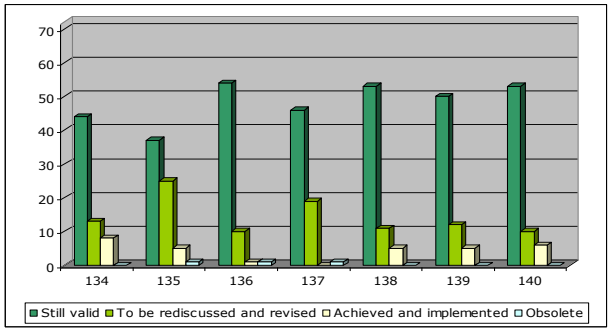
Total no. of questionnaires: 72. Multiple choice answers were possible

LMU Ludwig Maximilians Universität München

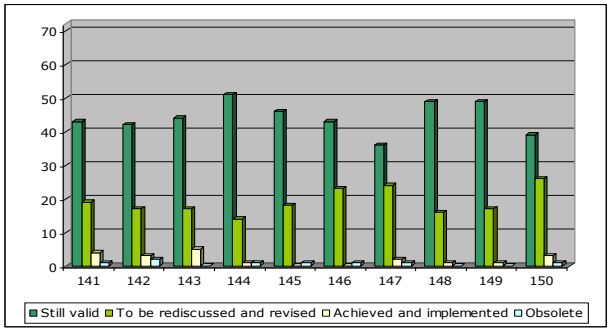
Survey European Symposium „Optimal use of blood components“

Actual perspective on the published recommendations of the Wildbad Kreuth Initiative 1999

Quality Management

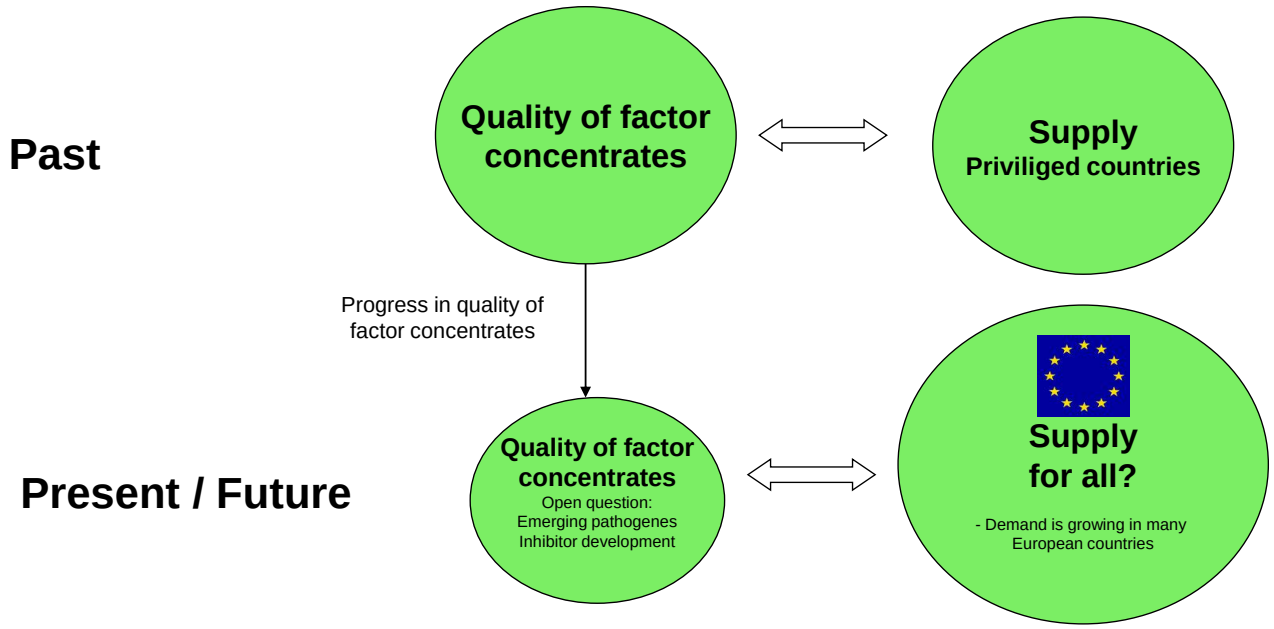


Economics



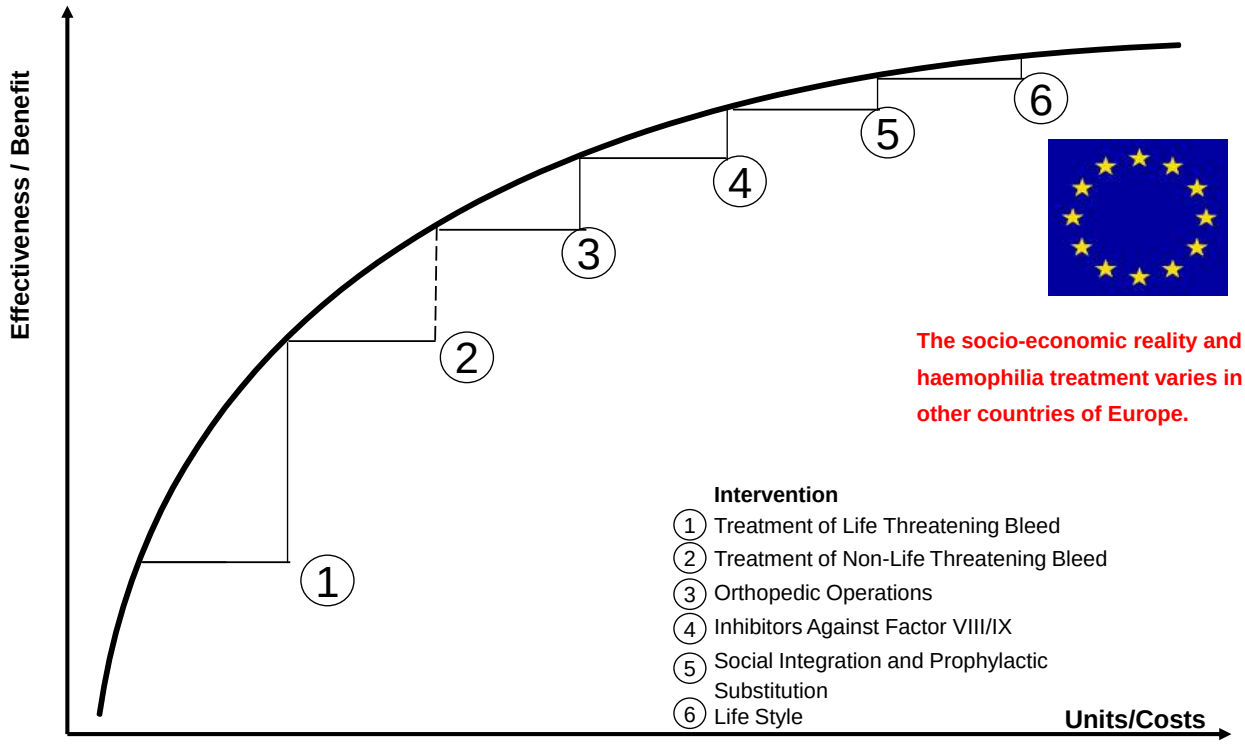
Total no. of questionnaires: 72. Multiple choice answers were possible

Haemophilia Care: Shared Concerns



LMU Ludwig Maximilians Universität München

Haemophilia Care in Europe



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

Intervention

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

LMU Ludwig Maximilians Universität München

125. In order that future requirements for expensive blood products within the European Community can be assessed, registers of patients with haemophilia and related disorders should be established and maintained in each Member State of the Community.
126. A haemovigilance or pharmacovigilance programme should be established in the Community... to gather information on patient complications ...
127. A network of Comprehensive Care Centres should be established ... provide 24-hour clinical and laboratory service and be accessible to all patients.

Future Perspectives in Haemophilia Care:
the Wildbad Kreuth Initiative - Recommendations

128. Adequate amounts of coagulation factor concentrates for the treatment of patients with haemophilia and related disorders should be available in each Member State. Quantities of both plasma-derived and recombinant products should be maintained ... Individual patient preferences should be taken into consideration when choosing products.
129. Particular attention needs to be taken by the European Community on the possible adverse consequences should a monopoly for the production of coagulation factor concentrates emerge. Research on the development of emerging recombinant technologies in the Community needs to be encouraged and funded.

130. The numerous guidelines from medical bodies in the various Member States should be harmonised and expanded to include advice on dosages for the treatment of common spontaneous bleeding problems.
131. As a general rule, prophylactic treatment for children with severe haemophilia is recommended.
132. Immune tolerance should be offered to all patients with haemophilia who develop new inhibitory antibodies.
133. The outcome of treatment, including parameters related to quality of life and economic aspects, still needs to be assessed, and further studies, which will require funding, should be initiated.

Key elements and Rationale for the meeting

Jean-Marc Spieser

Optimal clinical use of Blood Components

KEY ELEMENTS and RATIONALE FOR THE MEETING

Wildbad-Kreuth Bavaria Germany

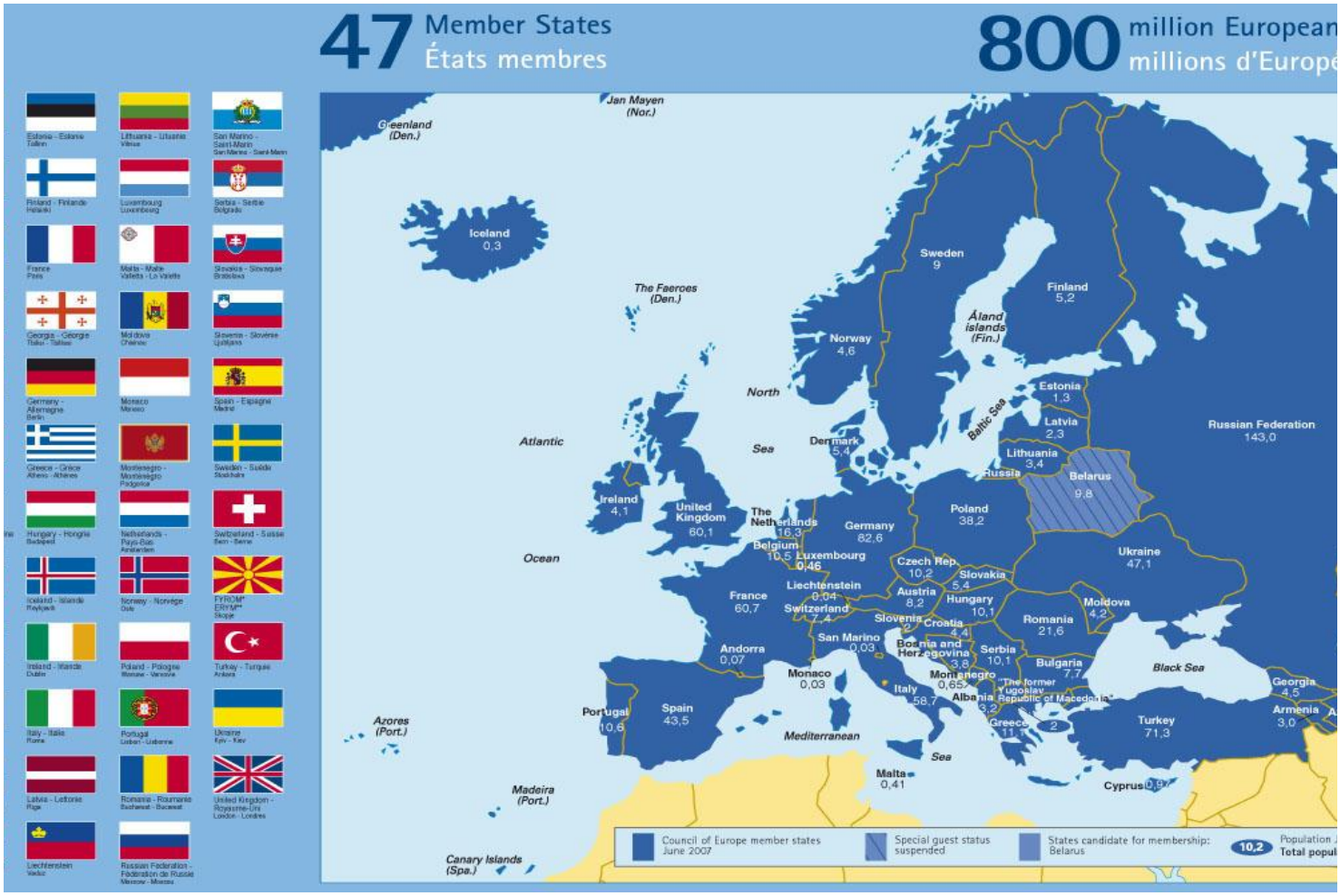
24-25 April 2009

Jean-Marc Spieser, Head of DBO Healthcare
EDQM

The Council of Europe

- Founded in 1949
- Development of European common and democratic principles
- 47 member countries
- Strasbourg

European Convention on Human Rights
(protection of individuals) &
European Court of Human Rights
European Direction for the Quality of Medicines & Healthcare



European Directorate for the Quality of Medicines & HealthCare (EDQM)

- Mission: to contribute to the basic human right of access to **good quality medicines and healthcare**

- Health is a social human right indispensable for the exercise of all other human rights, for prosperity and democratic stability of people in Europe

EDQM Activities

- **Blood Transfusion medicine (CTS)**
- Program based on three general principles:
  - Non-commercialisation of substances of human origin = volontary and non-remunerated donation
  - Protection of health of donors and receivers of blood transfusions
  - Quality of products and services in transfusion medicine

FACTS

- Heterogeneity in terms of clinical use of blood components and even plasma derivates between different European Countries
- Rationale not clear ?
- Often lack of well controlled clinical studies
- Therefore general interest from EDQM / CoE TS expert Committee

Preliminary achievments

In the past work has already been carried out in this field in particular through resolution of the CoE Committee of Ministers 2002 (11) on

Hospital's and clinician's role in the optimal use of blood and blood products

to assist member States to implement SPCs on blood components

General philosophy of EDQM / CoE

Not jeopardizing life-threatening blood component

Favour accessibility to Healthcare products in particular blood / blood components to all European citizens in need

Non commercialisation of substances of Human origin

General bioethical principles

How to achieve it

Develop common evidence based approaches

The present symposium Kreuth II

- You are here as experts not as representatives of countries
- Your contribution shall be scientifically based and not politically driven
- A gathering information exercice on the state of the art and how to optimise clinical use

Reasons for exchange of view points

- Optimal use of blood components is of particular importance in the context of raising needs of blood components but reaching sufficiency will be challenging
- Open debate and forum
- Proceedings will be made available by October 2009 but not narrative and no statement will be attributed to defined persons unless so claimed

Reasons for exchange of view points

- Not decision meeting but brainstorming and think tank
- Nevertheless all interesting ideas and in particular conclusions will be brought back to the attention of the TS Committee for consideration

The issue

What has been achieved, what needs to be improved?

These are the questions to be addressed in each of the work shops

And formulate possible ways of improvement for progressing towards

Optimal clinical use of Blood components

- Thank you

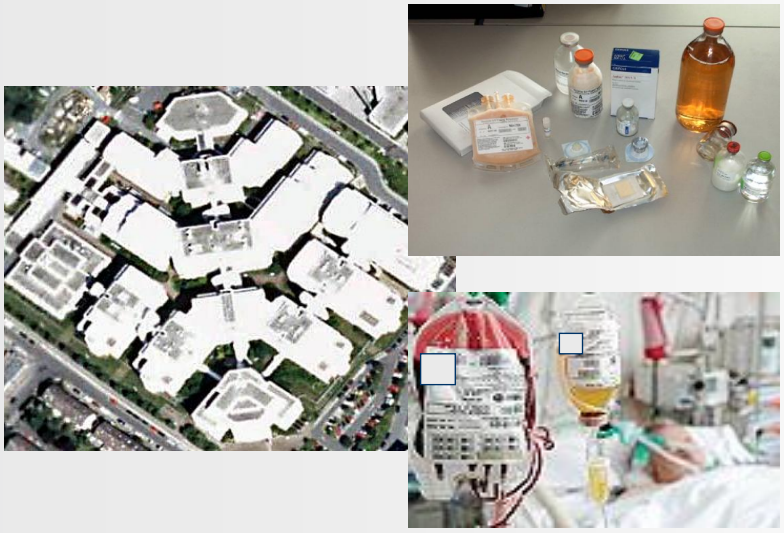
and

HAVE A SUCCESSFULL SYMPOSIUM

Status quo: safety, supply vs. demand, regulations

Rainer Seitz

Status quo: Safety, Supply vs. Demand, Regulations



Prof. Dr. Rainer Seitz

Paul-Ehrlich-Institut

Paul-Ehrlich-Straße 51-59
63225 Langen
GERMANY

☎ +49 (0) 6103 77 2600
🖷 +49 (0) 6103 77-1250

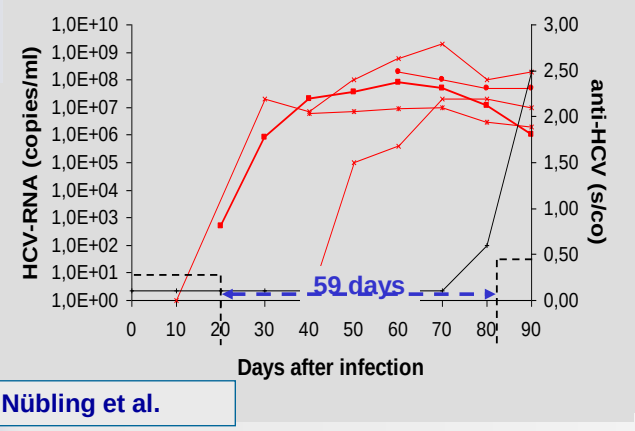
Email: haematologie@pei.de
Homepage: http://www.pei.de

Safety of blood products in the EC

- Commitment of blood services and industry
- Commitment of health politicians, strong legislation, reinforcement and continuous surveillance by authorities
- Advanced technology
  - Virus marker testing
    - For blood components according to national regulations
    - for plasma pools mandatory HCV NAT; NAT against further viruses (HIV, HBV, HTLV, HAV, B19) performed on a voluntary basis by industry
  - State-of-the-art blood banking and donor management
  - State-of-the-art manufacture of plasma derivatives with virus elimination steps, with experimentally validated efficacy

➔ No documented virus transmission by plasma products licensed within the European Community since > 10 years

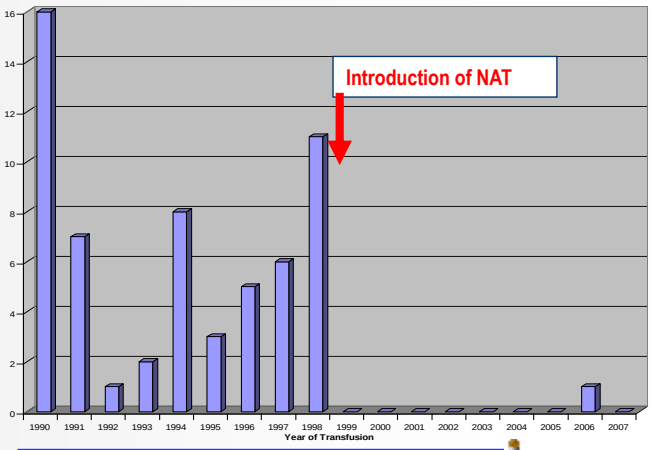
NAT reduces the diagnostic window period



M. Nübling et al.

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

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

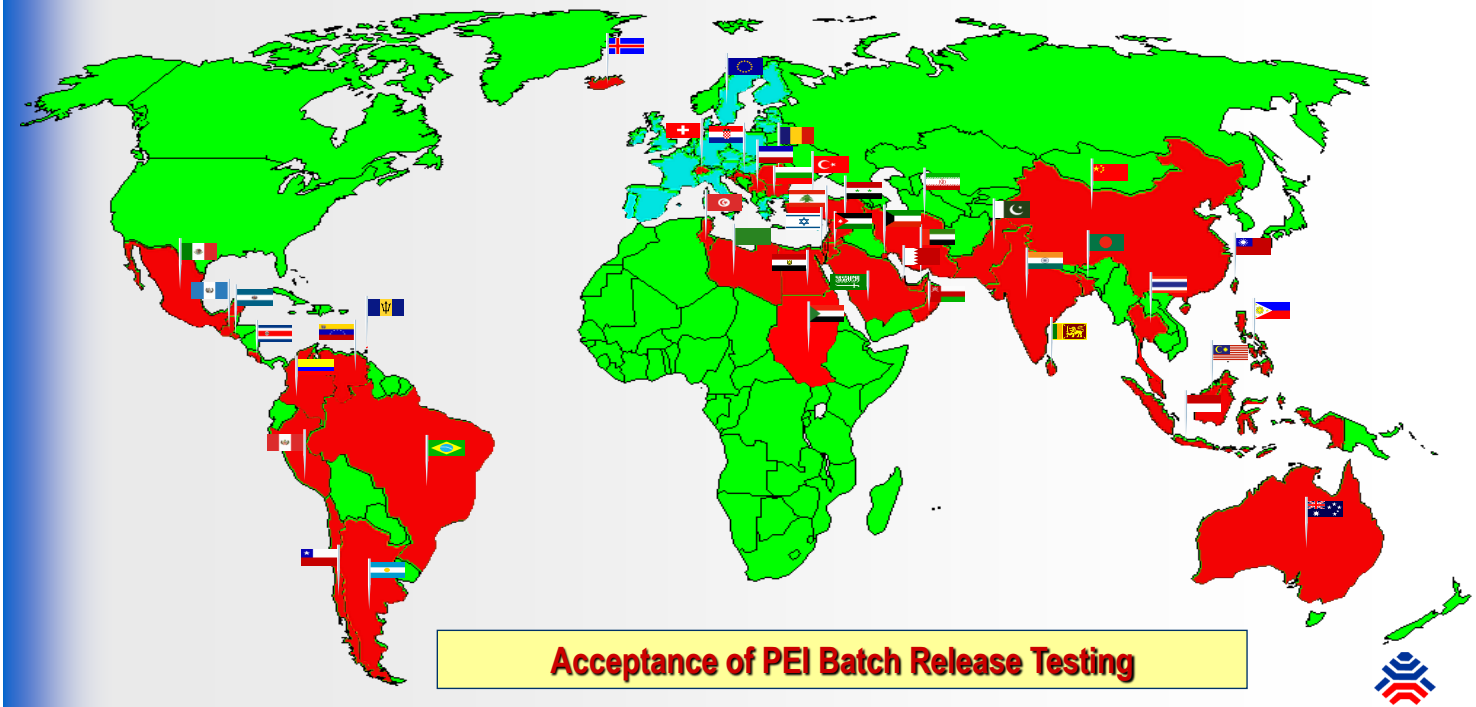


* ca. 6.5 million donations per year

One single case of HCV transmission reported in 2006 [E. Kretzschmar et al. Vox Sanguinis (2007) 92, 297–301]
One single case of HIV transmission in 2007; first case since 2001

edqm European Directorate for the Quality of Medicines & HealthCare

PEI is a member of the Official Medicines Control Laboratory (OMCL) Network, co-ordinated by EDQM



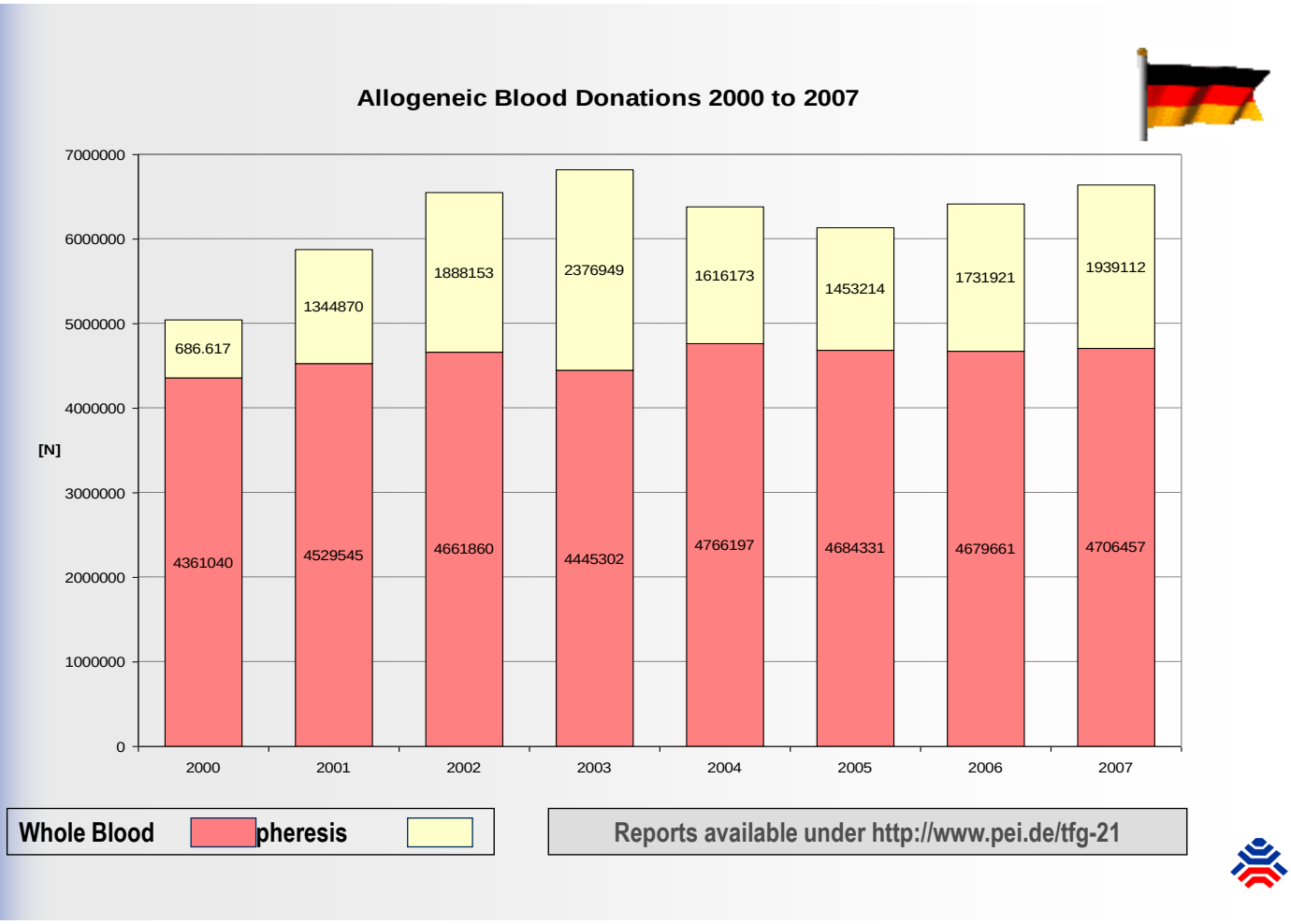
Acceptance of PEI Batch Release Testing

Supply

Section 21 Transfusion Act : Coordinated reporting system

(1) The entities responsible for donation facilities, the pharmaceutical entrepreneurs and the health care facilities shall **annually report** to the competent higher federal authority the figures indicating the scope of the **collection of blood and blood components, the production, import and export and quantities used** of blood products and plasma proteins as defined in section 14 paragraph 1 as well as the number of the treated persons with congenital haemostasis disorders. The reports shall be submitted after the end of the calendar year, at the latest by 1 March of the following year.

(2) The competent higher federal authority [the **PEI**] shall compile the data that have been rendered anonymous, in a **report** and publish it. It shall handle any data specific to the reporting entity on a strictly confidential basis.



COUNCIL OF EUROPE CONSEIL DE L'EUROPE

FINAL REPORT

THE COLLECTION, TESTING AND USE OF BLOOD AND BLOOD PRODUCTS IN EUROPE IN 2003

Table 1
2003

Donors, first time donors and inhabitants

country	regular and repeat donors	first time donors	% first time donors	total donors	inhabitants x 1,000	donors per 1,000 inhabitants
Andorra						
Armenia	1.532	5.661	78,7	7.193	3.212	2,2
Azerbaijan						
Albania						
Austria	505.080	45.552	8,3	550.632	8.174	67,4
Belgium	230.048	39.005	14,5	269.053	10.000	26,9
Bosnia / Herzegovina	32.992	8.034	19,6	41.026	3.900	10,5
Bulgaria	116.747	31.294	21,1	148.041	7.973	18,6
Croatia	79.335	18.334	18,8	97.669	4.437	22,0
Cyprus						
Czech Republic	332.400	33.300	9,1	365.700	10.300	35,5
Denmark	211.969	25.000	10,5	236.969	5.000	47,4 1)
Estonia						
Former Yug. Rep. Macedonia	19.852	8.057	28,9	27.909	2.202	12,7
Finland	149.192	18.944	11,3	168.136	5.220	32,2
France	1.195.109	345.219	22,4	1.540.328	60.186	25,6
Georgia	7.000	1.000	12,5	8.000	5.000	1,6
Germany	1.787.471	569.086	24,1	2.356.557	82.532	28,6 2)
Greece	301.005	58.180	16,2	359.185	10.500	34,2
Hungary						
Iceland	7.374	2.441	24,9	9.815	291	33,7
Ireland		25.405			3.917	
Italy	1.191.000	292.000	19,7	1.483.000	57.000	26,0
Latvia	35.615	13.131	26,9	48.746	2.300	21,2
Liechtenstein						
Lithuania						
Luxembourg	12.847	758	5,6	13.605	435	31,3
Malta						
Moldovia						
Netherlands	474.488	35.091	6,9	509.579	16.193	31,5
Norway	90.985	13.853	13,2	104.838	4.577	22,9
Poland	238.137	180.663	43,1	418.800	38.500	10,9
Portugal						
Romania	142.656	80.916	36,2	223.572	22.435	10,0
Russian Federation						
San Marino						
Serbia and Montenegro	9.531	6.391	40,1	15.922	650	24,5
Slovak Republic	112.719	26.435	19,0	139.154	5.300	26,3
Slovenia	95.607	11.190	10,5	106.797	1.964	54,4
Spain						
Sweden	261.481	39.996	13,3	301.477	8.973	33,6
Switzerland	195.000	24.989	11,4	219.989	7.364	29,9
Turkey						
Ukraine	768.102	293.297	27,6	1.061.399	47.442	22,4
United Kingdom	1.431.944	297.491	17,2	1.729.435	58.785	29,4

1) Denmark: only total number of donors available
2) Germany: data on repeat and regular donor by extrapolation

Table 3
2003

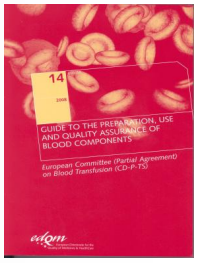
Use of blood and blood components for transfusion

country	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)*
Andorra								
Armenia	70	2,8	2.464	0,8	4.456	70	0	70
Azerbaijan								
Albania								
Austria	0	0,0	447.200	54,7	89.000	40.002	17.383	22.619
Belgium	0	0,0	478.401	47,8	92.279	38.000	27.333	10.667
Bosnia / Herzegovina	8.753	24,4	27.174	9,2	24.276	2.961	2.214	747
Bulgaria	4.954	3,7	129.167	16,8	86.669	17.210	16.939	271
Croatia	4.074	2,7	148.714	34,4	93.299	11.049	9.176	1.873
Cyprus								
Czech Republic	1.200	0,3	412.800	40,2	171.000	22.600	5.600	17.000
Denmark	151	0,0	354.034	70,8	60.766	94.755	91.267	3.488
Estonia								
Former Yug. Rep. Macedonia	53.716	51,2	51.298	47,7		1.681	1.581	100
Finland	26	0,0	270.962	51,9	43.060	31.700	31.030	670
France	0	0,0	1.952.304	32,4	265.332	199.931	24.700	175.231
Georgia	1.500	5,6	25.500	5,4	24.000	1.500	1.400	100
Germany	30.810	0,7	4.113.511	50,2	1.304.870	333.745	114.402	219.343
Greece	5.100	0,9	594.212	57,1	154.232	132.626	114.902	17.724
Hungary								
Iceland	0	0,0	14.128	48,5	4.388	985	599	386
Ireland			130.088		22.171	16.521	9.689	6.832
Italy	48.000	2,2	2.150.000	38,6	503.333	192.250	127.750	64.500
Latvia	0	0,0	49.738	21,6	47.971	4.130	917	3.213
Liechtenstein								
Lithuania								
Luxembourg	0	0,0	19.835	45,6	3.718	8.014	4.312	3.702
Malta								
Moldovia								
Netherlands	301	0,0	608.671	37,6	111.620	47.314	45.751	1.563
Norway	258	0,1	183.289	40,1	39.702	13.664	9.428	4.236
Poland	1.608	0,2	831.045	21,6	355.864	40.091	16.808	23.283
Portugal								
Romania	149.460	45,9	176.030	14,5	171.914	41.243	38.321	2.922
Russian Federation								
San Marino								
Serbia and Montenegro	4.467	32,6	9.256	21,1	9.256	1.028	1.028	0
Slovak Republic	23.742	12,1	172.698	37,1	19.256	8.477	4.474	4.003
Slovenia			78.075		32.671	21.737	20.605	1.132
Spain								
Sweden	169	0,0	445.474	49,7	120.954	32.531	19.122	13.409
Switzerland	5.255	1,7	308.965	42,7	81.261	23.000	2.500	20.500
Turkey								
Ukraine	2.117	9,5	20.203	0,5	22.438	5.917	5.917	0
United Kingdom	754	0,0	2.568.896	43,7	377.560	266.089	163.719	102.370

1) Italy: plasma for transfusion data given in Litres, here recalculated into Units of 300 mL

Regulatory Background

- Blood and plasma products have long been considered as replacement of physiological substances, which can only be a benefit, but not harmful to the patient
- As a consequence of the disaster of HIV transmissions in the early 80ies, this view changed. Plasma-derived products became subject to the pharmaceutical legislation in the year 1989 (Directive 89/381/EC)
- The transfusion products (blood components) became regulated on the EC level in the year 2002 (Directive 2002/98/EC)
- A most influential document is the Council of Europe Guide, continued by the EDQM



The harmonization of the regulation of blood products: a European perspective

R. Seitz, M. Heiden, C. M. Nübling, G. Unger & J. Löwer
Paul-Ehrlich-Institut, Langen, Germany

Vox Sanguinis (2008) 94:267-276

Table 1 European institutions and regulatory bodies involved in the regulation of blood products

Political organization	Institutions	Involved regulatory bodies	Function
European Community (EC)	European Council, European Parliament, European Commission		Legislation as foreseen in the Treaty: • pharmaceuticals, which includes plasma derivatives • blood and blood components
	European Commission		Granting marketing authorization according to the CP
	EMEA	CHMP and other scientific committee and working parties composed of delegates and experts from EC member states	• Preparing scientific opinions as a basis for decisions of the European Commission on granting marketing authorization according to the CP • Scientific and technical guidance on quality, preclinical and clinical issues
		Secretariat	• Administrative advice • Support to applicants, delegates and experts • Support to CMD(h)
	Member states	National competent regulatory authorities	• Contribution to the scientific assessment during CP (EMEA) • Marketing authorization of pharmaceuticals including plasma derivatives according to a national procedure (exclusively for the respective member state), DCP or MRP • Regulatory control of blood and blood components • Official batch release of plasma derivatives
Council of Europe (CoE)	EDQM	PhEur OMCL network CD-P-TS	Monographs and methods Co-ordination of official batch release of plasma derivatives Guide to the preparation, use and quality assurance of blood components

CP, centralized procedure; CMD(h), Coordination Group for Mutual Recognition Procedures and Decentralized Procedure (for human products); EMEA, European Medicines Agency; DCP, decentralized procedure; MRP, mutual recognition procedure; EDQM, European Directorate for the Quality of Medicines and Health Care; OMCL, Official Medicines Control Laboratory or Laboratories; CD-P-TS, European Committee (partial agreement) on Blood Transfusion.

DIRECTIVE 2002/98/EC OF THE EUROPEAN PARLIAMENT AND THE COUNCIL of 27 January 2003

setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

- **"It is essential, that whatever the intended purpose, Community provisions should ensure that blood and its components are of comparable quality and safety throughout the blood transfusion chain in all Member States, bearing in mind the freedom of movement of citizens within Community territory."**

→ ***Comment: The aim is not free movement of ("open market" for) blood components for transfusion, but free movement of people.***

THE TREATY ON EUROPEAN UNION AND OF THE TREATY ESTABLISHING THE EUROPEAN COMMUNITY

Article 152

4. The Council, acting in accordance with the procedure referred to in Article 251 and after consulting the Economic and Social Committee and the Committee of the Regions, shall contribute to the achievement of the objectives referred to in this Article through adopting:

(a) measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;

5. Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care. In particular, measures referred to in paragraph 4(a) shall not affect national provisions on the donation or medical use of organs and blood.

- **The EC is empowered to regulate quality and safety of blood products, but not medical use**
- **The use of blood products is addressed by national laws and/or guidelines**
- **Nevertheless, an approximation of existing guidelines, and quality assurance of the clinical use of blood products with the aim of promoting best practice, is an important objective**

Quality Assurance

German Transfusion Act, Section 15

"Health care facilities that use blood products shall establish a **quality assurance system for the use of blood products** which meets the state of medical science and technology. They shall appoint a licensed **physician that shall be responsible** for the tasks related to transfusion medicine who shall possess the competence required to perform this function (physician responsible for transfusion). In addition, they shall appoint a licensed physician for each treatment unit in which blood products are used who shall provide medical care and have a basic knowledge of and experience in transfusion medicine (physician in charge of transfusion)…."

Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives

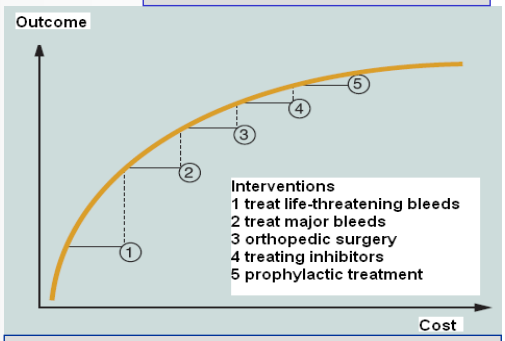
Published by: Executive Committee of the German Medical Association on the recommendation of the Scientific Advisory Board

BUNDESÄRZTEKAMMER

Important Considerations

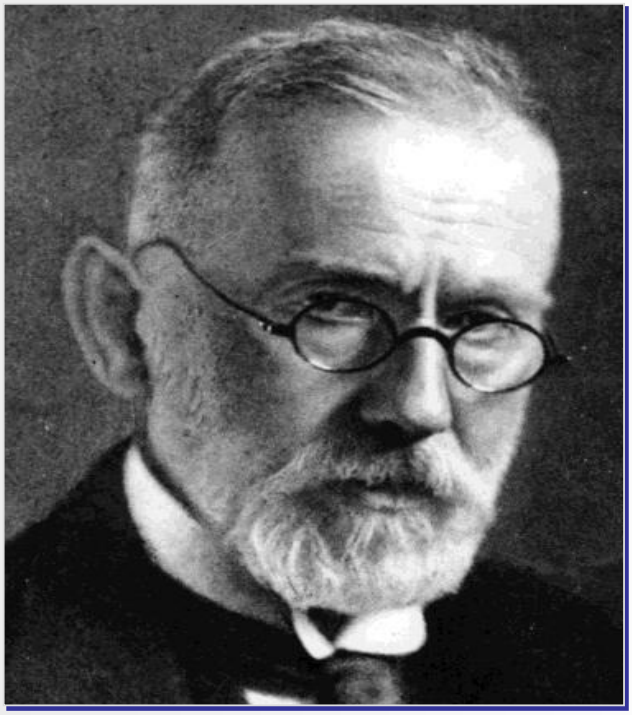
- **Bear in mind circumstances**
  - regulatory framework
  - guidelines, recommendations
- **Consider the resources available**
  - financial situation
  - scientific and organizational structures
  - donor population
- **Determine expected outcomes**
  - e.g. prolong survival, prevent severe outcomes, maintain working capacity, improve quality of life
- **Evaluate the most promising resource applications**

W. Schramm, 2006; modified



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

Thank you for your attention !



Paul Ehrlich

Optimal use of Blood

Brian McClelland

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Optimal Use of Blood

Project co-funded by EU and Scottish National Blood Transfusion service

Brian McClelland

Meeting of the Competent Authorities on blood and blood components

27 January 2009

63

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Purpose

To encourage the **optimal use** of blood components across Europe through sharing of information and best practice for the benefit of patients.

By providing resources to improve the quality and safety of the therapeutic transfusion process

64

Wildbad Kreuth Report 1999

Transfusion of blood …involves numerous steps …which need to be strictly controlled to ensure the safety of patients and to prevent (avoidable) adverse events.

The patient, including assessment of physical condition and the need for blood under emergency or non emergency conditions; verification of identity; informed consent to the transfusion and taking a blood sample for pretransfusion testing

The (blood) product, including; reserving products in the transfusion service; identification of the assigned unit; delivery to the clinical ward and management of used and unused blood products

The product and the patient including: identification before transfusion; administration to the patient; documentation of outcomes"

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Wildbad Kreuth Report 1999

"Every effort should be made to establish a quality management system in the clinical part of the blood transfusion chain"

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Project participants

- Austria
- Czech Republic
- Denmark
- Estonia
- France
- Germany
- Greece
- Hungary
- Italy
- Malta
- Netherlands
- Poland
- Portugal
- Romania
- Slovenia
- U K
  - England
  - Northern Ireland
  - Scotland

67

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Project Methods

- **Surveys**
  - Organisation and staffing of transfusion in hospitals
  - Priorities for content of the manual
  - Documentation – SOPs and records
- **Participant workshops**
- **Develop and evaluate manual of best practice**
- **Website to share and communicate**
- **Translate into 5 European languages**
- **Disseminate via website**

68

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Workgroups

1: Safe Administration of Blood Blood Component Information for Users

2: Methods for evaluating the clinical use of blood and Use of blood components in specific clinical situations

3:Developing and delivering a training programme

4: Glossary and evaluated list of websites (from October 2008)

Each workgroup tasked to complete a series of work packages

69

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Challenges

In the participating countries

- **Different types of staff do a particular task in different countries**
- **Same job title may apply to different roles**
- **Some jobs titles don't exist in some countries**
- ***Therefore* identify training needs for defined roles**
  - **'taking blood samples' - not Phlebotomist.**
  - **'transport of blood' - not Porter.**

70

Another challenge: WORDS

Multiple meanings – even before translation

Specialised usage of non technical terms

- **Collection**
- **Distribution**
- **Issue**

Project Glossary must support translation

Scope of the manual
Spans the hospital blood bank and the clinic

The therapeutic transfusion process

Transfusion of the

- right unit of blood
- to the right patient
- at the right time, and
- in the right condition

Given according to

- appropriate guidelines
- and sound clinical indications

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Contents of the manual

Promoting & sharing best practice across the EU

Chapter 1
Why Optimal Blood Use is Important

Blood is

- **a human tissue**
- **a precious and scarce resource**

Accountability for the donation

Compliance with EU laws

Cost

Implications of adverse reactions

Scope of the manual

The clinical transfusion process

Transfusion of the

- **right unit of blood**
- **to the right patient**
- **at the right time, and**
- **in the right condition**

Given according to

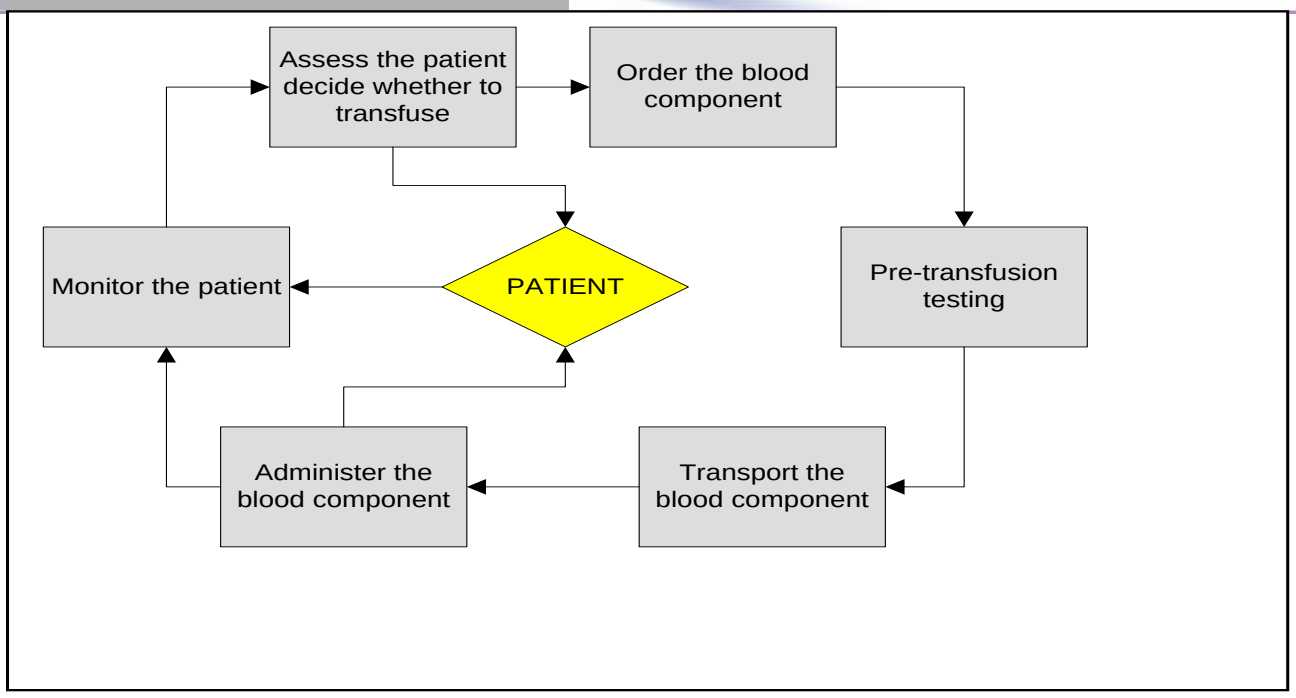
- **appropriate guidelines**
- **and sound clinical indications**

75

Promoting & sharing best practice across the EU

Optimal Blood Use Project

The clinical transfusion process



76

Chapter 3
Quality assurance in the clinical transfusion process
What to do, how to do it right and how to learn from errors

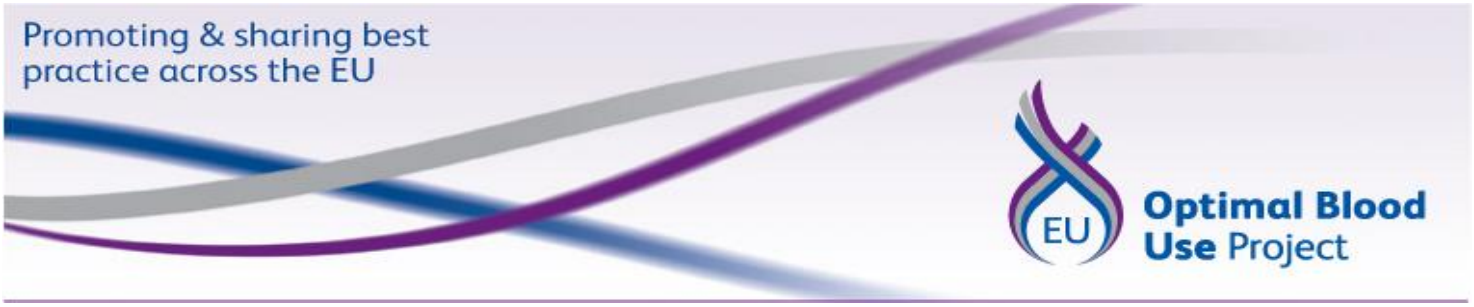
Quality systems have developed largely in relation to manufacturing processes.

The broad principles apply to the clinical setting

Vocabulary and methods may be unfamiliar to clinicians and may not easily translate directly to the clinical context,

In the manual, non specialist terms are used where possible

77



Quality assurance means all the activities from blood collection to distribution made with the object of ensuring that blood and blood components are of the quality required for their intended use

2005/62/EC Article 1(f)

78

Quality assurance means all the activities of the clinical transfusion process that have the object of ensuring that blood and blood components are used optimally

79

Promoting & sharing best practice across the EU

Optimal Blood Use Project

Errors: where, what, why, how to prevent

2 Patient sample and request for blood				
Steps in the process	**What can go wrong**	**Consequences**	**Why it goes wrong**	**Prevention and avoidance**
Identify patient correctly Decide which component is needed and the quantity Complete blood request form or electronic order Take pre-transfusion sample Send blood sample and request to hospital blood bank If required, initiate major haemorrhage procedure (MHP)	Failure to communicate transfusion requirements Failure to provide transfusion history Incorrect blood group in pregnant patient's record Inappropriate dose / volume Patient receives blood intended for another person Failure to recognise a major haemorrhage Major haemorrhage procedure not activated	Immunosuppressed patient put at risk of Graft versu Host Disease DelayedHaemolyticTransfusionReaction Young female sensitised to RhD Patient transfused with wrong component or quantity Fatal ABO incompatibility reaction Death or serious complications due to delayed transfusion	Inadequate information on form Correct form completed incorrectly Incorrect details on sample tube Correct patient, but sample tube wrongly labelled Sample taken from wrong patient Sample transport inappropriate for situation Ignorance of major haemorrhage procedure (MHP) No MHP available	Wristband policy in place and observed Minimum data set for patient ID in place and observed Prescriber knows procedure for pretransfusion sample and blood request Prescriber knows the indications for particular type of component (eg irradiated) , establishes patient's requirement, orders correctly. Clinical laboratory and transport staff are familiar with and trained in major haemorrhage protocol MHP is practised periodically ("fire drill") Compliance with procedures is audited Errors, events and reactions are investigated Procedures improved by lessons learned

80

Chapter 9
How to evaluate transfusion practice

Introduction to methods for clinical audit

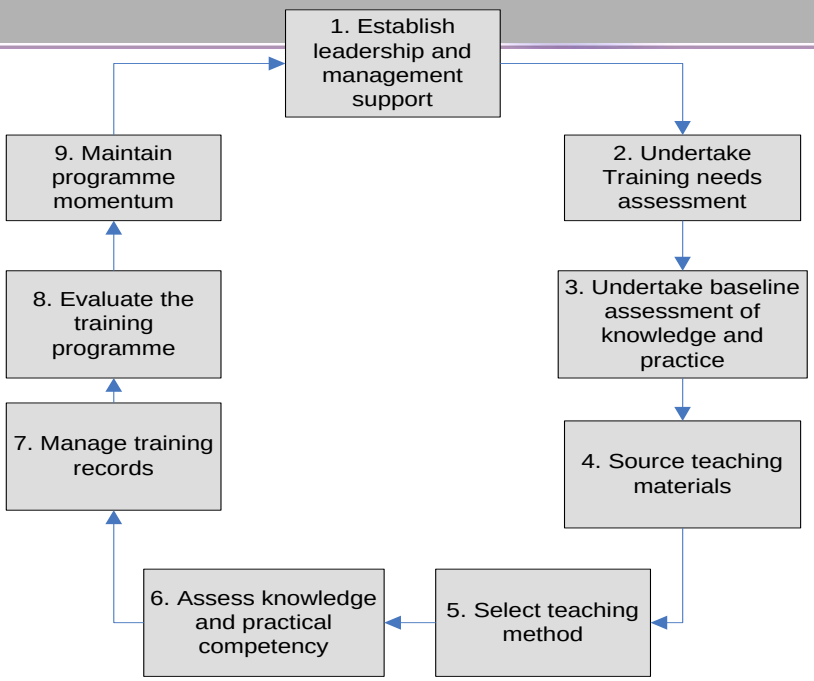
Auditing compliance with safety and administrative guidelines

Quantitative comparisons (audits) of blood component use

Transfusion quality indicators

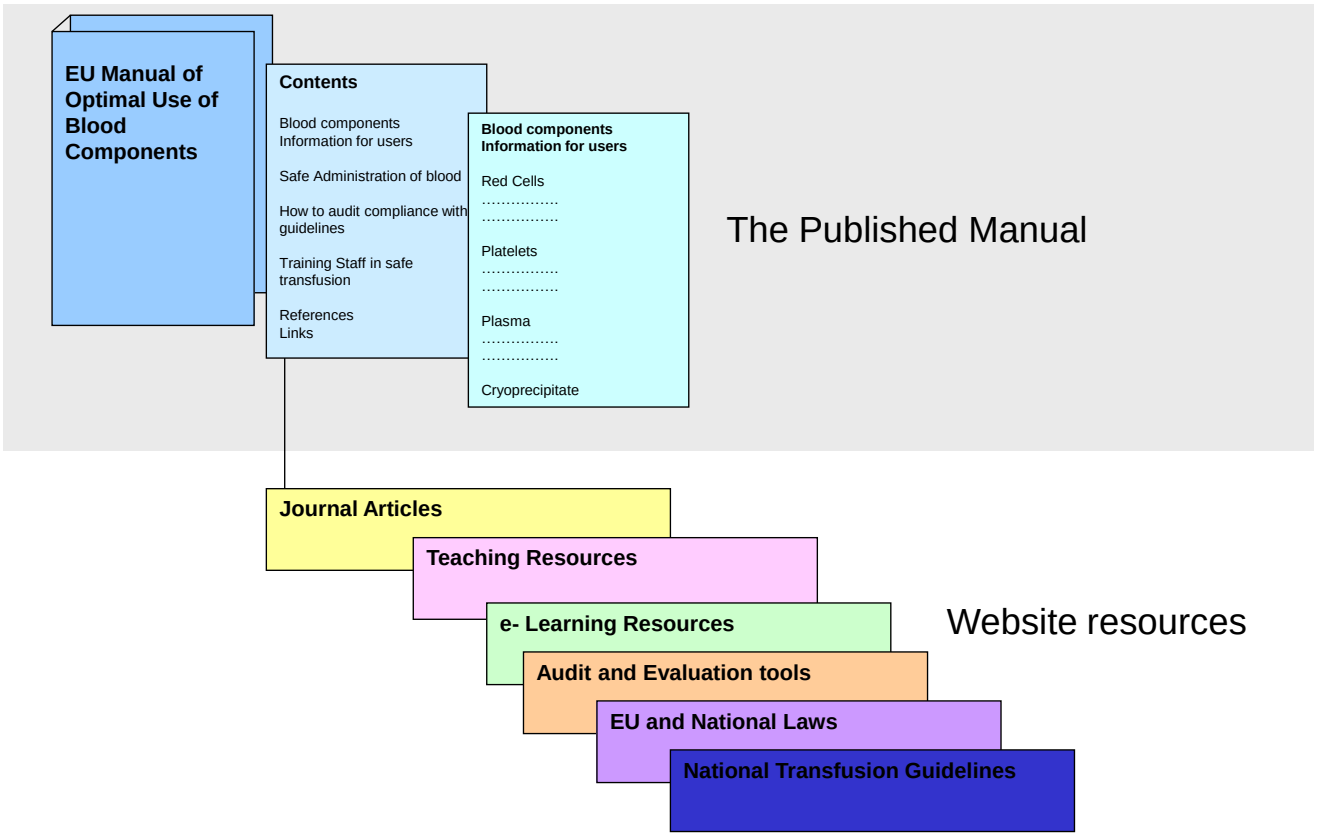
81

Chapter 10
How to implement a training programme for clinical transfusion practice

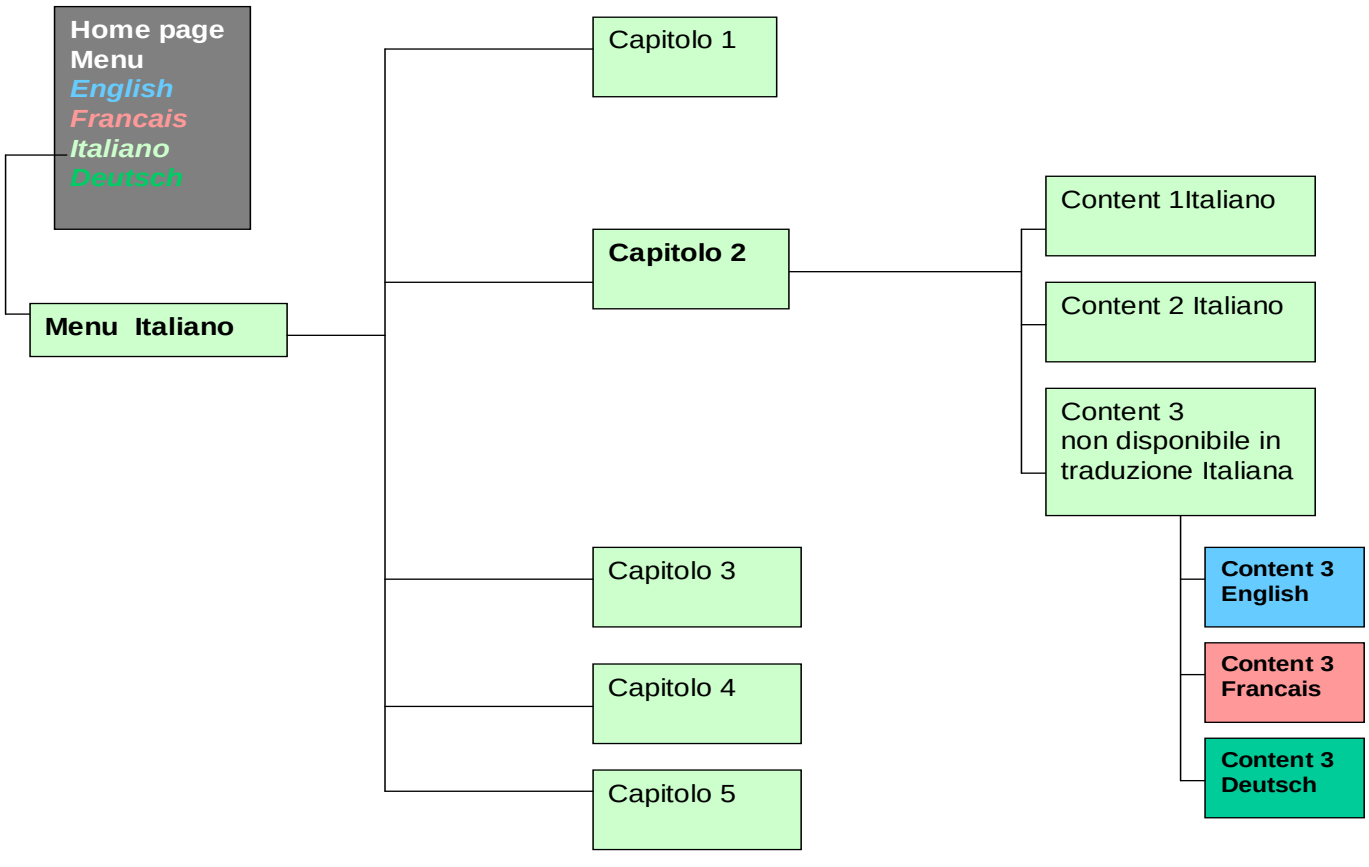


82

Manual and website



Multi language example - Italian



Contact Details

Thank you for surviving till now!

EU Optimal Blood Use Project Team

Telephone: +44 (0) 131 536 5902

Email: eu@snbts.csa.scot.nhs.uk

85

Cross-sectional guidelines (BÄK) Therapy with blood components and plasma derivates

Harald Klüter

Cross-sectional Guidelines (BÄK) Therapy with Blood Components and Plasma Derivates

4th revised edition 2009

Prof. Dr. Harald Klüter
Working Group Coordinator

European Symposium on
"Optimal Clinical Use of Blood Components"
April 2009, Wildbad Kreuth, Germany

Regulative Frame-work

European Regulations

EU-Directive 2002/98/EG and technical (blood donation & preparation)

German Transfusion Act
Preparation and Administration of blood products

German Guide for Haemotherapy (BÄK & PEI)
(Preparation and Administration of blood products, ratification by PEI)

Cross-sectional Guidelines Haemotherapy (BÄK)
(Treatment with blood components / indications/ adverse reactions)

History of German Haemotherapy Guidelines

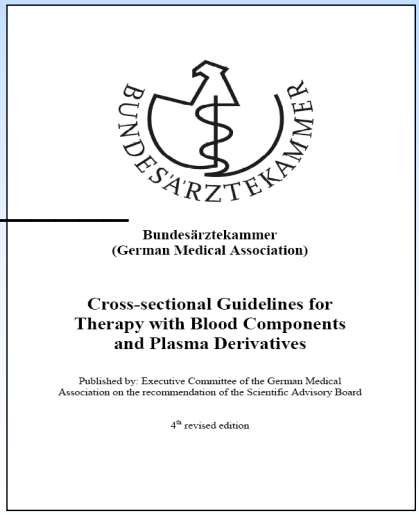
1995 First Edition
(coordinator: Prof. Dr. Deicher)

2001 Second Edition

2003 Third Edition

2005-2008 General revision
(coordinator: Prof. Dr. Klüter)

2009 Fourth Edition



Goals: indications and recommendations for treatment with blood and plasma derivates

- restrictive recommendations
  (‚Transfusion trigger' for Red cells, Platelet Concentrate)
- Negative recommendations
  - Humane albumine
  - ivIG for prophylaxis in preterms or in CMV-infection
- Spread knowledge about adverse reactions and their specific treatment
- Focussing on legal framework conditions „Off-Label-Use"
  Statements when differences to expert information

Content Cross-sectional Guidelines

1. Red Cell Concentrates
2. Platelet Concentrates
3. Granulocyte Concentrates
4. Plasma for Transfusion
5. Humane Albumine
6. F VIII / F IX (Haemophilia-Treatment)
7. Procoagulation Factors (Fibrinogen, PPSB, F VII, rFVIIa, F XIII, Fibrin glue)
8. Inhibitors (Antithrombin, Protein C, rProtCa, C1-INH)
9. Humane Immunoglobulines
10. Autologous Haemotherapy
11. Adverse Reactions

Structure of the chapters

1 Red Cells (RC)
1.1 Preparation
1.2 Active constituents
1.3 Physiological function, consequences of storage
1.4 Storage and shelf life
1.5 Range of application, dosage, mode of administration
1.6 Adverse effects
1.7 Documentation
1.8 References

2 Platelet concentrates
2.1 Preparation
2.2 Active constituents
2.3 Physiological function
2.4 Storage and shelf life
2.5 Range of application, dosage, modes of administration
2.6 Control of treatment
2.7 Selection of the platelet concentrate
2.8 Management of the refractory patient
2.9 Fetal and neonatal alloimmune thrombocytopenia
2.10 Adverse effects
2.11 Documentation
2.12 References

New in 4th Edition: Classification of recommendations

- Different international and national classification systems:

- International: e.g. SIGN versus Oxford
- national: different classification in guidelines of AWMF (Association of the scientific Medical Societies in Germany)

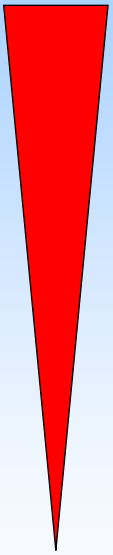
- System ACCP (Guyatt et al. Chest 2004; 126: 179S-87S)

New in 4th Edition: Classification of recommendations

- Level of Evidence
- Grade of recommendation

example:
Patients with chronic anaemia (haematocrit <24–21% and haemoglobin concentrations of <8–7 g/dL [<5.0–4.3 mmol/L]) should receive RC transfusions. [**1 C**]

Classification of Recommendations



1 A strong recommendation

1 C+

1 B

1 C intermediate recommendation

2 A

2 C+ weak recommendation

2 B

2 C very weak recommendation

(Guyatt et al. Chest 2004; 126: 179S-87S)

Classification of Recommendations (I)

Level of recommendation	Risk-benefit ratio	Level of evidence	Assessment of the methodological validity of the underlying data	Overall assessment, classification	Implications	key-words
1	Unambiguous	A	Randomized, controlled studies without essential methodological flaws with unambiguous results	1 A	**Strong recommendation**, valid for most patients	**shall**
1	Unambiguous	C+	No randomized, controlled studies, but unambiguous data available	1 C+		
1	Unambiguous	B	Randomized, controlled study with methodological flaws. Despite unambiguous results of the study it cannot be safely ruled out that methodical flaws have influenced the results	1 B	**Strong recommendation**, probably valid for most patients	
1	Unambiguous	C	Observational studies without control group, but with convincing results	1 C	**Medium strong recommendation**, seems to be plausible, may be changed once improved data become available	**should**
2	Ambiguous	A	Randomized, controlled study without methodological reservations, but with conflicting results	2 A	**Medium strong recommendation**, depending on the individual case, a different course of action may be indicated. The interpretation of results by the Working Group Guidelines are taken into account in the recommendation.	

Classification of Recommendations (II)

Level of recommendation	Risk-benefit ratio	Level of evidence	Assessment of the methodological validity of the underlying data	Overall assessment, classification	Implications	key-words
2	Ambiguous	C+	No randomized, controlled studies, but data can be extrapolated from other studies	2 C+	**Weak recommendation**, depending on the individual case, a different course of action may be indicated. The interpretation of results by the Working Group Guidelines are taken into account in the recommendation.	**can**
2	Ambiguous	B	Randomized, controlled study with severe flaws	2 B	**Weak recommendation**, depending on the individual case, a different course of action may be indicated.	**can**
2	Ambiguous	C	Observational studies, case reports	2 C	**Very weak recommendation**, depending on the individual case, a different course of action may be indicated.	**could**

Decision making

Working Group:

Definition of goals
System of classification for recommendations

11 Subgroups

For each chapter
Draft recommendations & text

3 meetings
until July 2007

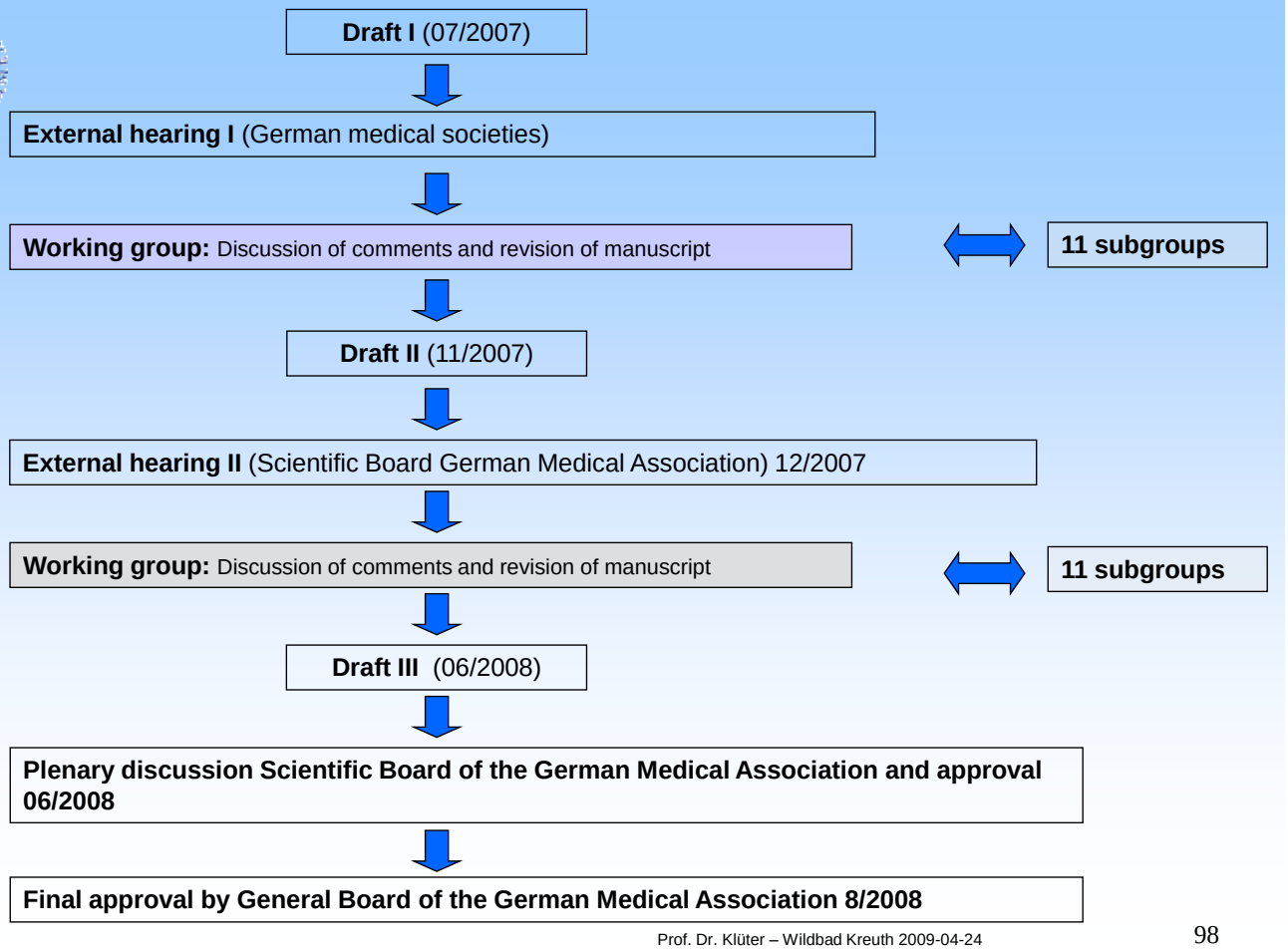
Working Group

Discussion of draft manuscript of each subgroup
(2 closed meeting)

Consensus recommendations & text

(final consultation and written decision making)

Draft Manuscript (07/2007)



Members of the Working Group

- Prof. Dr. med. Gregor Bein, Gießen
- Prof. Dr. med. Jürgen Biscoping, Karlsruhe
- Prof. Dr. med. Joachim Boldt, Ludwigshafen
- Prof. Dr. med. Jürgen Bux, Hagen
- Dr. med. Wolfram Ebell, Berlin
- Prof. Dr. med. Hermann Einsele, Würzburg
- PD Dr. med. Lorenz Frey, München
- Prof. Dr. med. Andreas Greinacher, Greifswald
- Prof. Dr. med. Marcell U. Heim, Magdeburg
- Prof. Dr. med. Peter Hellstern, Ludwigshafen
- Prof. Dr. med. Dr.-Ing. Holger Kiesewetter, Berlin
- Prof. Dr. med. Harald Klüter, Mannheim (coordinator)
- Prof. Dr. med. Johannes Oldenburg, Bonn
- Prof. Dr. med. Hans-Hartmut Peter, Freiburg
- PD Dr. med. Ullrich Sachs, Gießen/Marburg
- Prof. Dr. med. Abdulgabar Salama, Berlin
- Prof. Dr. med. Wolfgang Schramm, München
- PD Dr. Michael Spannagl, München
- Prof. Dr. med. Martin Welte, Darmstadt

Acknowledgements

- Scientific Board German Medical Association

  Prof. Dr. P. Scriba

- Department 6 BÄK

  Dr. H. Bäsler

- Robert-Koch-Institute / Paul Ehrlich-Institute / EDQM / LMU

  English translation Ms. Erikli

Optimal use of blood components: The relevance of transfusion services

Erhard Seifried

Optimal use of blood components: The relevance of transfusion services

Erhard Seifried

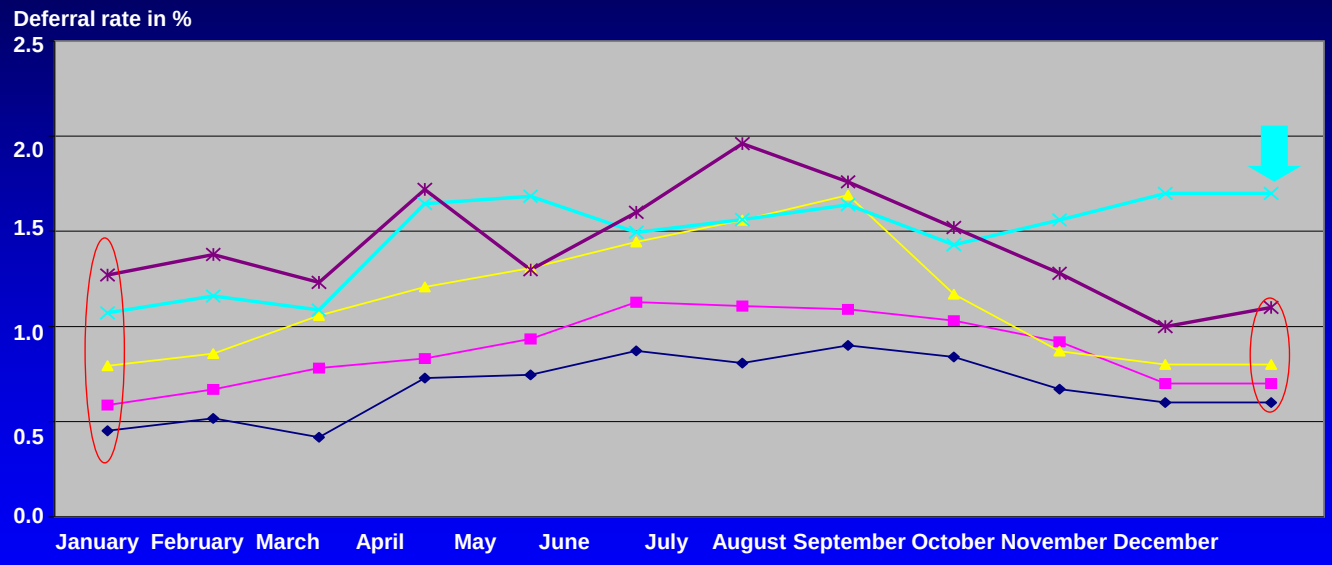
Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt/Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Wildbad Kreuth, April 24-25, 2009

Overview: What is the relevance of transfusion services in optimal use of blood products?

- Optimal use of blood donations
  - Donor management
    - adequate deferral rates: e.g. temporary deferral due to low hemoglobin levels
  - Donor screening: optimization
    - e.g. low levels of false positive test results
  - Production processes: optimization
    - e.g. plasma recovery / hemoglobin content of the final product
    - e.g. optimal medical devices like blood bags (materiovigilance)
- Benchmarking
  - Internal
  - External

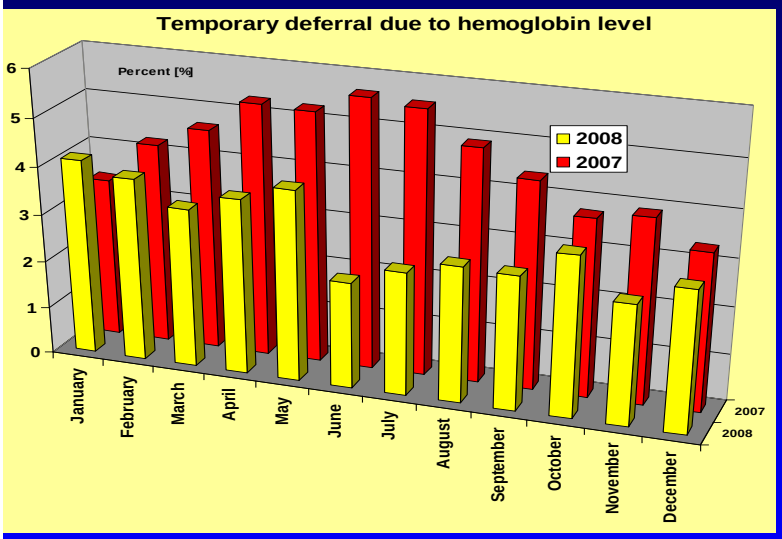
Donor deferral due to low hemoglobin levels



2007

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Donor deferral due to low hemoglobin levels in the region Nord

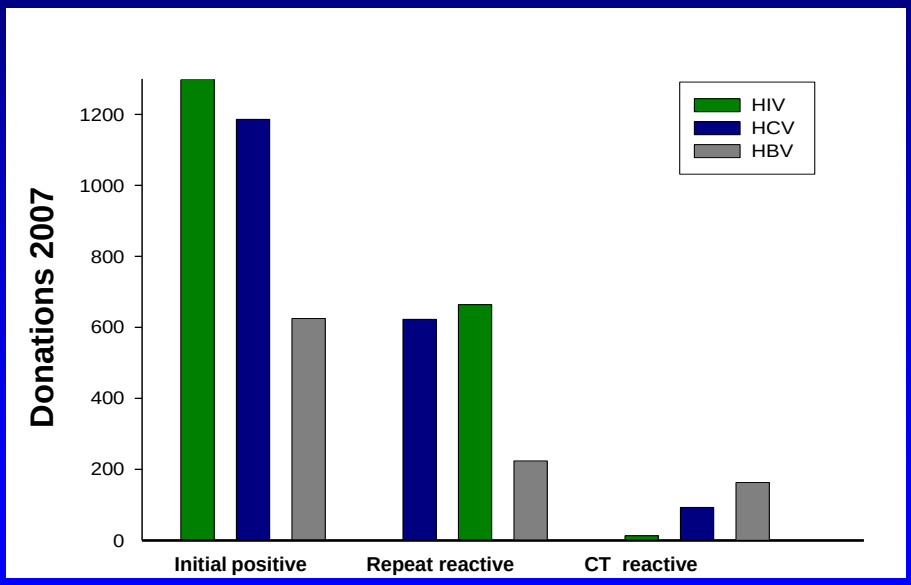


- Harmonisation of hemoglobin testing and iron supplementation in repeat donors:
- Hesse: +2,700 donations / year
- North: +3,400 donations / year

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Results of screening and confirmatory testing (CT)

Mobile Donor IT system blocks reactive donors at the donation site and prevents wastage of material and reduces risk for donors & recipients



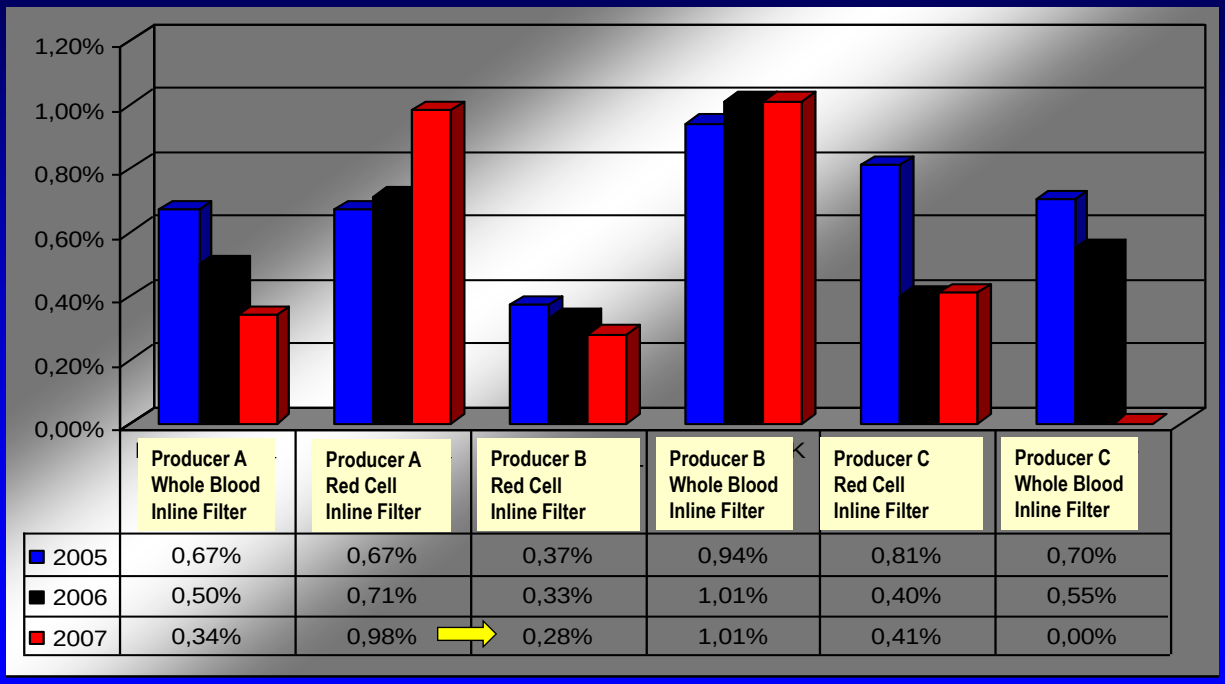
Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Benchmarking in production

- **Harmonisation of procedures, material, logistics, equipment, issuing, etc.**
  - **High yield of products:** **Supply**
  - **Reduction of wastage:** **Ethics**
  - **Reduction of leukocytes & plasma:** **Safety**
  - **Increase in active substances:** **Quality**
  - **One marketing authorisation:** **Supply**

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Reduction in Production Failures (in % per year)

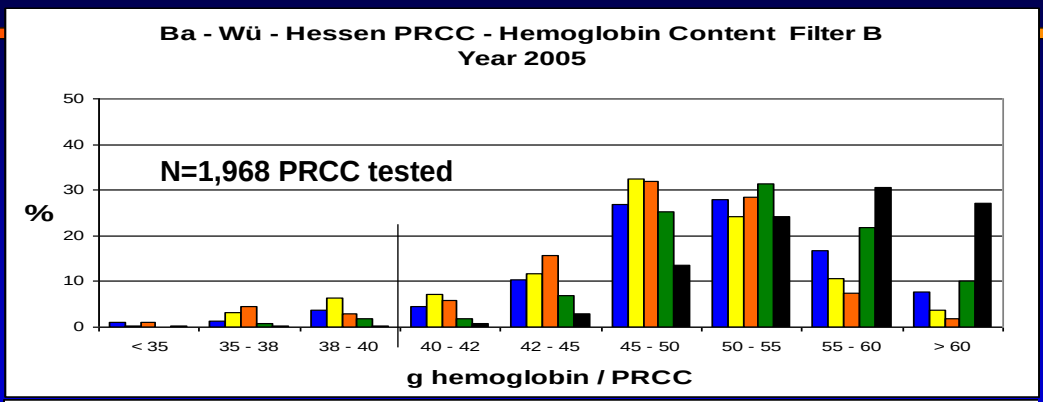


	Producer A Whole Blood Inline Filter	Producer A Red Cell Inline Filter	Producer B Red Cell Inline Filter	Producer B Whole Blood Inline Filter	Producer C Red Cell Inline Filter	Producer C Whole Blood Inline Filter
2005	0,67%	0,67%	0,37%	0,94%	0,81%	0,70%
2006	0,50%	0,71%	0,33%	1,01%	0,40%	0,55%
2007	0,34%	0,98%	0,28%	1,01%	0,41%	0,00%

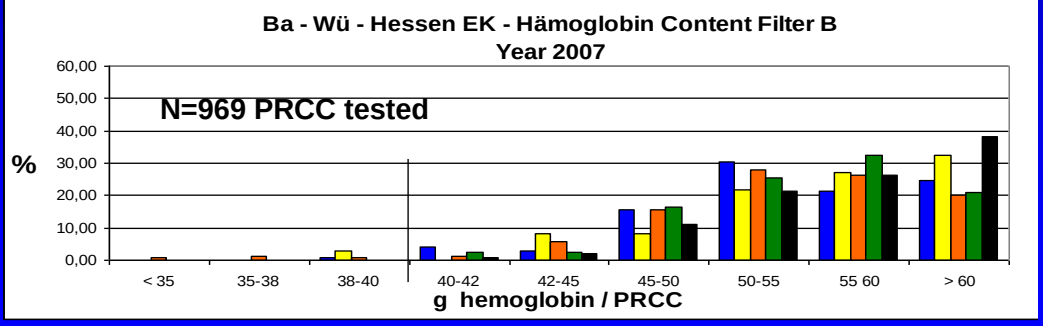
Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Hemoglobin Content of Final Packed Red Cell Concentrate (PRCC): Leukodepletion Filter & Technique used

2005:



2007:

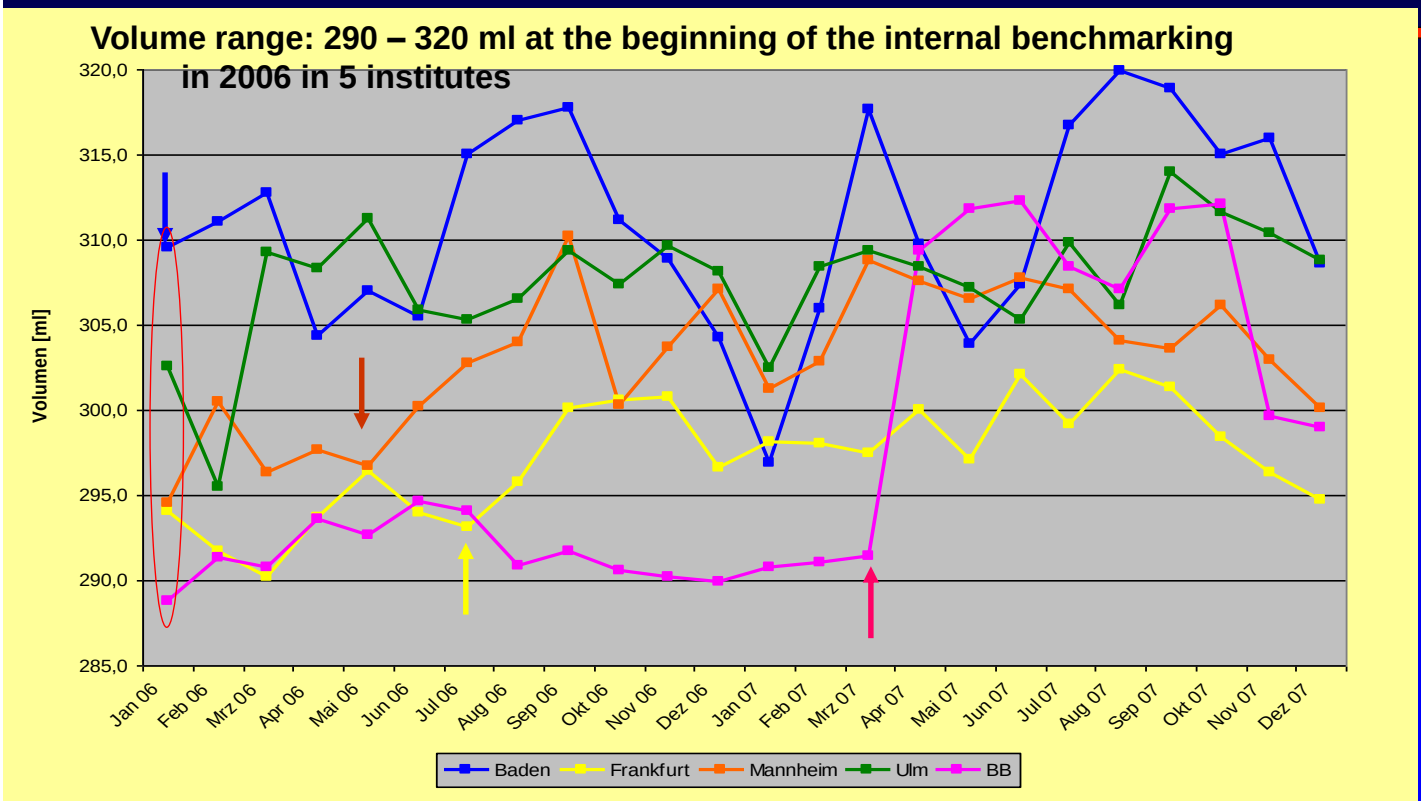


Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Quality Control data; different colour coded bars denote different production sites in our blood service

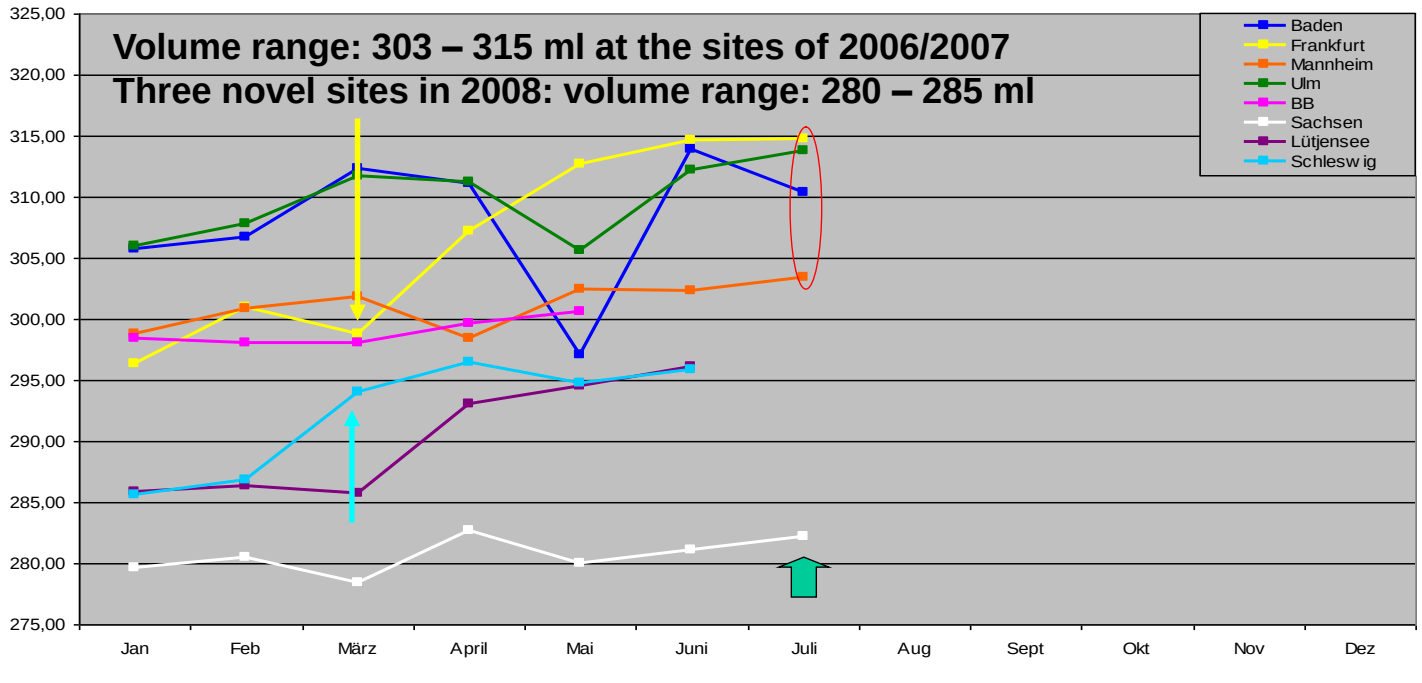
Production: Plasma Volume – FFP 2006 and 2007

(arrows mark introduction of improvements at a single production site)



Production: Plasma Volume – FFP 2008

(arrows mark introduction of improvements at a single production site)



Overview: What is the relevance of transfusion services in optimal use of blood products?

- Quality of blood components
  - Source
  - Production specifics: additive solution, etc.
  - Age of the blood product
  - Indication for transfusion
  - Diagnostics: minimal / optimal / mandatory
  - Transfusion triggers
  - Which product for which patient?
  - Dose: overtransfusion / undertransfusion / adequate transfusion
  - Logistics & storage
  - Documentation
- Supply chain management
- Temperature control during transportation & storage
- Documentation
- Education of personnel
- Clinical studies & observation programs / health services research

Packed Red Cells (PRC)

- Quality
  - Function: transportation of oxygen, hemostatic function
  - Range and perspective: From warm whole blood transfusions to genetically engineered oxygen carriers from embryonal stem cells
  - Further options: erythropoietin?; ESAs?; (“artificial“) oxygen carriers?
  - Contaminants
    - Leukocytes
    - Plasma
    - Platelets

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Packed Red Cells (PRC) - II

- Which product for which patient?
  - Product specifications:
    - Anticoagulants
    - Plasma
    - Additive solution
  - AB0 / Rhesus / Kell blood groups
    - Identical
    - Compatible
  - Different ethnical background / rare blood groups / complex antibodies
  - Age of the product
    - More vulnerable patient populations?
  - Indication
  - Transfusion triggers

Packed Red Cells (PRC) - III

- Aim for patient´s hemoglobin level
  - In different patient populations
  - Co-morbidities
  - Acute / chronic anemia
- Irradiation
- CMV testing
- Leukodepletion
- Quality control
  - Products
  - Storage: e.g. cold chain
  - Transfusion chain - look-back
  - Wastage of products

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Platelet Concentrates (PC)

- Quality
  - Function: cellular hemostasis; inflammation; wound healing; others
  - Leukodepletion: yes? /no?
  - Pathogen inactivation
  - Bacterial testing
    - Methods
      - Culture
      - PCR
      - FACS
  - Further options: thrombopoietin?; TSAs?; others?
  - Contaminants
    - Leukocytes
    - Red cells
    - Plasma?

Platelet Concentrates (PC) - II

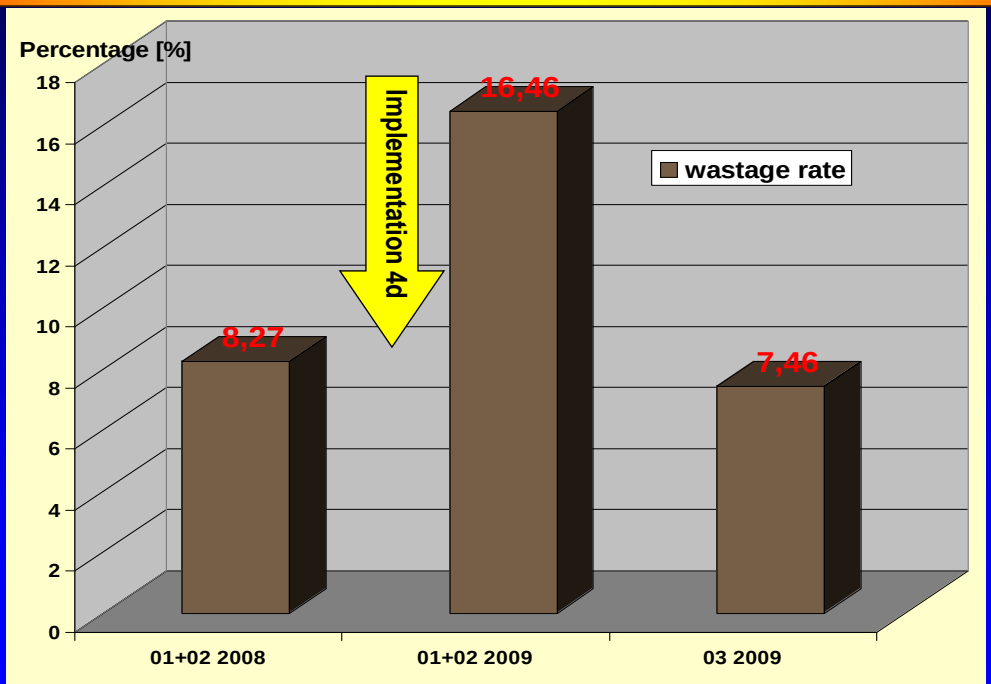
- Which product for which patient?
  - Single donor vs. Pool PC
  - Apheresis vs. Whole blood derived
  - Product specifications
    - Plasma
    - Additive solution
    - Pathogen inactivation
  - AB0 / Rhesus / Kell blood groups
    - Identical
    - Compatible
  - Age of the product
    - Bacterial contamination
  - Indication

Platelet Concentrates (PC) - III

- Transfusion triggers
  - Prophylactic
  - In bleeding patients
  - Preoperative / before invasive procedures
- Dose / aim for patient´s platelet count
  - In different patient populations
  - Co-morbidities
  - Velocity of thrombopenia
- Irradiation
- CMV testing
- Quality control
  - Products
  - Transportation & Storage: agitation; temperature
  - Transfusion chain - look-back
  - Wastage of products: Assessment of demand in the clinics; Communication with the clinics

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Example: wastage rate of platelet concentrates (PC) at one university hospital: changes during implementation of a reduced shelf life of 4 days



Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Fresh Frozen Plasma (FFP)

- Quality
  - Function: hemostasis; others
  - Further options: PPSB?; single factors?; others?
  - Contaminants
    - Leukocytes
    - Red cells
    - Platelets

Fresh Frozen Plasma (FFP) - II

- Which product for which patient?
  - Product specifications
    - Single donor vs. pooled plasma
    - Apheresis plasma versus whole blood derived
    - Leukodepletion: whole blood vs. red cell
    - Quarantine plasma
    - Pathogen inactivation
      - Solvent / detergent (SD)
      - Methylene blue (MB)
      - Amotosalen
    - FVIII content
  - Indication

Fresh Frozen Plasma (FFP) - III

- Transfusion triggers
  - Prophylactic
  - In bleeding patients
  - Preoperative / before invasive procedures
- Dose / aim for patient´s coagulation results
  - In different patient populations
  - Co-morbidities
  - Velocity
- Irradiation: yes? / no?
- CMV testing
- Quality control
  - Products
  - Storage
  - Transfusion chain - look-back
  - Wastage of products

Diagnostics: Immunohematology

- Algorithm
  - Type & screen strategy
  - Crossmatching
    - Frequency
    - Technique
  - Antibody screening
    - Frequency
    - Technique
  - Antibody identification
    - Frequency
    - Technique
- Communication & counselling

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Quality Management: Transfusion Chain

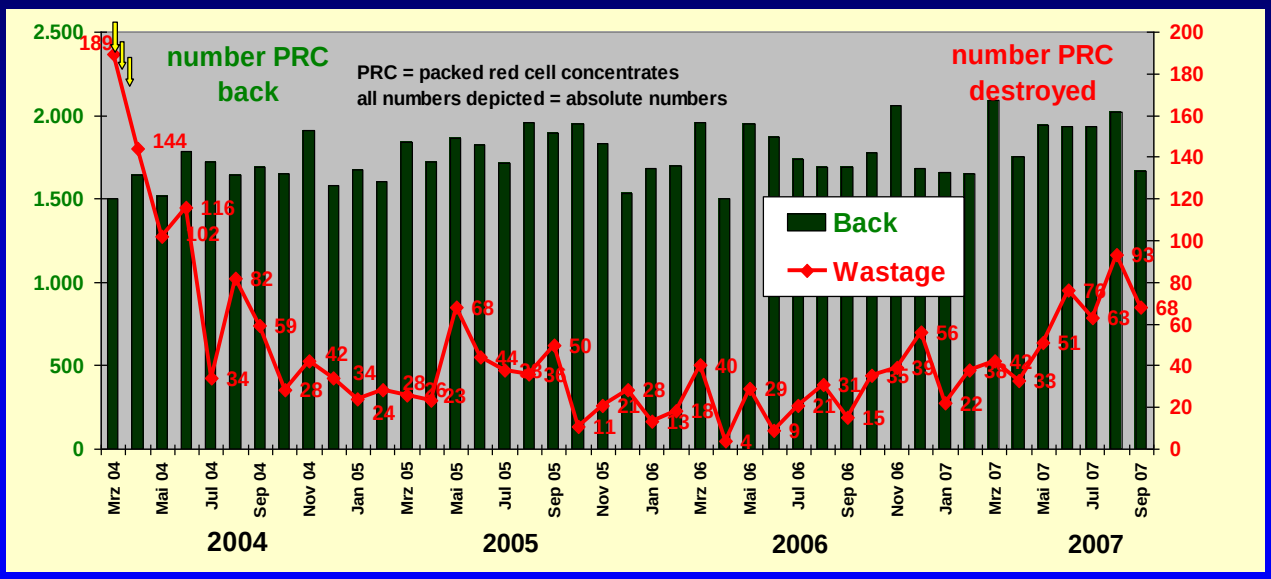
- Transfusion commission
- Transfusion consultants: Counselling
- Regimes: diagnostic & treatment algorithms
- Emergency management / rare blood groups / complex antibodies: Supply chain!
- Risk management
  - Near misses
- Audits: e.g. selective control of indication, transfusion triggers, benefit to the patient, clinical success, etc.
  - Internal
  - External
  - Analysis of audit reports, documentation & information
- Information technology
- Education of personnel
  - Physicians
  - Nurses
  - Technicians
  - Support personnel

Logistics & Documentation

- Storage & transportation in clinics
- Stock management
  - e.g. packed red cells (PRC) “B“ and “AB“: “goods on sale or return“
- Preparation of a transfusion
- Patient identification
  - Bedsite test
  - Wrist bands
- Documentation
  - Who?
  - What?: Documentation requirements: e.g. indication, success
  - Filing of the results: How long?
- Look back
- Waste management: documentation, analysis, education

Example: stock management at one university hospital: numbers of PRCs back from the hospital storage and number of PRCs wasted out of PRCs sent back

Yellow arrows show three obligatory training courses for physicians and nurses showing effective ways of reducing waste rate



Wastage rate: 13 % 0.3 % 4 %

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Clinical Hemotherapy

PROCESS: Donor management, donation , production, donor screening, quality control, indication for transfusion, informed consent, immunohematology, transportation of products, storage, patient identity, surveillance of recipient, documentation, etc., …

Product

Donor management

Donation

Production

Testing

Quality control

Release

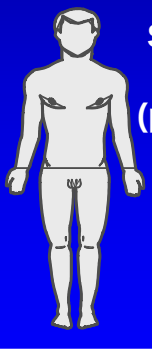
Indication for transfusion

Informed consent

Immunohematology

Transportation & storage

Identity control transfusion surveillance documentation



Success AEs (possibly look-back)

„Transfusion is a Process, Not only a Product!“ W. H. Dzik

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Thank you very much for your attention!

www.blutspende.de

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

BACKUP SLIDES

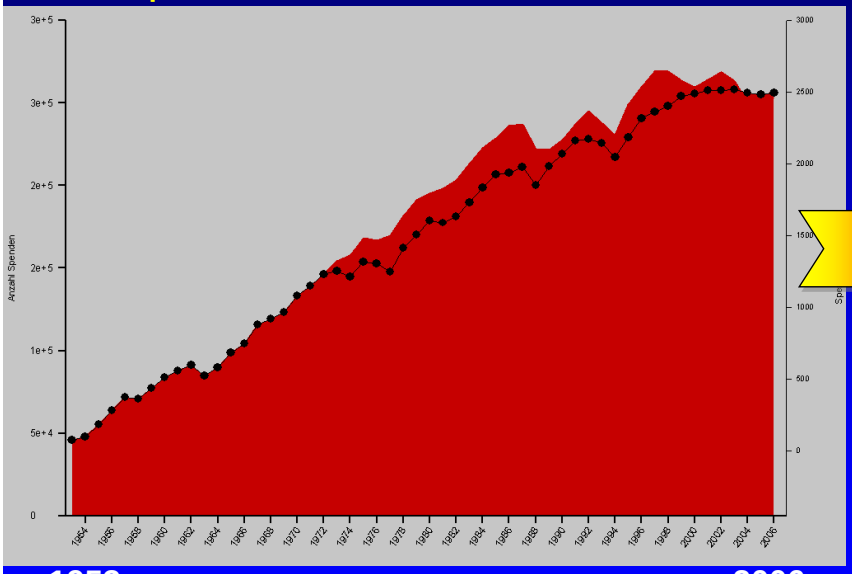
Aims of Benchmarking in Blood Donor Services are

- to guarantee:
  - the best donor
  - donor safety
  - optimal inclusion / exclusion criteria for donors
  - safety of the whole process chain
  - highest possible productivity
  - quality of blood products
  - recipient´s safety
  - 100% blood supply
  - reasonable costs
  - others

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Blood Products: Demand in Hessen

Development of blood donations in Hessen 1953-2006



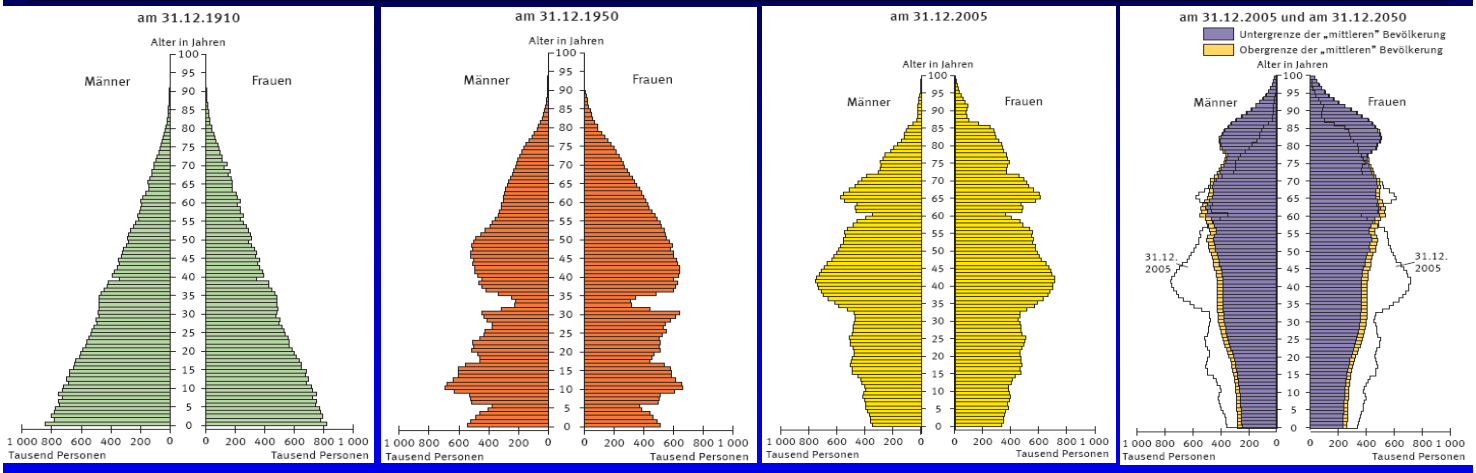
1953 **2006**

- surgery
- intensive care
- traumatology
- emergency care
- hematology
- oncology
- transplant. medicine
- pediatrics
- gynecology
- urology
- …

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Demographics of the German Population

1910 – 2050 (prognosis)



1910 **1950** **2005** **2050**

(prognosis)

Source: Statistisches Bundesamt, Wiesbaden, 2006

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

The Haunted Blood Donor

Paid versus unpaid ?
Regularly versus occasionally?

Plasma Industry

Red Cross Blood Donor Services

University & Municipal Blood Donor Services

Commercial Blood Donor Services

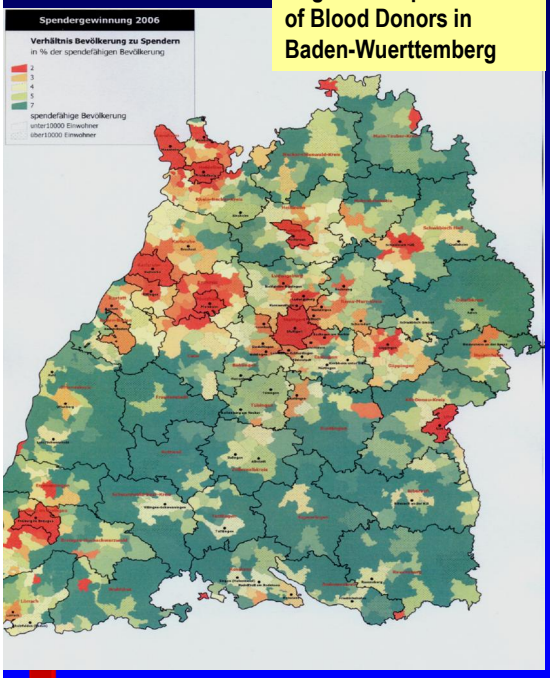
Blood Donation

- Analysis of donor population
- Introduction of uniform mobile IT system
- Harmonisation of:
  - Organisation of blood collection
  - Uniform processes:
    - Donor deferral
    - Hemoglobin (Hb) testing
    - Hygiene regimens, etc.
  - Material & Equipment: Central purchasing
  - Education & Training

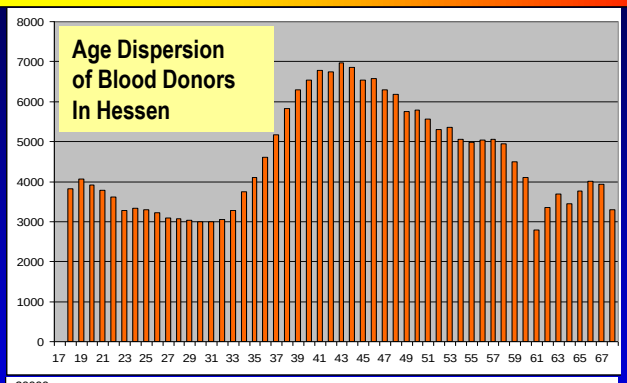
Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Blood Donors: Age and Regional Dispersion in Baden-Wuerttemberg & Hessen 2006 & 2007

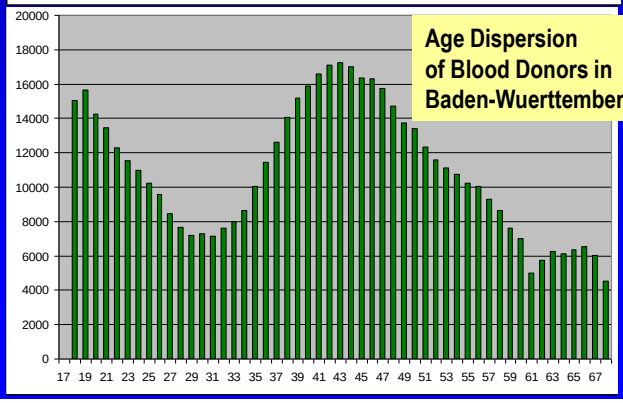
Regional Dispersion of Blood Donors in Baden-Wuerttemberg



Age Dispersion of Blood Donors In Hessen



Age Dispersion of Blood Donors in Baden-Wuerttemberg



Regulatory Framework

Laws, legal requirements

- Transfusion Law (Transfusionsgesetz (TFG))
- Drug Law (Arzneimittelgesetz (AMG))
- Infection Protection Law (Infektionsschutzgesetz (IfSG))
- Calibration Law (Eichgesetz)
- Technician Law (Gesetz über technische Assistenten in der Medizin)
- Medical Devices Law (Medizinproduktegesetz)
- Gene Technique Law (Gentechnikgesetz)
- Data Safety & Protection Law (Datenschutzgesetz)
- Decree for Pharmaceutical Operations (Betriebsverordnung für pharmazeutische Unternehmer)
- Good Manufacturing Practice (GMP)
- Good Laboratory Practice (GLP)
- Laboratory Report Decree (Laborberichtsverordnung)
- Medical Device Order (Medizingeräteverordnung)
- Order for Irradiated Drugs and Products (Verordnung über bestrahlte Arzneimittel)

Regulatory Framework

Directives, guidelines, recommendations

- Directive for Procurement & Therapy with Blood Components (Hemotherapy) (Richtlinien zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Hämotherapie))
- Directive for Quality Assurance in Immunohematology (Richtlinien zur Qualitätssicherung in der Immunhämatologie)
- Directive for Quality Management in Medical Laboratories (Richtlinien zur Qualitätssicherung in medizinischen Laboratorien)
- Guidelines for Therapy with Blood Components and Plasma Derivatives (Leitlinien zur Therapie mit Blutkomponenten und Plasmaprodukten)
- EU Directives and EU Guidelines (EU-Direktiven und EU-Guidelines)
- Recommendations of the European Council (Empfehlungen des Europarates „Leitfaden für die Herstellung und Qualitätssicherung von Blutbestandteilen“)
- World Health Organisation Recommendations for Blood Products (Empfehlungen der WHO „Anforderungen an die Entnahme, Verarbeitung und Qualitätskontrolle von Blut, Blutbestandteilen und Plasmafraktionen“)

Regulatory and Supervising Agencies

- Commission & Council of the European Union
- German Federal Health Minister (Bundesministerium für Gesundheit (BMG))
- German Medical Association (Bundesärztekammer (BÄK))
- Federal Agency for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM))
- Paul-Ehrlich-Institut (PEI)
- Robert Koch-Institut (RKI)
- Supervisory Agencies (Aufsichtsbehörden):
  - Regional Councils (Regierungspräsidien (RP))
  - Regional Health & Hygiene Boards (Gesundheitsämter)
- Expert Advisory Panel for Hemotherapy of the German Health Minister (Arbeitskreis Blut (Ak Blut))
- German Society for Transfusion Medicine and Immunohematology (Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (DGTI))
- Sections and Committees of Medical Societies for Transfusion Medicine (Sektionen und Kommissionen für Teilgebiete des Fachbereiches Transfusionsmedizin (z.B. Plasmapherese, etc.))

Institute for Transfusion Medicine and Immunohematology
Clinics of the Johann Wolfgang Goethe University Frankfurt / Main
German Red Cross Blood Donor Service Baden-Wuerttemberg – Hessen

Optimal use of allogeneic blood products

Hans Gombotz

Optimal use of allogeneic blood products

H. Gombotz

Department of Anesthesiology and Intensive Care
General Hospital Linz, Austria

PROBLEMS

- Shortages
- Remaining risks
- Storage lesions
- Different standards
- Guidelines ineffective
- „Physiologic“ transfusion trigger
- Monitoring impossible
- Variability
- Reduction of morbidity and mortality unclear

Wildbad Kreuth, Mai 1999

On the one hand…

Dopingsünder Jaksche

„Eine Bluttransfusion ist wie eine Atombombe"

"Man muss personelle Altlasten beseitigen": Jörg Jaksche

20. September 2007 Dank der Kronzeugenregelung kam der geständige Dopingsünder Jörg Jaksche mit einer milden Strafe davon. Der Anti-Doping-Ausschuss des Österreichischen Radsportverbandes sperrte den Ansbacher Profi wegen des Gebrauchs von Epo und Wachstumshormonen sowie wegen Blutdopings für ein Jahr und folgte damit den Vorstellungen der Jaksche-Verteidigung.

Sie sind aufgrund Ihres Dopinggeständnisses am Mittwoch zu einem Jahr Sperre verurteilt worden, bis Anfang Juli 2008. Sind Sie einverstanden?

Österreichs Blut-Pool trocknet aus - Chronik - Österreich / oe24.at

Datei Bearbeiten Ansicht Favoriten Extras ?

Zurück Suchen Favoriten

Adresse http://www.oe24.at/oesterreich/chronik/Oesterreichs_Blut-Pool_trocknet_aus_422710...

Inland Welt Sport Wirtschaft Digital Leute Wissen Kultur Life &

Sie sind hier: News > Inland > Chronik

Drucken | Versenden | Leserbrief

Zu wenig Spender

Österreichs Blut-Pool trocknet aus

Wien, 27. Jänner 2009 Immer weniger Menschen spenden Blut, dabei wird immer mehr davon benötigt. Nach den Ferien und der Grippewelle ist das Lager quasi leer.

© buenas dias

Ohne verstärkte Mithilfe der Bevölkerung geht es nicht. Österreichs Pool an Blutkonserven - zum größten Teil gemanagt vom Roten Kreuz - gerät zunehmend aufs Trockene. Immer weniger Menschen sind zur Blutspende bereit, Wien ist im Länder-Vergleich besonders schlecht. Und jetzt - wie alle Jahre wieder - schlägt das traditionelle Spender-Manko zu Grippe- und Urlaubszeiten extrem zu.

"Null im Pool"

"Wir haben praktisch Null im Pool." Dr. Eva Menichetti, medizinische Leiterin der Blutspendezentrale für Wien, Niederösterreich und das Burgenland blickt auf den Bildschirm vor sich. Österreichs Blutspendezentralen in Wien, Linz, Klagenfurt und Feldkirch sowie die Blutdepartments an den Universitätskliniken bzw. LKHs in Graz, Innsbruck und Salzburg stellen im Computerverbund jene Blutkonserven ins Netz, die sie bei Engpässen in anderen Regionen abgeben könnten. Aktualisiert wird das alle 48 Stunden. Ende Jänner 2009 ist de facto nichts vorhanden.

Ferien und Grippe

Der Grund dafür: Während der Weihnachtsfeiertage und in den Ferien kommen an sich schon weniger Spender in die Zentralen. In diesem Jahr stellte sich unmittelbar nach den Ferien die Influenza in Österreich - etwas ...kral, Leiterin des Spendermanagements der ..."Die Situation ist zunehmend dramatisch. Mit ...ederösterreich und das Burgenland haben wir ...ven auf Lager. Es sollten 4.000 bis 4.500 sein."

...ng offenbar zu wenig bekannt ist: Die ...ren in den österreichischen Spitälern mit Blut ... oder "die Anderen" betreiben können. Das ist ...nten österreichischen Bevölkerung. Wo sonst ...mmen?

http://austria1.adverserve.net/RealMedia/ads/click_lx.ads/oe24.at/oesterreich/chronik/article422710/1987670581/Right1/oe24/oe24

Internet

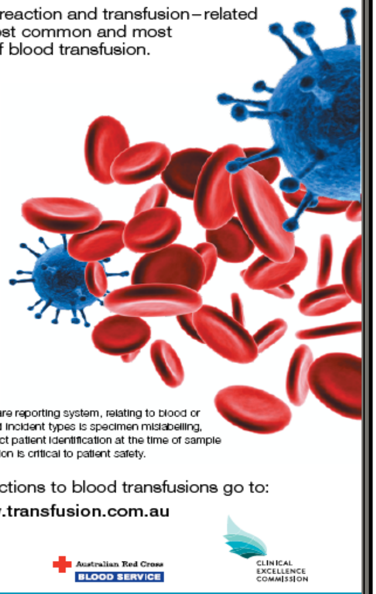
Start F:\wildbadKreuth2008 wildbadkreuth2009.ppt kreuth-gombotz.ppt Österreichs Blut-Pool ... Posteingang - Micros... Office Zubehör 11:47

On the other hand...

Blood,
it's safer than it's ever been...

MYTH BUSTED

Bacterial contamination, incompatibility reaction and transfusion–related acute lung injury (TRALI) are still the most common and most immediately dangerous complications of blood transfusion.



SERIOUS RISKS

Non Infectious Risk		RISK PER UNIT USED Unless otherwise specified
Haemolytic reactions	Acute	1:12,000 to 38,000
	Delayed	1:4,000 to 12,000
Bacterial sepsis	Platelets	1:100,000
Anaphylaxis - IgA deficiency		1:20,000 to 50,000
Fluid overload / cardiac failure		Up to 1% of patients receiving transfusions
TRALI#		1:5,000 to 100,000
Transfusion-associated graft v host disease		Rare

ARCBS Blood Component Information Booklet 2006 #Table based on overseas estimates

Patients are often still concerned about the risk of Hepatitis or HIV from blood transfusions. However recent ARCBS statistics show us that the risks of contracting transmissible viruses is a rare occurrence in Australia.

VIRAL RISKS

Current estimated viral risks for Australian blood supply*	
HBV	1 in 660,000
HCV	Less than 1 in 10,000,000
HTLV I and II	Less than 1 in 10,000,000
HIV	Less than 1 in 10,000,000
vCJD	Possible, not yet reported in Australia. Donors at risk excluded

*point estimates for risk of transfusion transmitted viral infection from ARCBS donations, calculated using data from 1 January 2005 to 31 December 2006

A recent review of incidents reported in IIMS, the NSW healthcare reporting system, relating to blood or blood products shows that one of the most commonly reported incident types is specimen mislabelling, including wrong blood in tube (WBIT). The importance of correct patient identification at the time of sample collection and labelling as well as the administration of transfusion is critical to patient safety.

For more information about adverse reactions to blood transfusions go to:
www.cec.health.nsw.gov.au and **www.transfusion.com.au**

BLOOD WATCH every drop counts | NSW HEALTH | Australian Red Cross BLOOD SERVICE | CLINICAL EXCELLENCE COMMISSION

Blood Myth #1

A blood transfusion
will get my patient home sooner...

MYTH BUSTED

There is emerging evidence that patients transfused after surgery stay longer in hospital and have more infections following discharge.

The CRIT Study[1] shows that RBC transfusions are independently associated with longer ICU and hospital length of stay and increased mortality. Overall there were more complications in the patient cohort and the number of RBC units transfused was an independent predictor of worse clinical outcome.

> Multivariate Analyses. The number of RBC units transfused was significantly associated with increased ICU and hospital LOS compared with patients who did not receive transfusions. Patients with
> **a transfusion amount of 1-2, 3-4, and >4 units had a corresponding increase in median ICU LOS of 2.1, 3.8 and 10.1 days, respectively;**
> **and an increase in median hospital LOS of 3.5, 6.7 and 16.6 days,**
> respectively, as compared with the median ICU LOS of 4.6 days and hospital LOS of 11.0 days observed in patients who did not receive transfusions.

In addition, a 2006 study[2] of blood transfusions during cardiac surgery concluded that there was

- a dose–dependent relationship between reductions in functional recovery for the patient and an increase in the units of red blood cells transfused.
- a persistently negative, risk–adjusted effect on health–related quality of life after cardiac surgery that extends well beyond initial hospitalisation.

A blood transfusion is a living tissue transplant.
With any transplant the human body is innately primed to react to something foreign.
The safety implications of this are significant.

Remember– consider all the factors, not just Hb, before transfusing.

For details on these studies and best practice guidelines on blood transfusions go to:
www.cec.health.nsw.gov.au and **www.transfusion.com.au**

1 The CRIT Study: Anemia and blood transfusion in the critically ill- Current clinical Practice in the United States. Corwin, Howard L.. Gettinger, Andrew. Pearl, Ronald G. Fink, Mitchell P. Levy, Mitchell M. Abraham, Edward. MacIntyre, Neil R. Shabot, M Michael. Duh, Mei-Sheng. Shapiro, Marc J. Critical Care Medicine. 32(1):39-52, 2004 Jan.

2 Persistent effect of red cell transfusion on health-related quality of life after cardiac surgery. Koch, Colleen Gorman. Khandwala, Farah. Li, Liang. Estafanous, Fawzy G. Loop, Floyd D. Blackstone, Eugene H. Annals of Thoracic Surgery. 82(1):13-20, 2006 Jul

BLOOD WATCH every drop counts | NSW HEALTH | Australian Red Cross BLOOD SERVICE | CLINICAL EXCELLENCE COMMISSION

Blood Myth #2

Blood
transfusions improve healing...

MYTH BUSTED

Current, emerging evidence shows that patients who receive blood transfusions are at greater risk of transfusion associated adverse outcomes such as infection, kidney failure, lung injury or death.

A recent study on red cell transfusions and nosocomial infections in critically ill patients[1] concluded that infection rate was higher in those patients transfused compared to those who weren't. Mortality and length of stay (intensive care unit and hospital) were significantly higher in transfused patients, even when corrected for illness severity.

Transfused patients, even after adjusting for survival probability, had significantly:

- Higher nosocomial infection (NI) rates (14.3% vs 5.8%; P<.0001)
- Longer ICU LOS (8.2 vs 3.3 days; P<.0001)
- Longer hospital LOS (18.3 vs 9.9 days; P<.0001)
- Higher mortality rates (21.8% vs 10.2%; P<.0001)

A blood transfusion is a living tissue transplant.
With any transplant the human body is innately primed to react to something foreign.
The safety implications of this are significant.

Remember– consider all the factors, not just Hb, before transfusing.

- **GO** — **Hb < 70 g/L** Lower thresholds may be acceptable for patient without symptoms and/or where specific therapy is available.
- **Caution** — **Hb 70-100 g/L** Likely to be appropriate during surgery associated with major blood loss or if there are signs or symptoms of impaired oxygen transport.
- **Stop** — **Hb > 100 g/L** Not likely to be appropriate unless there are specific indications.

1. Red blood cell transfusions and nosocomial infections in critically ill patients. Taylor, Robert W. MD, FCCM; O'Brien, Jacklyn RN; Trottier, Steven J. MD, FCCM; Manganaro, Lisa RN; Cytron, Margaret RN; Lesko, Mary F. RN, BSN; Arnzen, Kimberly RN; Cappadoro, Carla RN, MSN; Fu, Min MS, MBA; Plisco, Michael S. MD; Sadaka, Farid G. MD; Veremakis, Christopher MD Critical Care Medicine - Volume 34, Issue 9 (September 2006)

For more information about appropriate transfusion practices go to:
www.cec.health.nsw.gov.au and **www.transfusion.com.au**

BLOOD WATCH every drop counts | NSW HEALTH | Australian Red Cross BLOOD SERVICE | CLINICAL EXCELLENCE COMMISSION

Blood Myth #3

Autologous blood,
(pre-donated) is risk free...

MYTH BUSTED

Pre–donated autologous transfusion is not risk free and there are a variety of adverse events associated with this practice.

Use of autologous blood still carries equal, if not greater, risk of bacterial contamination. There are three reasons for this:

- autologous donor criteria are generally more flexible than allogeneic donor acceptance;
- it is possible that autologous donor screening, at the point of donation is less precise and rigorous
- the typically longer storage interval of autologous RBC units maximises the opportunity for bacterial proliferation.

Complications of Autologous transfusion

- Blood wastage
- Donor reactions
- Bacteremia
- Errors and accidents
- Iatrogenic anaemia
- Volume overload

Autologous donations may cost the patient $200 or more, per unit collected.

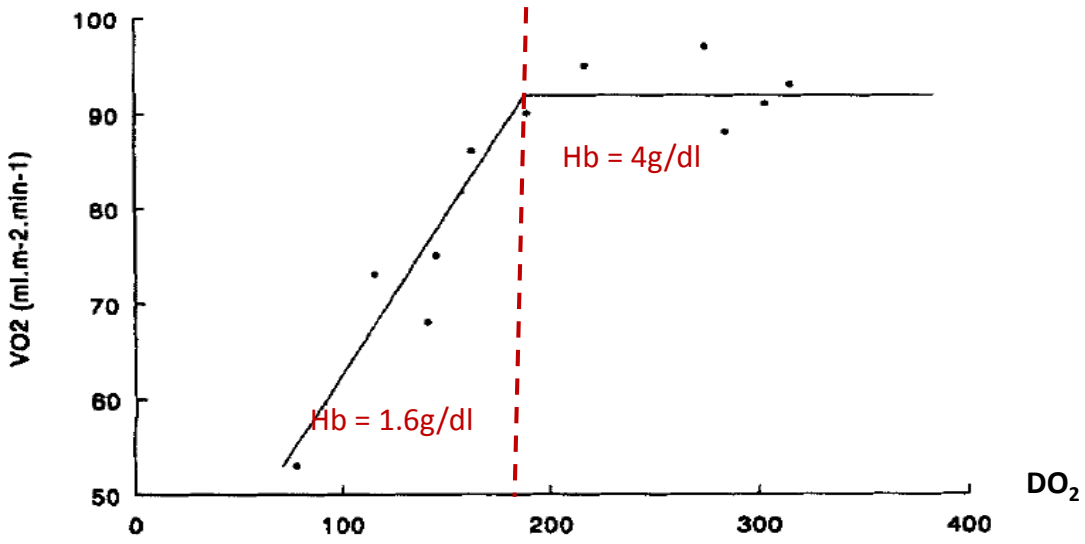
For more information about the risk of autologous transfusion go to:
www.cec.health.nsw.gov.au and **www.transfusion.com.au**

1 Wood, EM & Yomotovian, RA Adverse Consequences of Autologous Transfusion Practice in Popovsky MA, ed. Transfusion Reactions, 3rd Edition, Bethesda MD: AABB Press, 2007.

BLOOD WATCH every drop counts | NSW HEALTH | Australian Red Cross BLOOD SERVICE | CLINICAL EXCELLENCE COMMISSION

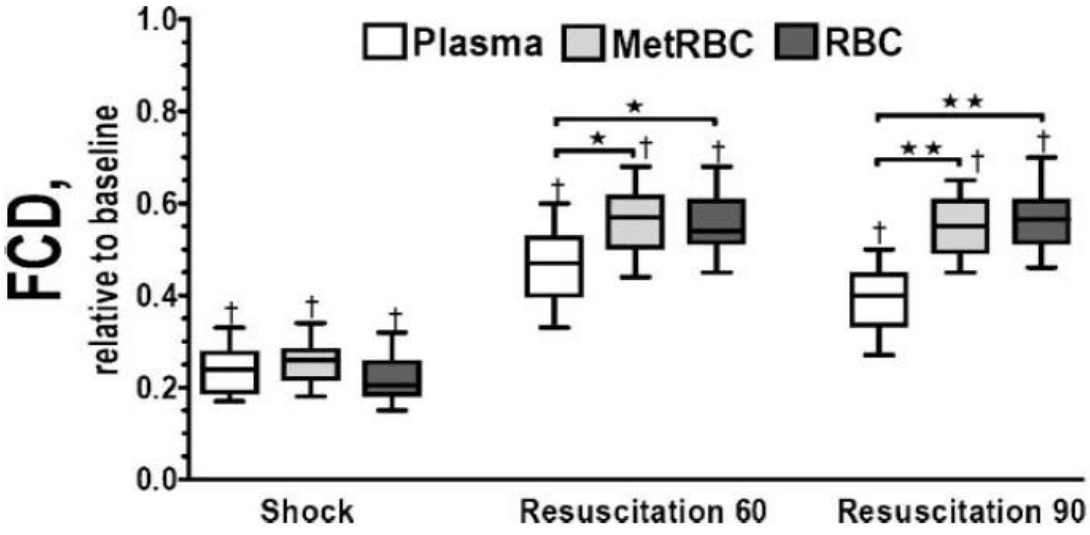
Blood Myth #4

Relationship between oxygen delivery (DoZ) and oxygen consumption (Vo,) during increasing hemodilution.



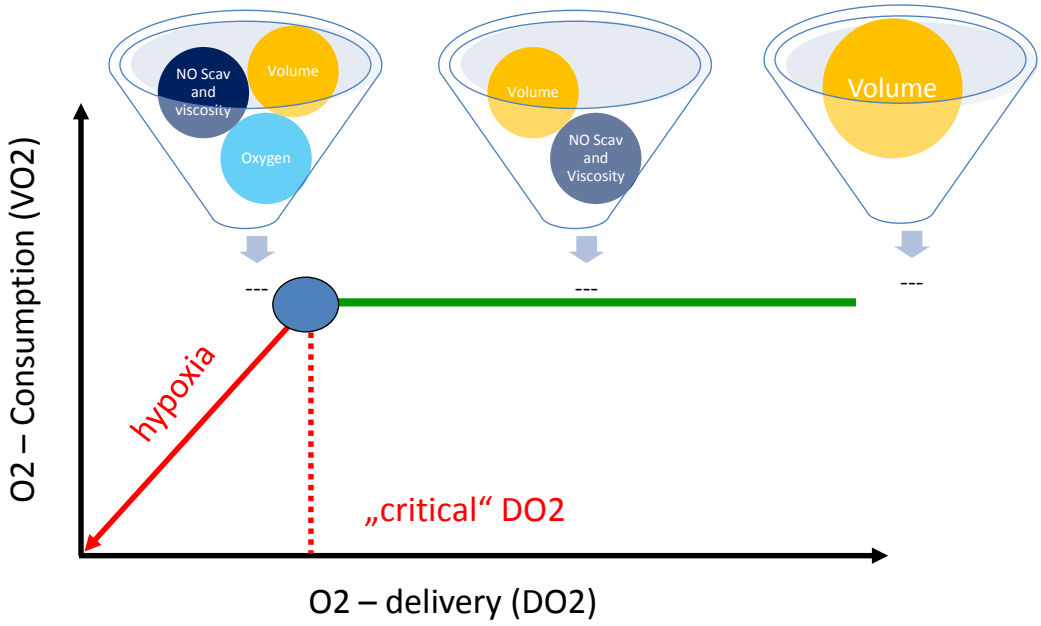
Woerkens et al: Anesth Analg 1992;75:818-21

Effects of plasma viscosity on capillary perfusion during hemodilution

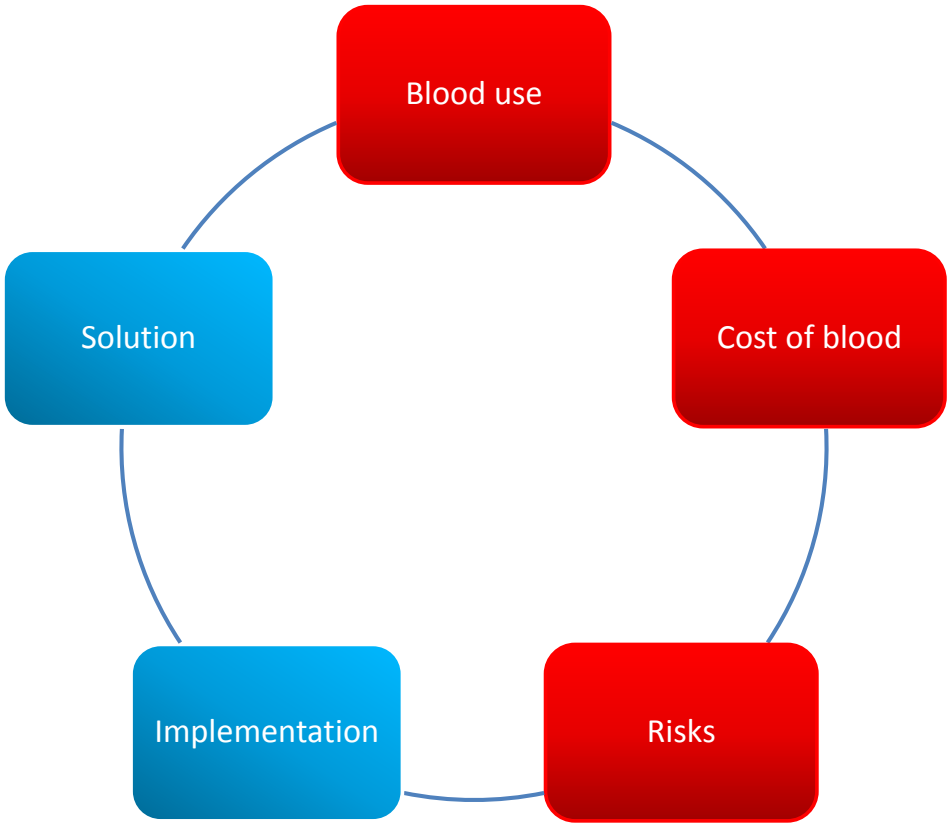


Cabrales et al: SHOCK: 27, 380-389, 2007

Limits of Hemodilution



Paradigm Shift

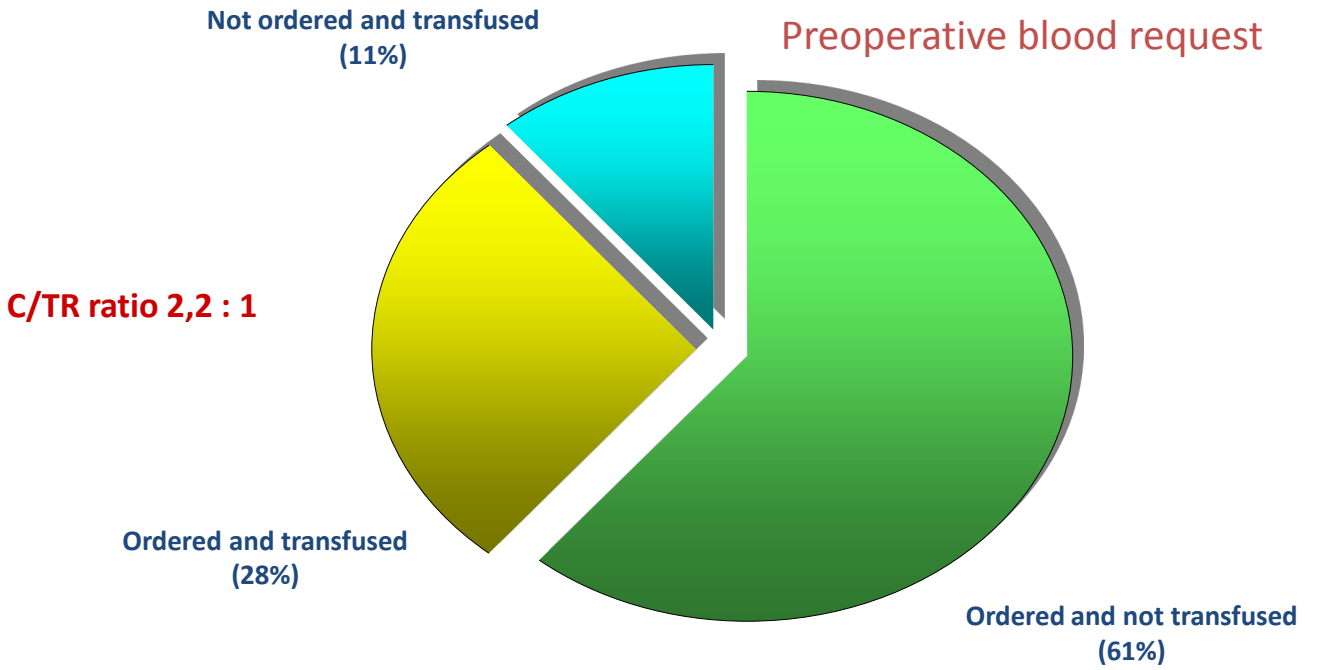


Measures to optimize the use of blood components in selected surgical procedures in Austrian hospitals

Randomised Centres

BUNDESMINISTERIUM FÜR GESUNDHEIT UND FRAUEN

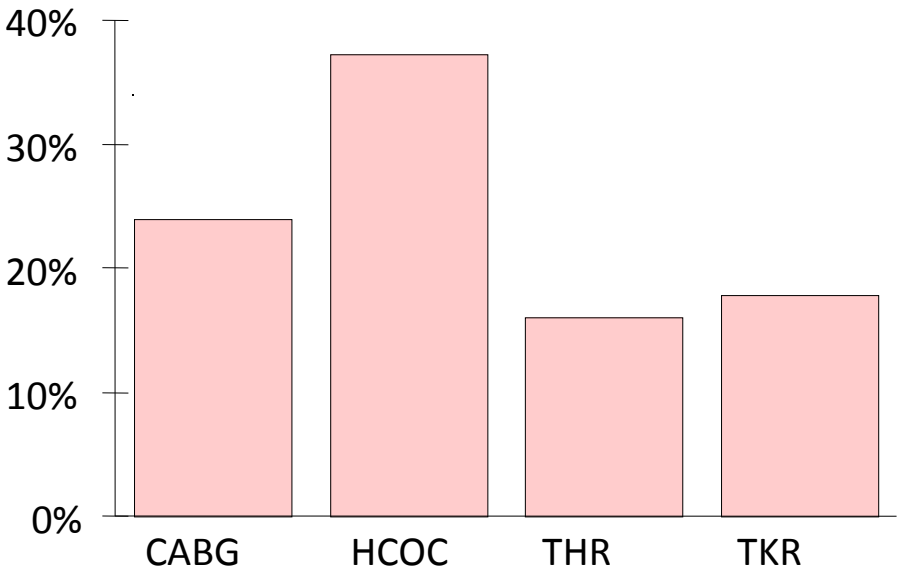
Measures to optimize the use of blood components in selected surgical procedures in Austrian hospitals



BUNDESMINISTERIUM FÜR GESUNDHEIT UND FRAUEN

Measures to optimize the use of blood components in selected surgical procedures in Austrian hospitals

Prevalence of Anemia



BUNDESMINISTERIUM FÜR GESUNDHEIT UND FRAUEN

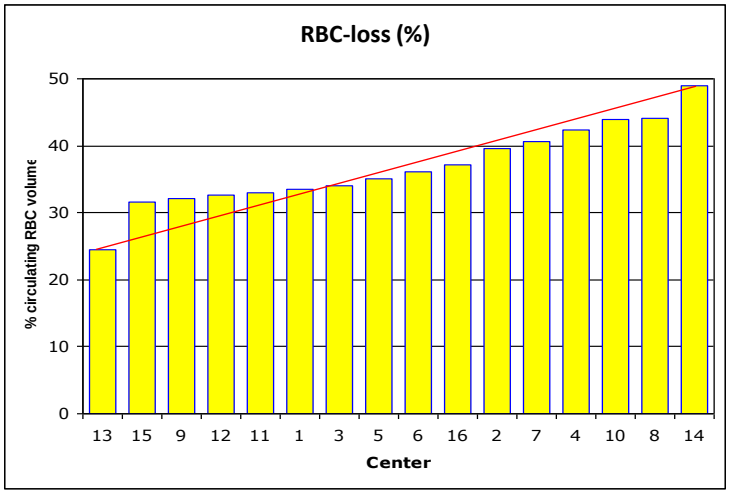
Consequences of Preoperative Anemia

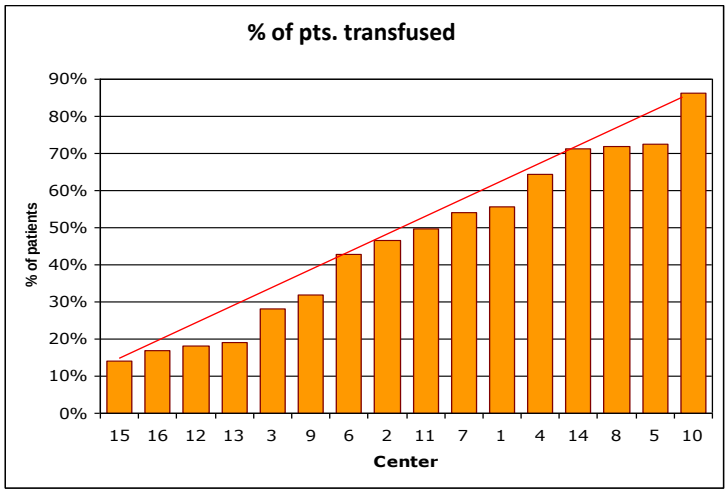
	N pts.	Anemic pts.	I	II	p-value
CABG	777	24%	48%	76%	<0.001
HECO	148	30%	11%	58%	<0.001
THR	1401	16%	28%	54%	<0.001
TKR	1296	18%	28%	60%	<0.001
total	**3622**	**19%**	**32%**	**62%**	**<0.001**

I = % non-anemic pts. transfused with allogeneic RBCs,
II = % of anemic pts. transfused with allogeneic RBCs
Fisher's exact test

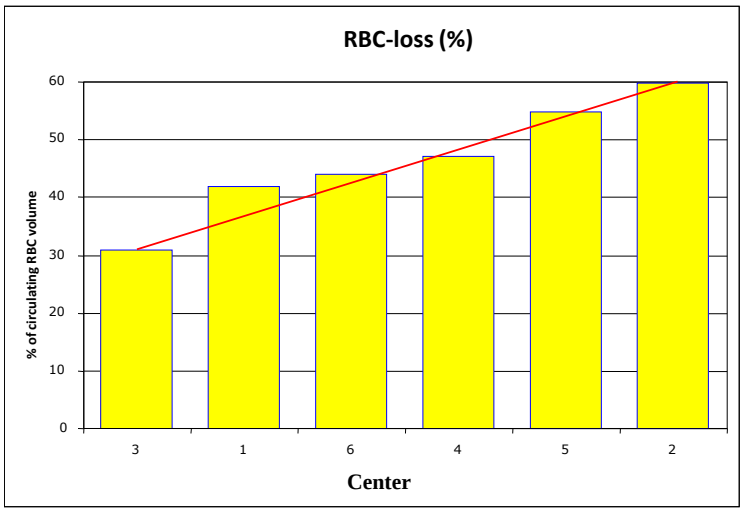
Measures to optimize the use of blood components in selected surgical procedures in Austrian hospitals

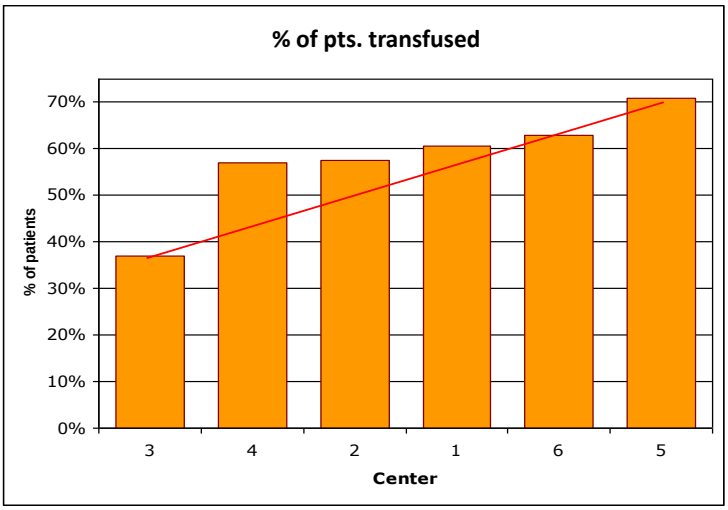
RBC loss (%) and % patients transfused in THR and TKR





RBC loss (%) and % patients transfused in CABG

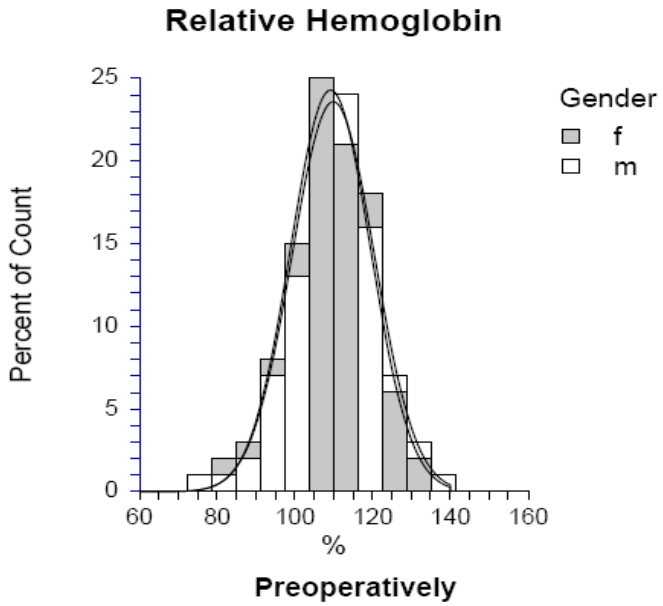


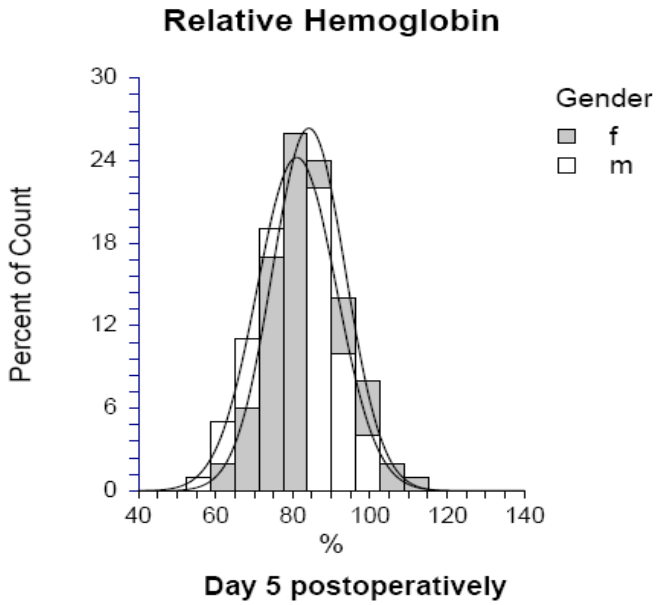


BUNDESMINISTERIUM FÜR GESUNDHEIT UND FRAUEN

Red cell transfusion and gender

Orthopedic Surgery





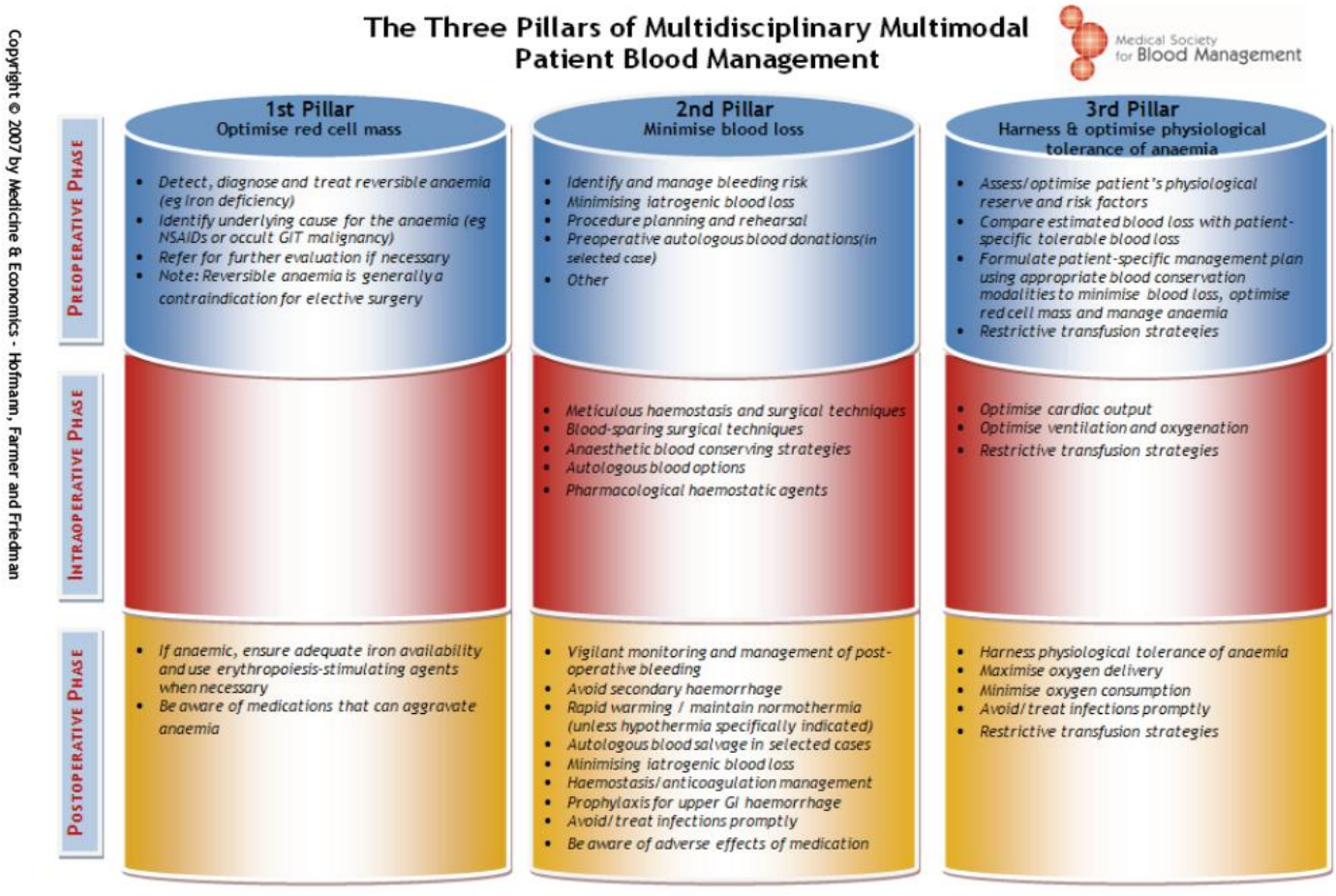
Absolute hemoglobin values in females were significantly lower throughout the perioperative course, whereby relative hemoglobin values were nearly identical before surgery but considerably higher on postoperative day 5 ($p<0.001$)

ESA 2008

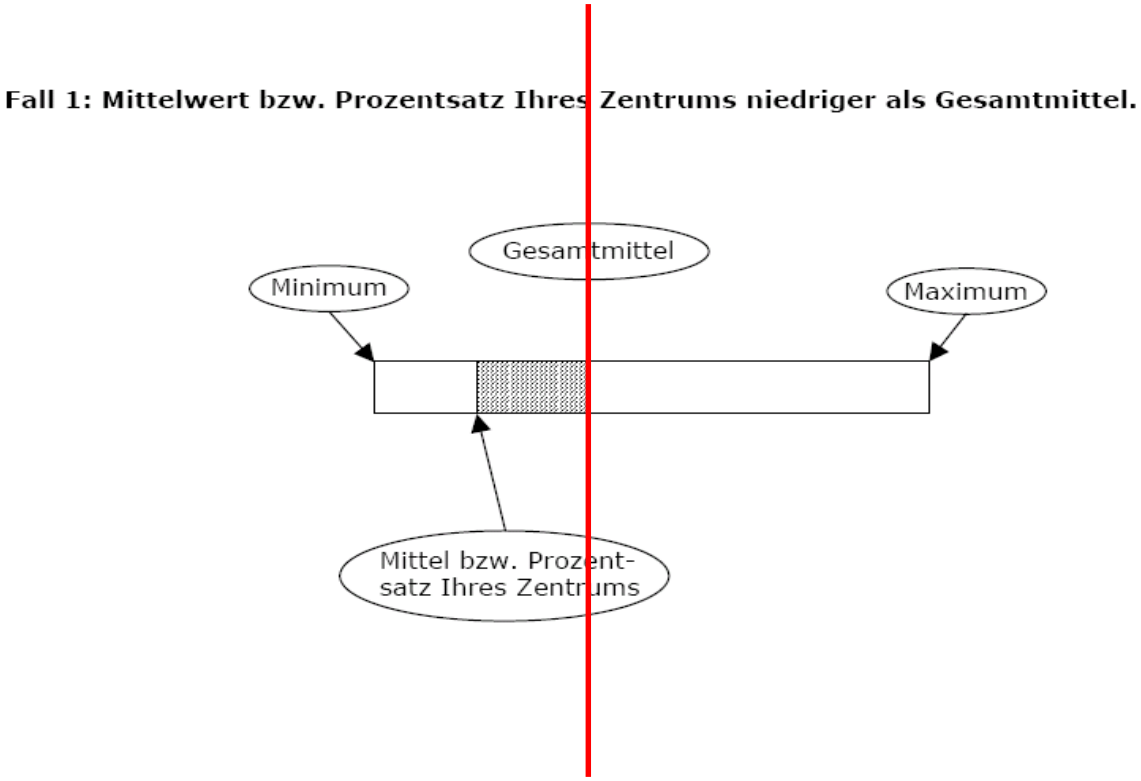
Predictors of RBC transfusions

Procedure	THR	TKR	CABG
Independent Variable	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Hemoglobin preop.(%)*	0.65 (0.60;0.70)	0.68 (0.63;0.73)	0.69 (0.63;0.75)
Min. hemoglobin postop. (%)*	1.50 (1.38;1.64)	1.48 (1.35;1.63)	1.52 (1.36;1.70)
Lost RBC -volume (%) **	1.82 (1.64;2.01)	1.81 (1.62;2.02)	1.81 (1.58;2.07)
Center rank‡	1.34 (1.24;1.46)	1.35 (1.25;1.46)	-
Correctly classified (%)	97.4%	97.2%	97.0%

* Percentage of WHO cut-off values
** Percentage of the preoperatively circulating RBC volume
‡ Centers ranked according to the mean perioperative RBC loss



Center Report (I)



TRANSFUSION PRACTICE

Blood use in elective surgery: the Austrian benchmark study

Hans Gombotz, Peter H. Rehak, Aryeh Shander, and Axel Hofmann

TRANSFUSION 2007;47:1468-1480.

Response

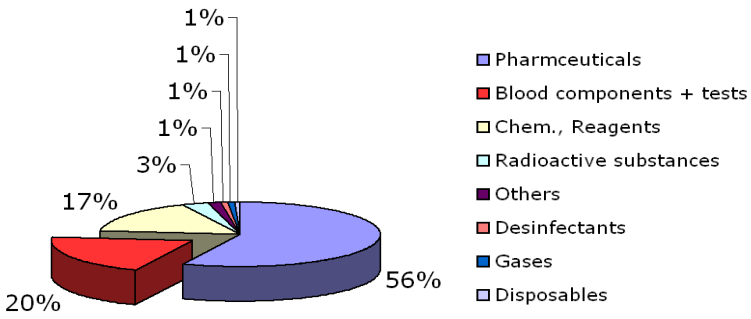
Health Authorities	Providers	Centers	Media	Medical Societies
Ø	Ø	Ø- ↑	↑↑	↓↓

Co-operation with Western Australian Patient Blood Management

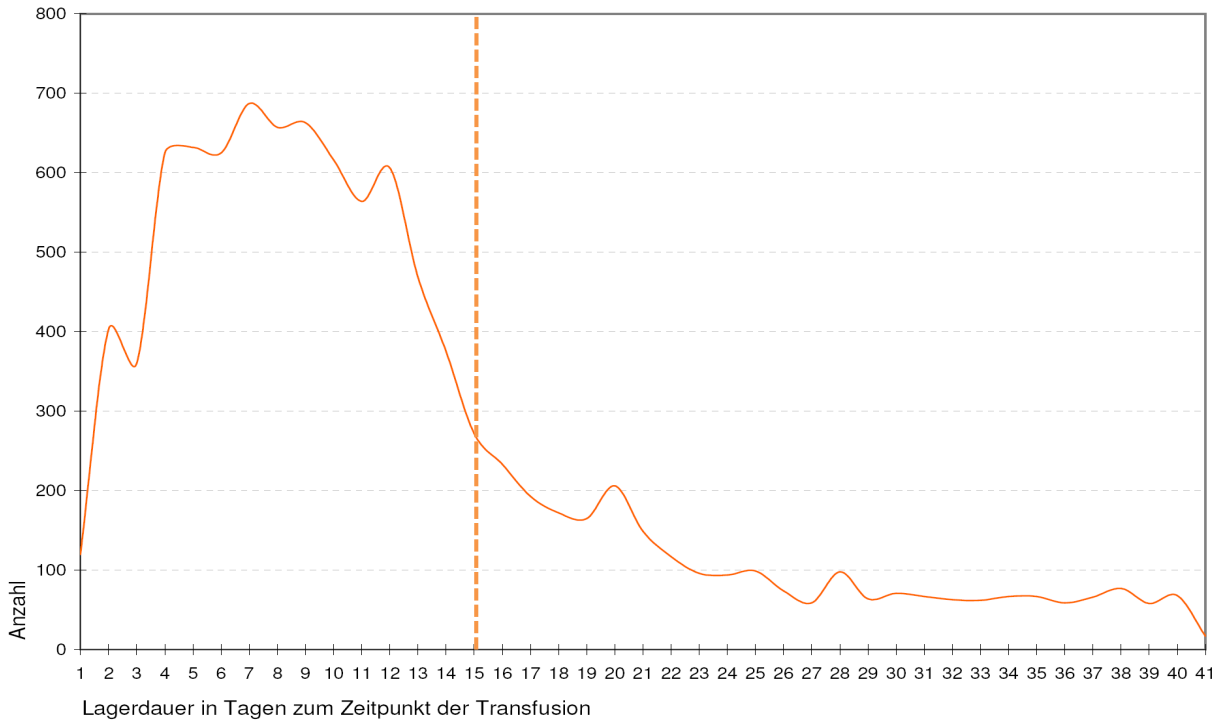
Problems continue

- Possible adverse outcome due to (at least) suboptimal use of allogeneic blood products
- Shortages (reduced donor recruitment, overuse, increasing age of population, etc.)
- Increasing costs (also to maintain existing structures)

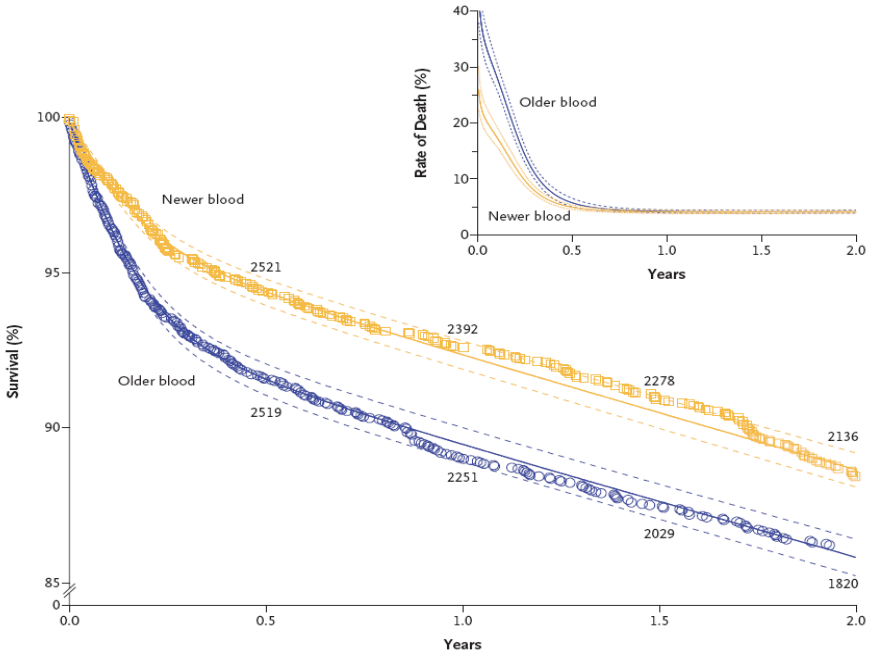
Pharmacy Expenditures
AKH 2005



Age of delivered RBC Units of an Austrian Blood Bank

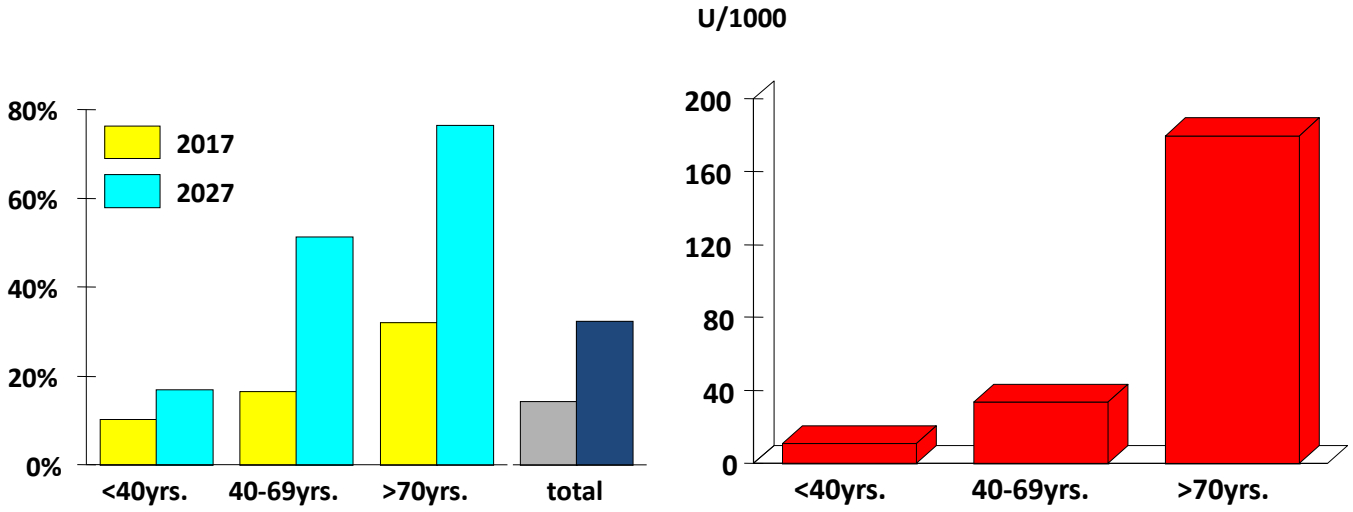


Duration of Red-Cell storage and Postoperative Complications



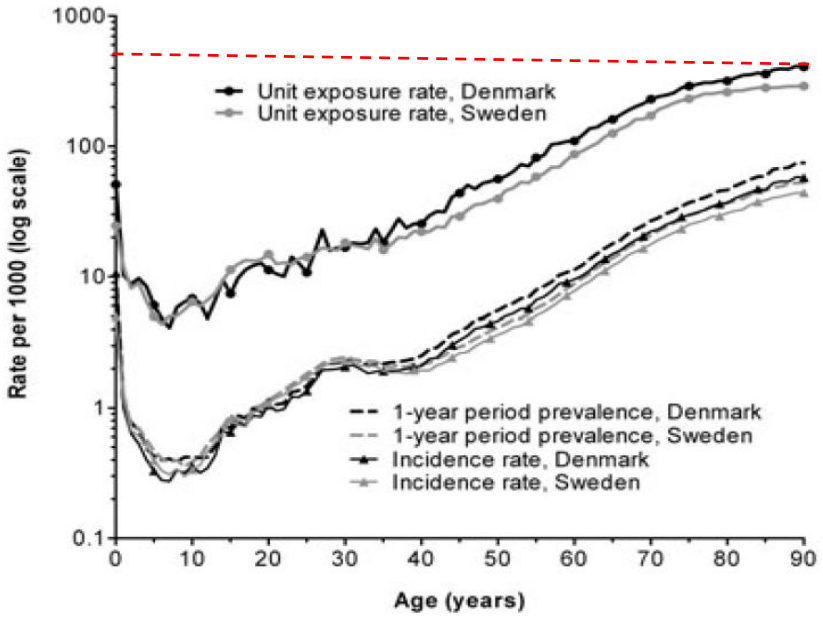
Koch et al: N Engl J Med 2008;358:1229-39.

Red cell transfusion and age of population



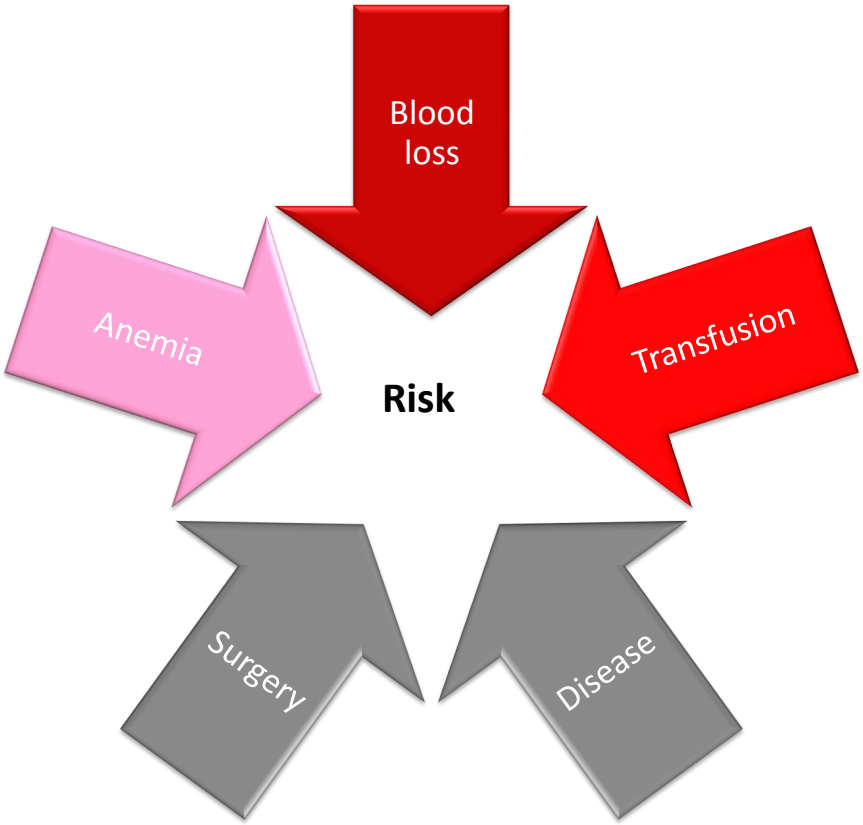
Source: Compiled from WA Tomorrow

Unit exposure rate, 1-year period prevalence, and incidence rate in Denmark and Sweden according to age at transfusion.



Kamper-Jørgensen et al: Transfusion, 2009

Total Perioperative Risk

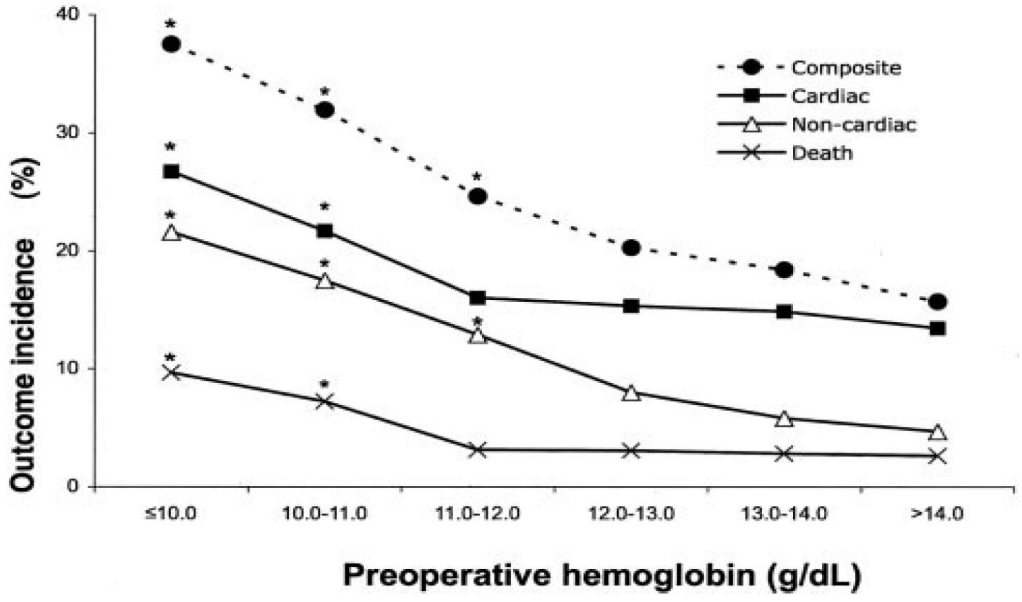


FACTORS THAT INCREASE THE RISK OF PERIOPERATIVE CARDIAC COMPLICATIONS IN PATIENTS UNDERGOING NONCARDIAC SURGERY

Risk Factor	Odds Ratio (95% CI)*	Perioperative Beta-Blocker Indicated
Ischemic heart disease†	2.4 (1.3–4.2)	Yes
Congestive heart failure	1.9 (1.1–3.5)	Yes
High-risk surgery‡	2.8 (1.6–4.9)	Uncertain, but probably
Diabetes mellitus (especially insulin-requiring)	3.0 (1.3–7.1)	Yes
Renal insufficiency	3.0 (1.4–6.8)	Uncertain, but probably if renal insufficiency is due to diabetes or vascular disease
Poor functional status§	1.8 (0.9–3.5)	Yes, if poor status is thought to be due to coronary artery disease or heart failure

Fleisher et al: NEJM, 345, 2001

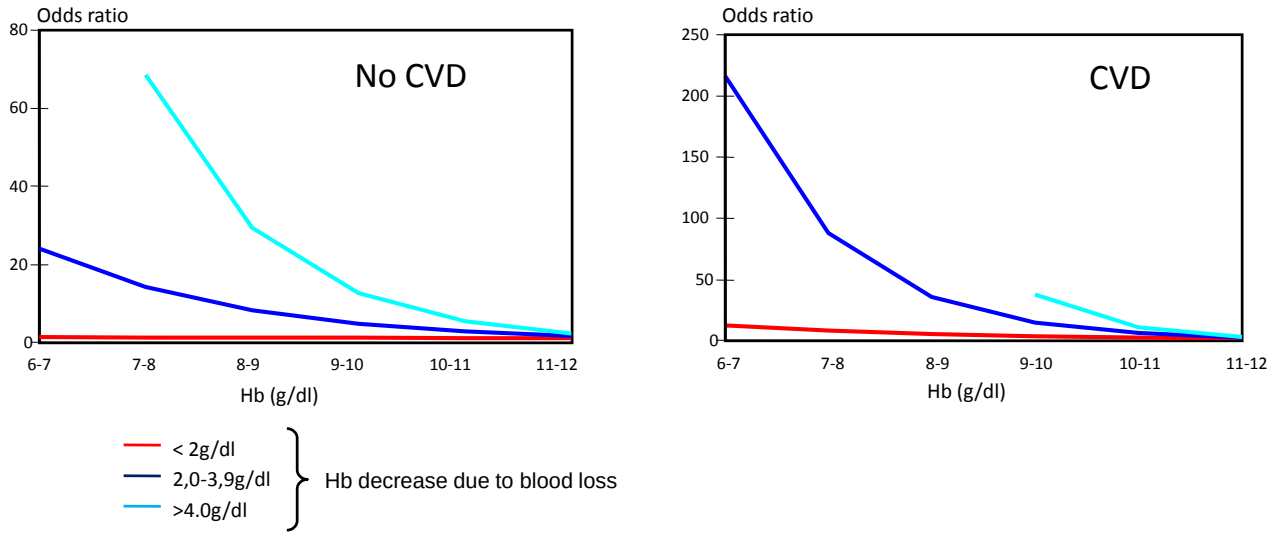
Impact of Preoperative Anemia on Outcome in Patients Undergoing Coronary Artery Bypass Graft Surgery



Kulier et al: Circulation 2007;116:471-479

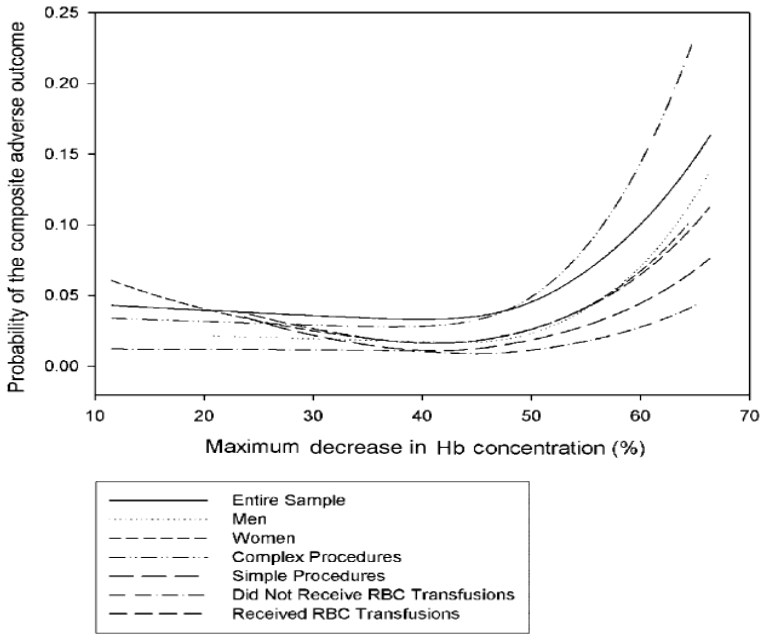
"Yes - that's my surgeon - the one who cuts himself shaving ..."

Adjusted Odds Ratio for Mortality and Preop. Hb. and Decline in Hb. Stratified by Cardiovascular Disease (n=1080)



Carson J. et al.: Lancet 348:1055-60, 1996

Relationship between maximum decrease in Hb concentration and probability of the composite adverse outcome



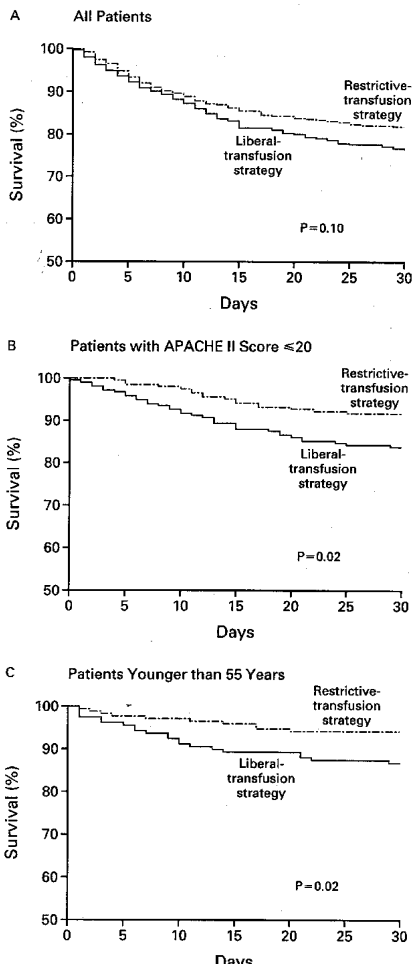
Karkouti et al: TRANSFUSION 2008;48:666-672.

Association of RBC transfusions with mortality and morbidity in critically ill in observational studies

Study: first author, year	Population	Design	Number	Outcomes
Ciesla, 2005[113]	Trauma	Prospective cohort	1,344	Increased multiorgan failure
Gong, 2005[106]	ICU patients	Prospective cohort	688	Increased risk of ARDS*
Lebron, 2005[109]	Liver transplant	Retrospective cohort	241	Increased early postoperative renal failure
Shorr, 2005[107]	ICU patients	Prospective cohort	3,502	Increased ICU acquired bacteremia
Silverboard, 2005,[112]	Trauma	Prospective cohort	102	Increased risk of ARDS
Smith, 2004[108]	Subarachnoid hemorrhage	Prospective cohort	441	Worse outcome with intraoperative transfusions
Vincent, 2004[5]	ICU patients	Prospective cohort	1,136	Increased ICU, hospital and 28-day mortality Increased organ dysfunction
Leal-Noval, 2003[104]	Cardiac surgery	Prospective cohort	103	Increased ICU LOS, mechanical ventilation, and pneumonia
Malone, 2003[98]	Trauma	Prospective cohort	15,534	Increased mortality
Chelemer, 2002[100]	CABG	Prospective cohort	533	Increased bacterial infections
Claridge, 2002[110]	Trauma	Prospective cohort	1,593	Increased infection
Corwin, 2002[4]	ICU	Prospective cohort	4,892	Increased ICU and hospital LOS Increased complications
Taylor, 2002[95]	ICU	Retrospective cohort	1,717	Increased nosocomial infections, ICU LOS, and mortality
Vamvakas, 2002[111]	Cardiac surgery	Retrospective cohort	416	Increased postoperative ventilation associated with volume of RBC supernatant
Leal-Noval, 2001[96]	Cardiac surgery	Prospective cohort	738	Increased ICU LOS, mechanical ventilation, and pneumonia
Chang, 2000[97]	Colorectal surgery	Retrospective cohort	282	Increased postoperative infection Increased mortality
Carson, 1999[101]	Hip fracture	Retrospective cohort	9,598	Increased risk of serious bacterial infection and pneumonia
Offner, 1999[105]	Trauma	Prospective cohort	61	Increased infection
Vamvakas, 1999[103]	Cardiac surgery	Retrospective cohort	416	Increased postoperative infection (5% /unit)
Carson, 1998[141]	Hip fracture	Retrospective cohort		No change in mortality or morbidity
Moore, 1997[102]	Trauma	Prospective cohort	513	Increased multiorgan failure
Martin, 1994[99]	ICU	Retrospective cohort	698	Increased mortality

* ARDS = acute respiratory distress syndrome.

Tinmouth et al: TRANSFUSION 2006;46:2014-2027.

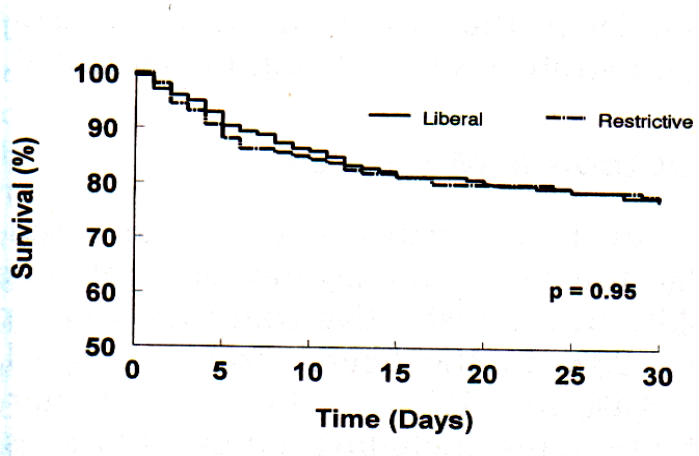


A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care

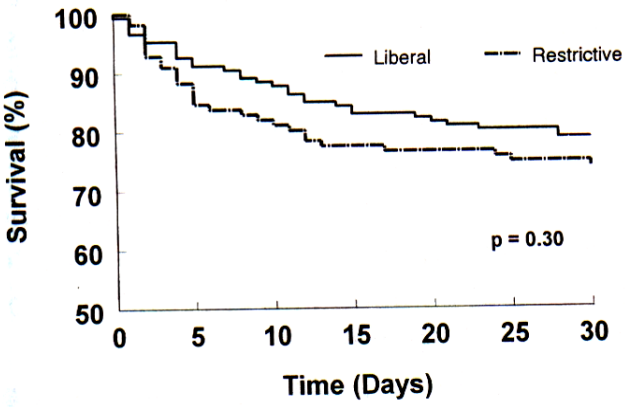
Hebert P.C. et al: NEJM 340, 409-17, 1999

CONCLUSIONS: A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.

Is low transfusion threshold safe in critically ill patients with cardiovascular diseases?



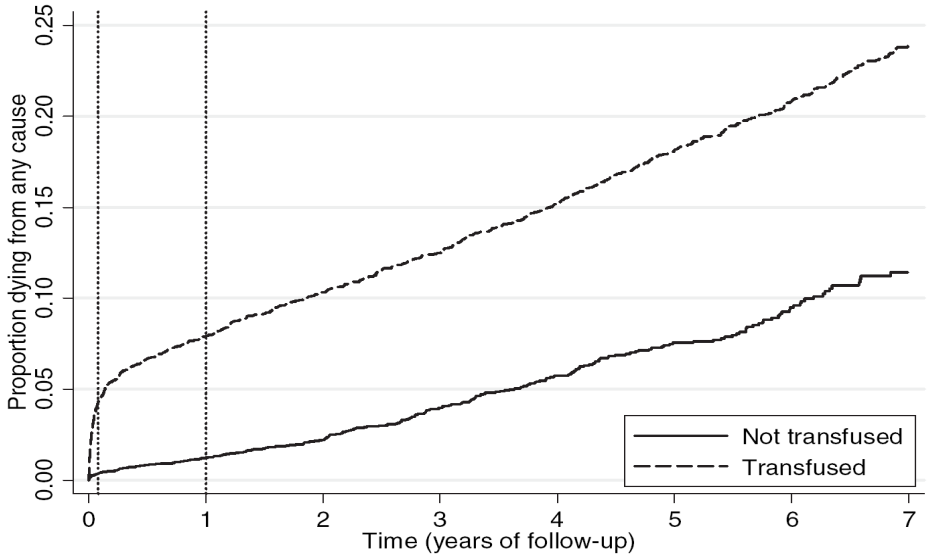
Cardiovascular disease



Myocardial Ischemia

Hebert P.C. et al: Crit. Care Med 29, 227-234, 2001

RBC transfusion and mortality



Number at risk:

Not transfused:	3689	3529	2925	2383	1842	1261	772	391
Transfused:	4909	4449	3913	3340	2773	2213	1713	1073

Murphy G. J. et al. Circulation (2007) 116: 2544

Table 2. Frequencies of Composite Infection and Ischemic Outcomes

	Not Transfused			Transfused		
Outcome	N	n	%	N	n	%
Infection*	3674	. . .	. . .	4842	. . .	. . .
Nadir hematocrit <21	52	1	1.9	982	120	12.2
Nadir hematocrit ≥21 and <24	390	16	4.1	2164	243	11.2
Nadir hematocrit ≥24 and <27	1176	42	3.6	1385	200	14.4
Nadir hematocrit ≥27	2056	82	4.0	311	33	10.6
Ischemia†	3670	. . .	. . .	4848	. . .	. . .
Nadir hematocrit <21	52	1	1.9	982	132	13.4
Nadir hematocrit ≥21 and <24	390	13	3.3	2167	307	14.2
Nadir hematocrit ≥24 and <27	1175	40	3.4	1389	231	16.6
Nadir hematocrit ≥27	2053	72	3.5	310	36	11.6

Murphy G. J. et al. Circulation (2007) 116: 2544

Table 3. Estimates of the Increase in Effects of Transfusion With Increasing Number of Units of RBCs

RBCs Transfused, U	Infection Outcome		Ischemic Outcome		Relative Increase in Cost*		Portion of Study Population, %
	Odds Ratio	95% CI	Odds Ratio	95% CI	Mean	95% CI	
Any	3.73	2.32–5.07	4.05	2.63–5.70	1.42	1.37–1.46	57.1
0	1.00	. . .	1.00	. . .	1.00	. . .	42.9
1	1.46	0.92–2.11	1.63	1.02–2.48	1.11	1.08–1.14	13.6
2	2.36	1.42–3.30	2.30	1.32–3.50	1.21	1.18–1.25	14.5
3 or 4	3.82	2.22–5.47	4.49	2.78–6.22	1.41	1.36–1.46	15.2
5–9	10.75	5.83–15.9	11.79	6.80–16.7	1.81	1.71–1.90	10.0
>9	45.44	22.6–73.6	46.39	24.5–75.4	3.35	3.03–3.70	3.8

Murphy G. J. et al. Circulation (2007) 116: 2544

The gap between best practice and actual clinical care

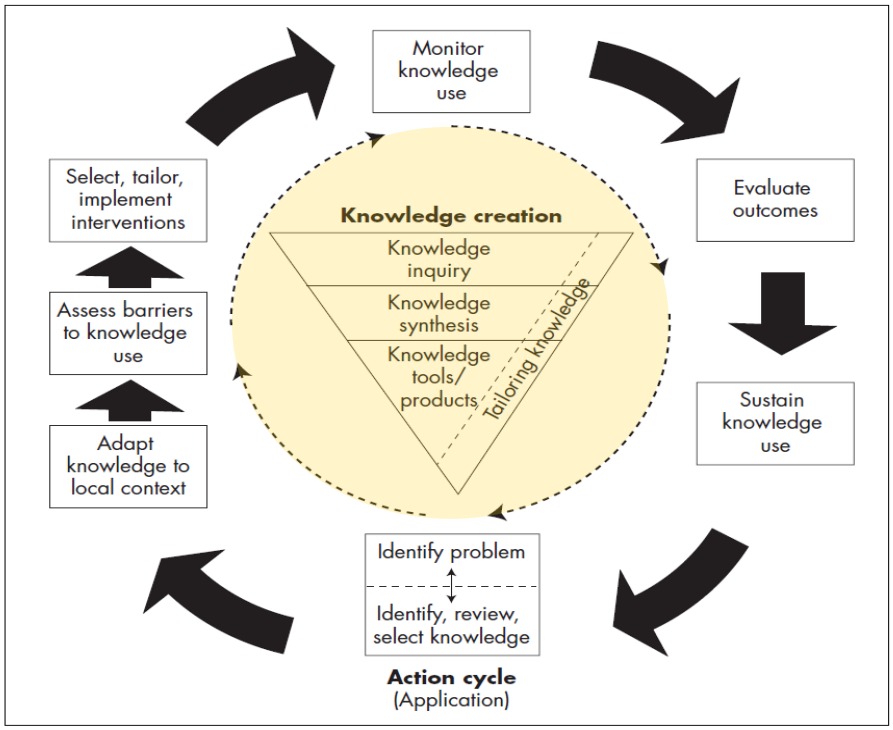
- One of the most consistent findings in research of health services is the gap between evidence and practice.
- About 30–40% of patients do not receive care according to present scientific evidence.
- About 20–25% of care provided is not needed or is potentially harmful.

Examples of clinical care gaps

- Suboptimal management of **dyslipidemia** (Yan et al: Am J Med 2006;119:676-83)
- Suboptimal management of **rheumatoid arthritis** (Lacaille et al: Arthritis Rheum 2005;53:241-8)
- Inadequate control of **diabetes** (Woodward et al: CMAJ 2006;174:327-9)
- Overuse of **benzodiazepines** (www.ti.ubc.ca/PDF/54.pdf, 2007)
- Suboptimal use of **blood products** (Sanguis, Ostheo, Austrian Benchmark Study, …… etc.)

Knowledge-to-action process

Reproduced from Graham et al,
Journal of Continuing Education in the Health Professions

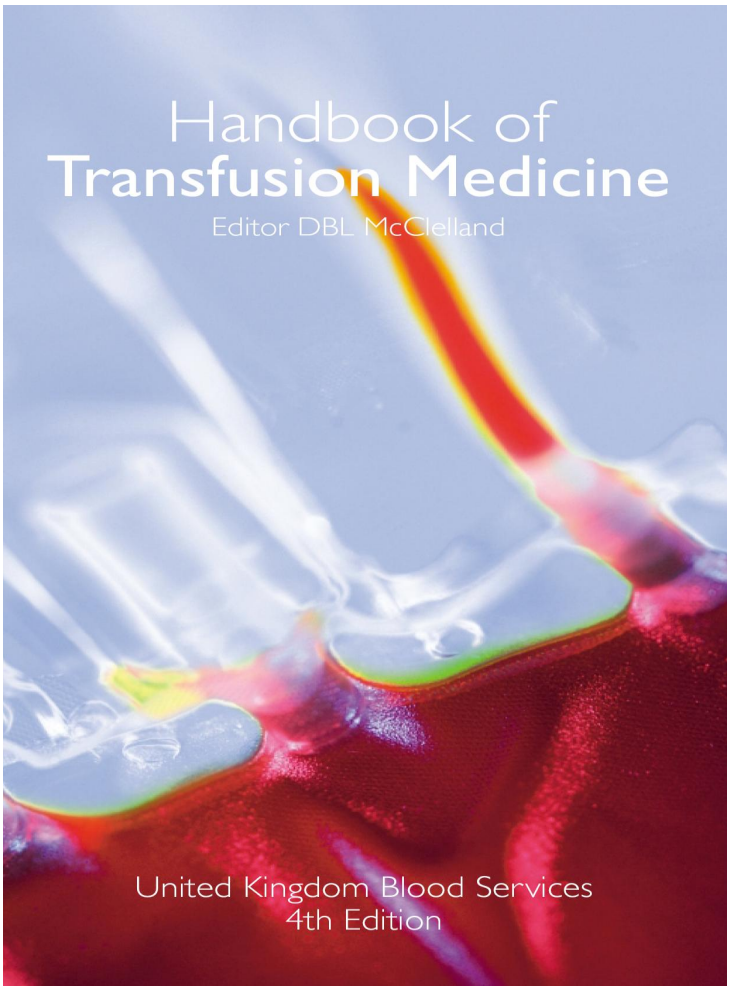


Querschnitts-Leitlinien (BÄK) zur Therapie mit Blutkomponenten und Plasmaderivaten

4. Auflage

(vgl. Änderungsanzeige im Dtsch Arztebl 2008; 105: A 2121 [Heft 40])

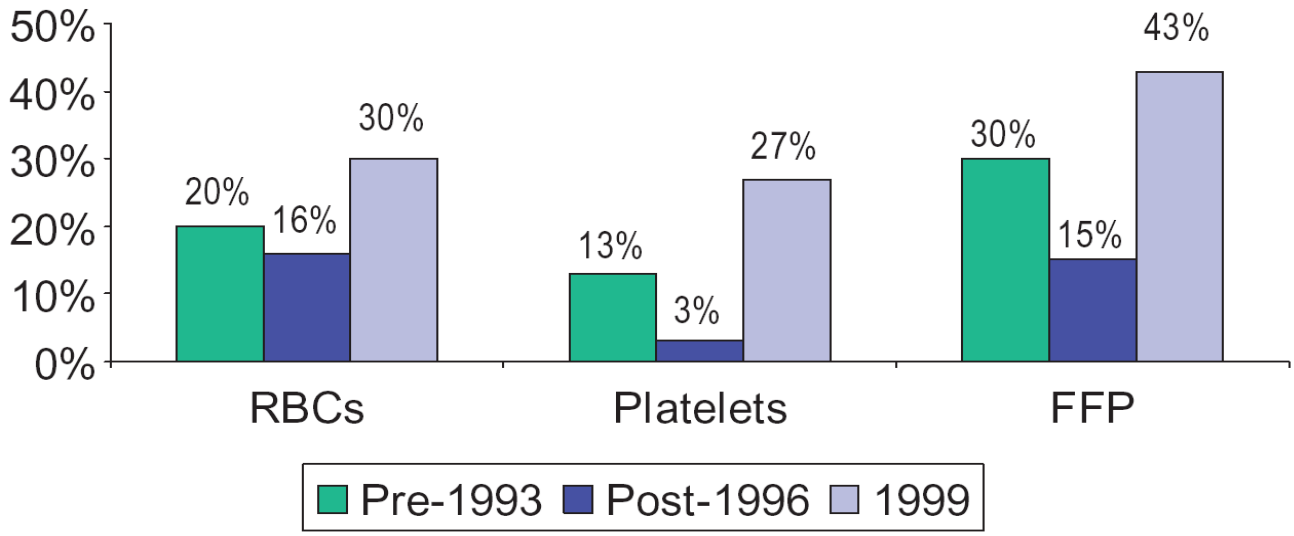
Herausgegeben vom Vorstand der Bundesärztekammer auf Empfehlung des Wissenschaftlichen Beirats



Reduction in Patients or UnitsTransfused by Intervention

Intervention	Products	Measure	Relative Change, %
Guideline			
As solitary intervention	RBCs	Proportion of patients receiving transfusions	−17
	Platelets	Units/patient per week	−20
		Units	−14
In combination with other interventions	RBCs	Proportion of patients receiving transfusions	−43
		Units/patient	−12 to −65
		Units	−21 to −62
	FFP	Proportion of patients receiving transfusions	64 to −21
		Units/patient	−18
		Units	−9 to −77
	Platelets	Units/patient	−23
		Units	−15
	Albumin	Grams	−44
	Cryoprecipitate	Units/patient	−44
Audit/feedback			
As solitary intervention	RBCs	Regression slope of units/patient per month	$t = -0.014$
	FFP	Regression slope of units/patient per month	$t = -0.017$
	Platelets	Regression slope of units/patient per month	$t = 0.05$
	Cryoprecipitate	Regression slope of units/patient per month	$t = -0.23$
In combination with other interventions	RBCs	Proportion of patients receiving transfusions	−79
		Units/patient	−12 to −29
		Units	−19 to −62
	FFP	Proportion of patients receiving transfusions	−21
		Units/patient	−18
		Units	−9 to −77
	Platelets	Units/patient	−23
		Units	−15
	Cryoprecipitate	Units/patient	−44
Audit/approval			
As solitary intervention	FFP	Units/admission	−55
In combination with other interventions	RBCs	Units/patient	−27
	FFP	Units/patient	−35 to −52
	Platelets	Units/patient	−22
		Units	−17
Form (reminder)			
As solitary intervention	RBCs	Regression slope of units/patient per month	$t = -2.53$
	Platelets	Regression slope of units/patient per month	$t = -1.88$
	FFP	Regression slope of units/patient per month	$t = -1.64$
In combination with other interventions	RBCs	Proportion of patients receiving transfusions	−27
		Units/patient	−12
		Units	−62
	FFP	Units/patient	−18 to −35
		Units	−9 to −52
	Platelets	Units/patient	−22 to −23
		Units	−15 to −17
	Cryoprecipitate	Units/patient	−44
	Albumin	Grams	−44
Education			
In combination with other interventions	RBCs	Proportion of patients receiving transfusions	−43 to −79
	FFP	Units/patient	−12 to −65
		Units	−46 to −77

Durability of change in transfusion practice — inappropriate transfusions



Multiple interventions evaluated 3 years after start of interventions: guidelines, education, new transfusion form, prospective audit

Tinmouth A: TRANSFUSION 2007;47:132S-136S

The NEW ENGLAND JOURNAL of MEDICINE

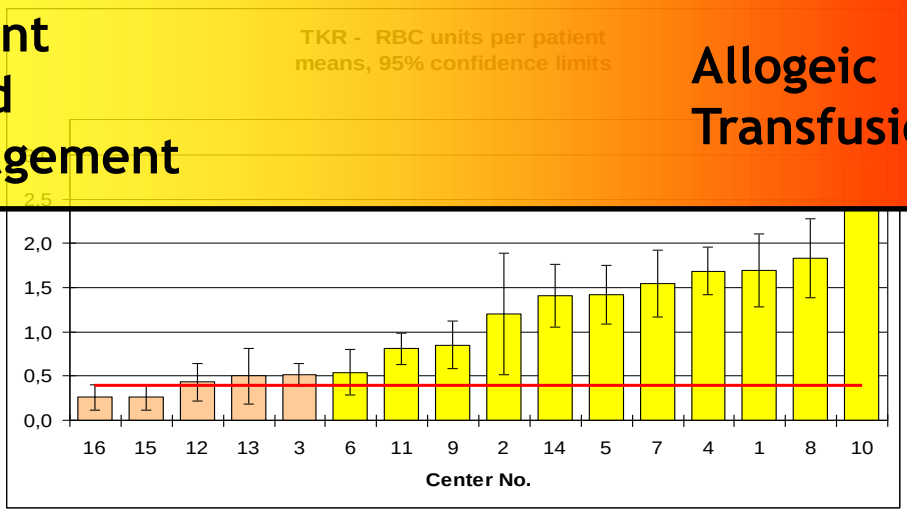
EDITORIAL

Blood Transfusion — When Is More Really Less?

Howard L. Corwin, M.D., and Jeffrey L. Carson, M.D.

clinical trials. Red-cell transfusion should no longer be regarded as "may help, will not hurt" but, rather, should be approached as "first, do no harm."

Patient Blood Management → **Allogeic Transfusion**



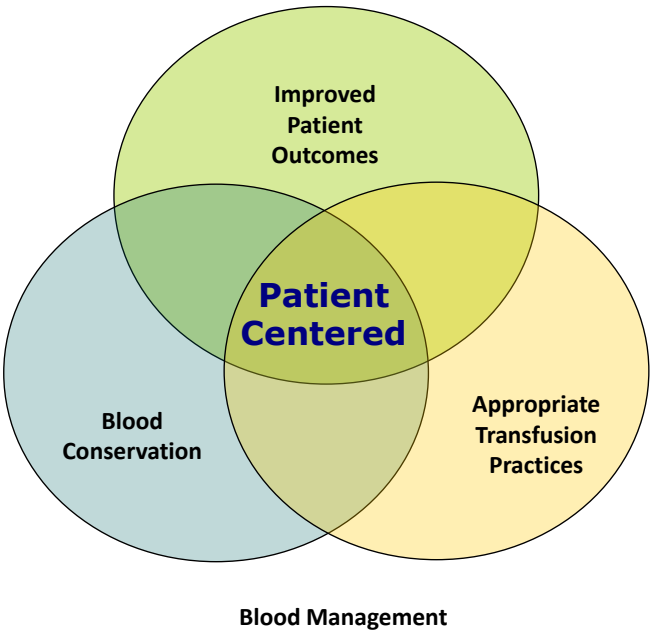
Spannweite 1:11,03 (0,26-2,84 EK)

Optimal Use of RBCs

Evaluating the use of blood products
Audit
Implementing guidelines
Blood ordering schedules
Focus on 3 pillars of blood conservation

preop. anemia	surgical blood loss	transfusion trigger
underlying disease iron therapy Epo	surgical technique cell salvage antifibrinolytics coagulation mgment	physiological trigger Cave: risk of anemia

Re-evaluation

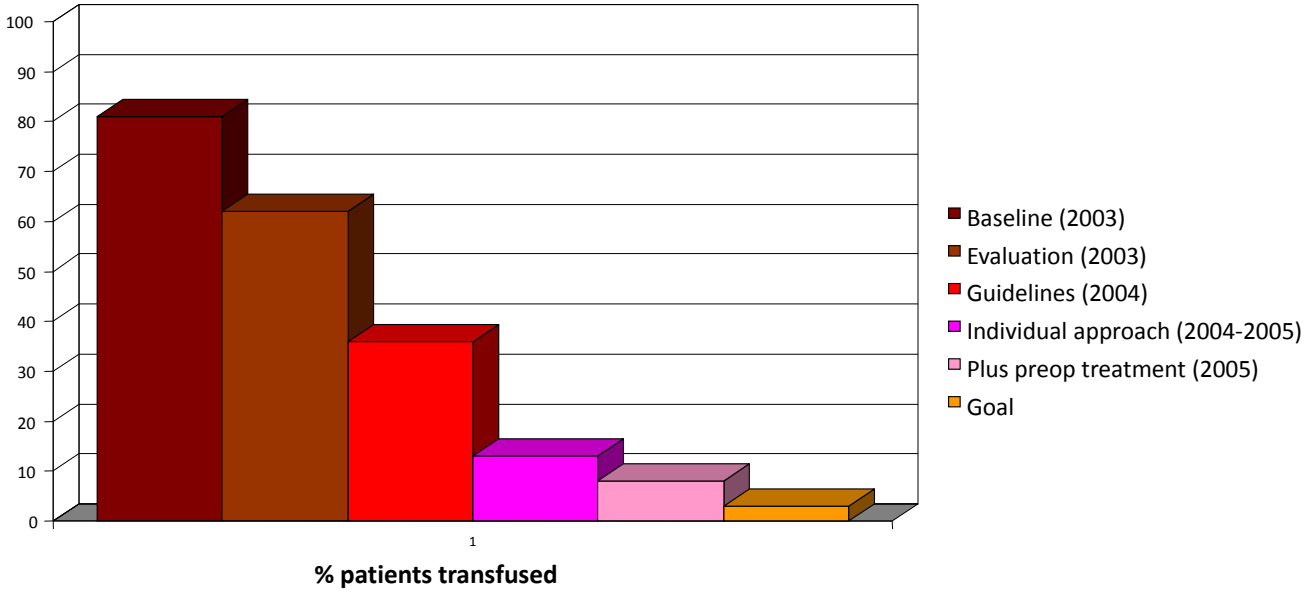


The Solution ???

Patient Blood Management (PBM)

Blood management is the appropriate provision and use of blood, its components and derivatives, and strategies to reduce or avoid the need for a blood transfusion.

AKH Linz Experience
Primary Hip and Knee Replacement



Gombotz H. et al. Unpublished data.

Search site GO

CURRENT ISSUE

(view larger image)

SUBSCRIBE

AD LINK

Breaking News

Apr 22 2009, 10:49 AM EST

Blood transfusions a

EUREKALERT

Experts find little evidence for transfusions improving health

Milwaukee--An exhaustive review and analysis of the medical literature by a panel of experts at the International Consensus Conference on Transfusion and Outcomes (ICCTO) held this month in Phoenix concluded that there is little evidence to support a beneficial effect from the greatest number of transfusions currently being given to patients. The vast majority of studies show an association between red blood cell transfusions and higher rates of complications such as heart attack, stroke, lung injury, infection and kidney failure and death.

The ICCTO conference brought together leading international physicians and scientists in the fields of anesthesiology, intensive care, hematology, oncology, surgery, and patient blood management, and was monitored by the Food and Drug Administration, the American and the Australian Red Cross, the Joint Commission, along with government health officials, and other organizations.

"The results of the conference firmly establish the view that, rather than being a benign procedure, blood transfusion is associated with increased risk of medical complications," said Aryeh Shander, M.D., Chief of the Department of Anesthesiology, Critical Care Medicine, Pain Management and Hyperbaric Medicine at Englewood Hospital and Medical Center in Englewood, NJ and a founding member of the Society for the Advancement of Blood Management (SABM). "The evidence tells us to restrict the practice of transfusion and to avoid unnecessarily transplanting stored blood that could harm a patient's recovery."

Blood Transfusion and Outcomes

REALTIME NEWS

News Blaze

Support Our Troops, Read Their Stories

Get News Enter to Win Newsletter

Search News Daily News

NEWS
Daily News
Top Stories
Breaking News
World
Politics
Business
Growth Minute
Sports
Health
Food & Wine
Women
Women in Business
Opinion
Letters to the Editor
Will Says...
High Tech
Horoscope
Entertainment
Music
Features
Books
Poetry
Movie Reviews
Home & Garden
Industry
States
Health Column
Senior Health
Environment
Education
SupportOurTroops

Breaking News: ***The Water Women of Barmer`s Sands***

Tell Friends about NewsBlaze and get a gift

Published: April 22,2009

Send to a friend

Blood Transfusion and Outcomes

International panel of experts finds little evidence for transfusions improving health

MILWAUKEE, Wis., April 22 /PRNewswire/ -- An exhaustive review and analysis of the medical literature by a panel of experts at the International Consensus Conference on Transfusion and Outcomes (ICCTO) held this month inPhoenix concluded that there is little evidence to support a beneficial effect from the greatest number of transfusions currently being given to patients. The vast majority of studies show an association between red blood cell transfusions and higher rates of complications such as heart attack, stroke, lung injury, infection and kidney failure and death.

The ICCTO conference brought together leading international physicians and scientists in the fields of anesthesiology, intensive care, hematology, oncology, surgery, and patient blood management, and was monitored by the Food and Drug Administration, the American and the Australian Red Cross, the Joint Commission, along with government health officials, and other organizations.

"The results of the conference firmly establish the view that, rather than being a benign procedure, blood transfusion is associated with increased risk of medical complications," said Aryeh Shander, M.D., Chief of the Department of Anesthesiology, Critical Care Medicine, Pain Management and Hyperbaric Medicine at Englewood Hospital and Medical Center inEnglewood, NJ and a founding member of the Society for the Advancement of Blood Management (SABM). "The evidence tells us to restrict the practice of transfusion and to avoid unnecessarily transplanting stored blood that could harm a patient's recovery."

seattlepi.com

US/World | Sports | Business | A&E | Life | Comics | Photos | Opinion | Blogs | Subscr

Autos
Homes
Rentals

PR Newswire

The information below is distributed by PR Newswire on behalf of the organizations featured. SeattlePI.com cannot confirm the accuracy of the content.

Press release distributed by PR Newswire

PR Newswire

Medical/Pharmaceuticals Press Releases

Blood Transfusion and Outcomes

International panel of experts finds little evidence for transfusions improving health

MILWAUKEE, April 22 /PRNewswire/ -- An exhaustive review and analysis of the medical literature by a panel of experts at the International Consensus Conference on Transfusion and Outcomes (ICCTO) held this month in Phoenix concluded that there is little evidence to support a beneficial effect from the greatest number of transfusions currently being given to patients. The vast majority of studies show an association between red blood cell transfusions and higher rates of complications such as heart attack, stroke, lung injury, infection and kidney failure and death.

blood 1958 13: 1198-1200

Editorial—Misuse of Blood Transfusion

WILLIAM H. CROSBY

- Thoughtless prescription of blood transfusion is playing Russian roulette with bottles of blood instead of a revolver.
- While the odds are in the physician's favor that nothing will go wrong, the patient takes the risk.

Achieving consensus on optimal treatment of haemophilia

Paul Giangrande

Achieving consensus on optimal treatment of haemophilia

Dr. Paul Giangrande
Oxford Haemophilia and Thrombosis Centre
&
Nuffield Department of Clinical Medicine,
University of Oxford
paul.giangrande@ndm.ox.ac.uk

The main conclusions in 1999:

- A network of comprehensive care centres should be established in each country
- National database is desirable
- Guidelines should be harmonised
- Prophylaxis should be recommended for children
- All patients with inhibitors should be offered immune tolerance
- Pharmacovigilance programme should be established

What has changed in the last decade?

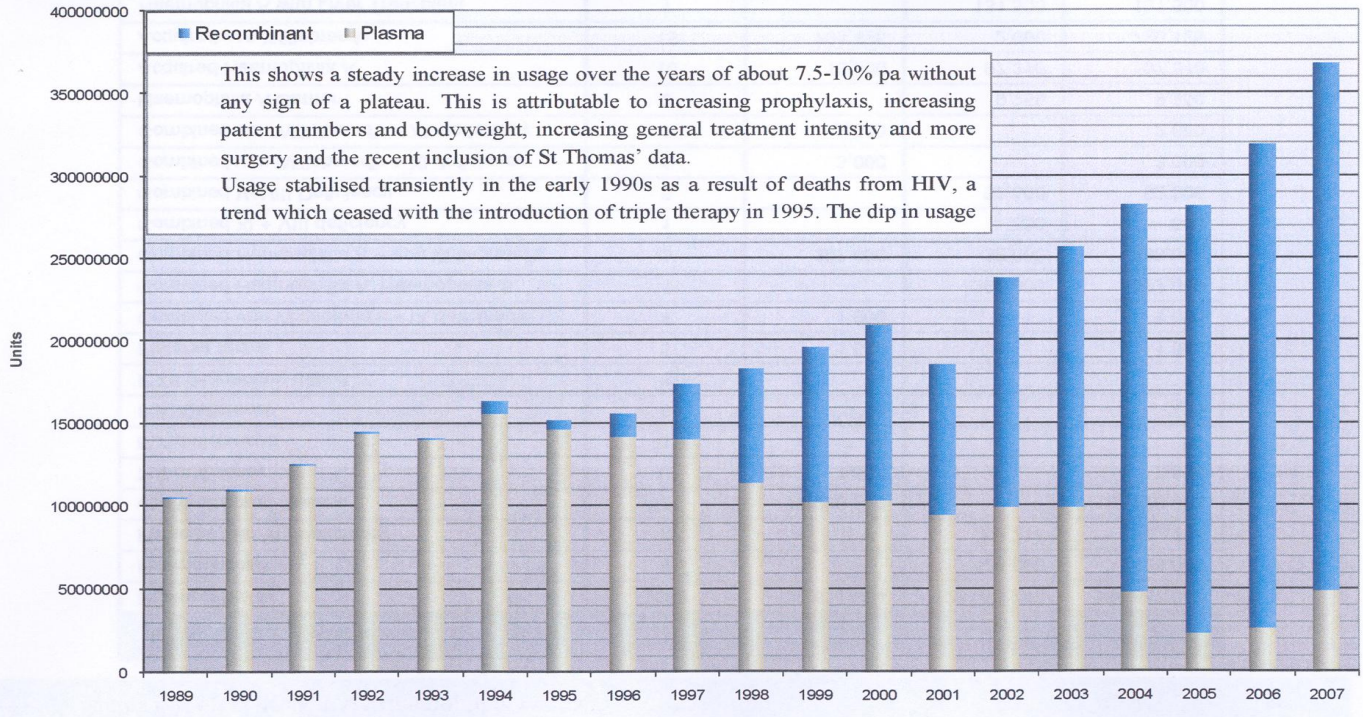
- More data available to guide decision making: e.g. benefits of prophylaxis, quality of life, incidence of inhibitors
- Continued rise in product usage (and cost)
- Wider adoption of recombinant products
- New pathogens: vCJD, avian influenza, SARS, west Nile virus
- Involvement of patients in decision making
- Other bodies gaining stronger influence: EHC, EHA, EAHAD
- Educational curiculum for haemostasis training formulated
- Expansion of EU (mainly towards east)
- WHO adds factor concentrates to list of essential medications
- EU funding for collaborative projects: ESCHQoL, EUHASS, Rare Bleeding Disorders,
- "Credit crunch": prospect of national budget deficits

EAHAD Principles of Care:

Haemophilia 14: 361-374 (2008)
www.eahad.org

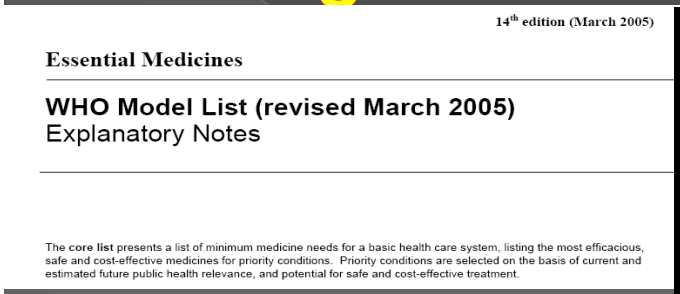
- Network of designated comprehensive care centres
- National registries
- Safe and effective concentrates at optimal treatment levels
- Home treatment
- Prophylaxis
- Immune tolerance for inhibitors
- Pharmacovigilance

Figure 5 – Factor VIII usage by UK Haemophilia Centres: between 1989 and 2007



≈6.3 iu/capita

Clotting factor is essential!



14th edition (March 2005)

Essential Medicines

WHO Model List (revised March 2005)
Explanatory Notes

The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

"Essential medicines are those that satisfy the priority health care needs of the population."

Source: WHO – What Are Essential Medicines?

"The Committee recommended that factor VIII and IX concentrates be retained on the Model List, accepting the inherent inconsistency caused by the fact that haemophilia is a rare disease.

"The Committee noted that factor VIII and IX concentrates are life-saving in the treatment for haemophilia, and that the alternative (cryoprecipitate) is less safe and more expensive."

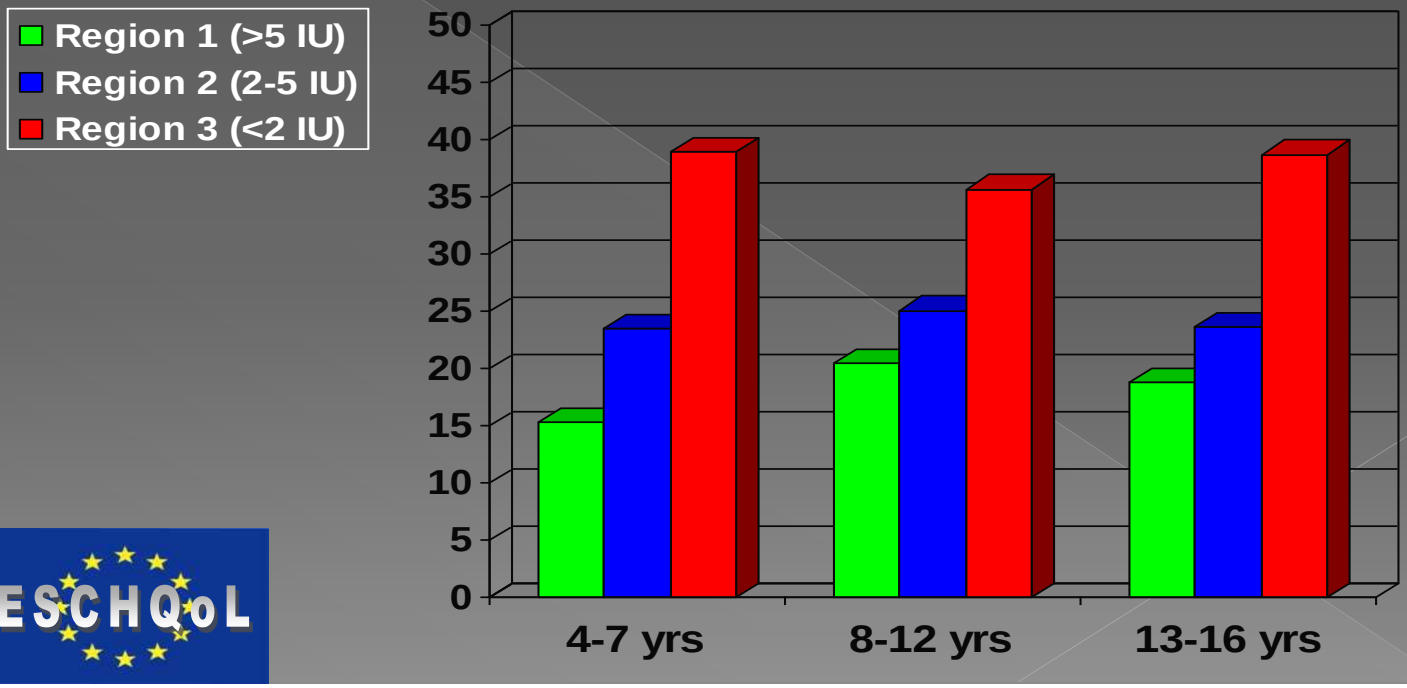
Quality of life in children and relation to among factor consumption:

Region 1 (> 5 IU)	Region 2 (2-5 IU)	Region 3 (< 2 IU)
Austria	Portugal	Poland
Denmark	Slovenia	Romania
France	Slovakia	Turkey
Germany	Spain	Czech Rep.
Sweden	Switzerland	Lithuania
UK	Belgium	
	Finland	
	Greece	
	Hungary	
	Italy	

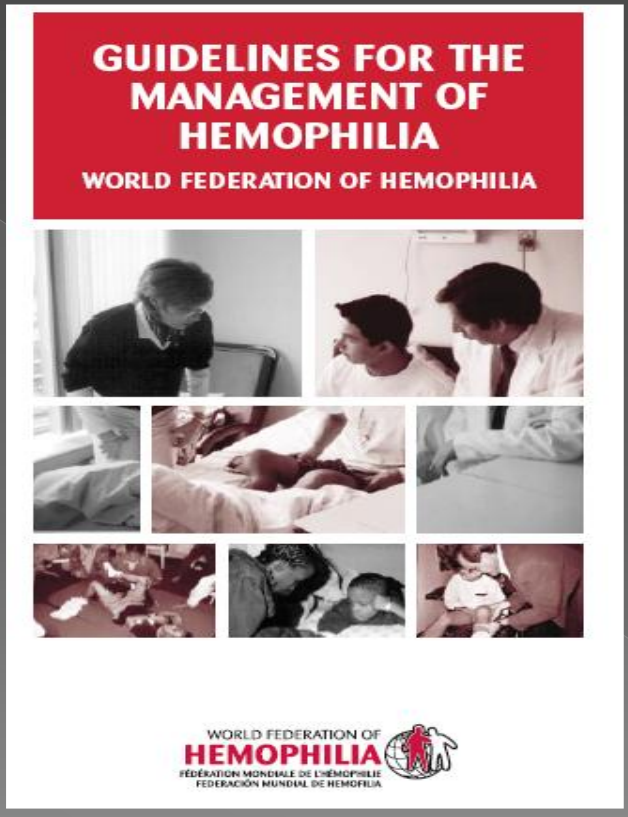
ESCHQoL

Quality of life in children and relation to factor consumption:

(lower scores=better quality of life)

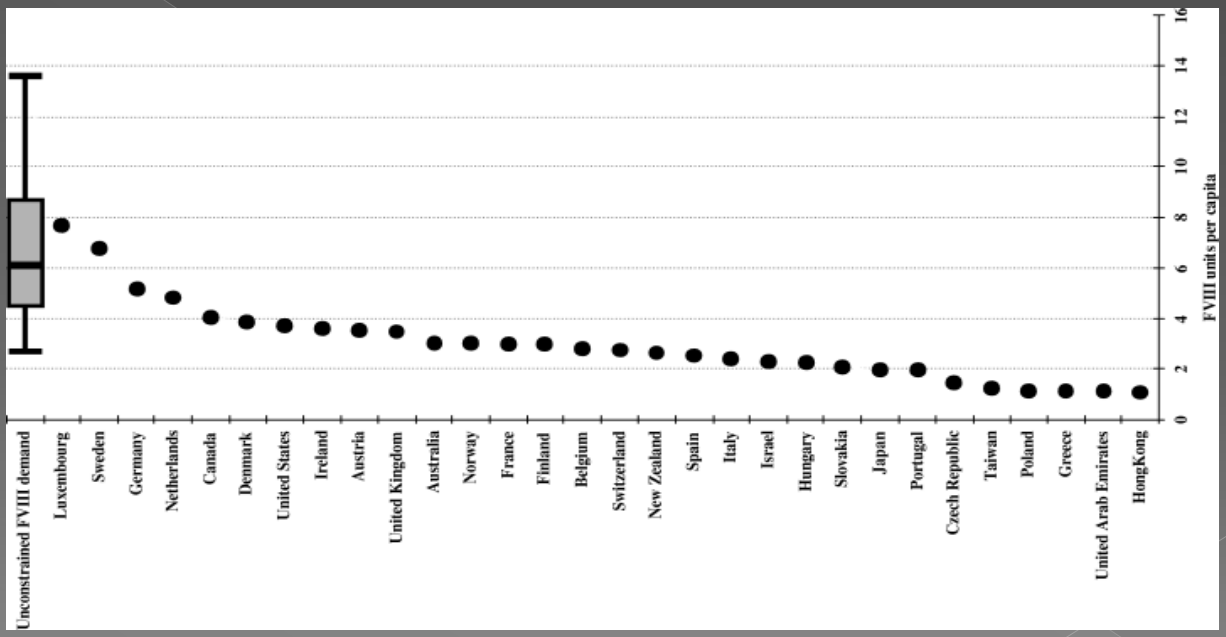


ESCHQoL



Modelling unconstrained factor VIII demand:

Stonebraker JS et al. Haemophilia 10: 18-26 (2004)



Probability-weighted average is 6.9 units per capita

Concentrate consumption related to economic capacity:

Stonebraker JS et al. Haemophilia 9: 245-250 (2003)

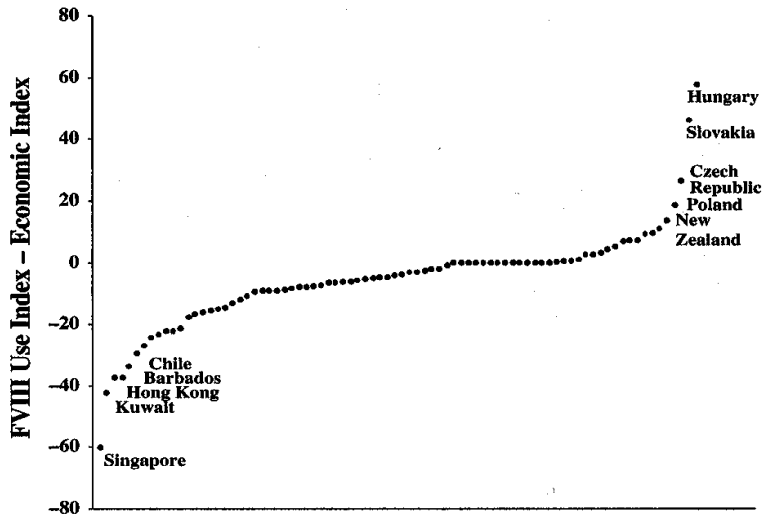


Fig. 1. The difference of the *FVIII Use Index* and the *Economic Index* was used to compare a country's FVIII concentrate consumption with its derived economic capacity. A country is consuming more FVIII concentrate units per capita than expected given its economic capacity when the *FVIII Use Index* > *Economic Index*, e.g. Hungary.

The basic questions:

- Which products?
- How much product?
- Who decides on treatment policy and formulates guidelines?
- Who pays for treatment?

Advantages of consensus on treatment:

- Natural justice in offering same treatment to all patients throughout a country
- Encourages collaboration between health care professionals around a country
- Facilitates clinical research
- Encourages dialogue between patient community and doctors

Some potential obstacles (1):

- Consensus often only achieved through compromise:
  - Resulting guidelines often lack detail
  - Good advocacy skills and detailed knowledge required to make your points effectively
- Reliance on evidence-based data:
  - Few data from randomised controlled studies are available
  - Lack of data often confused by non-experts with lack of effect or benefit

Some potential obstacles (2):

- Competition between treatment centres can be a positive force for change:
  - Agreement on formal guidelines typically lags behind innovation (not *vice versa*)
- Existence of national fractionation plant:
  - Effectively caps supply of product
  - Can limit choice of products through exclusion of imported products
- Rigidity in policy restricts individual choice:
  - Possibility to make exceptions needs to be accommodated

Advantages of national tender:

experience from the United Kingdom

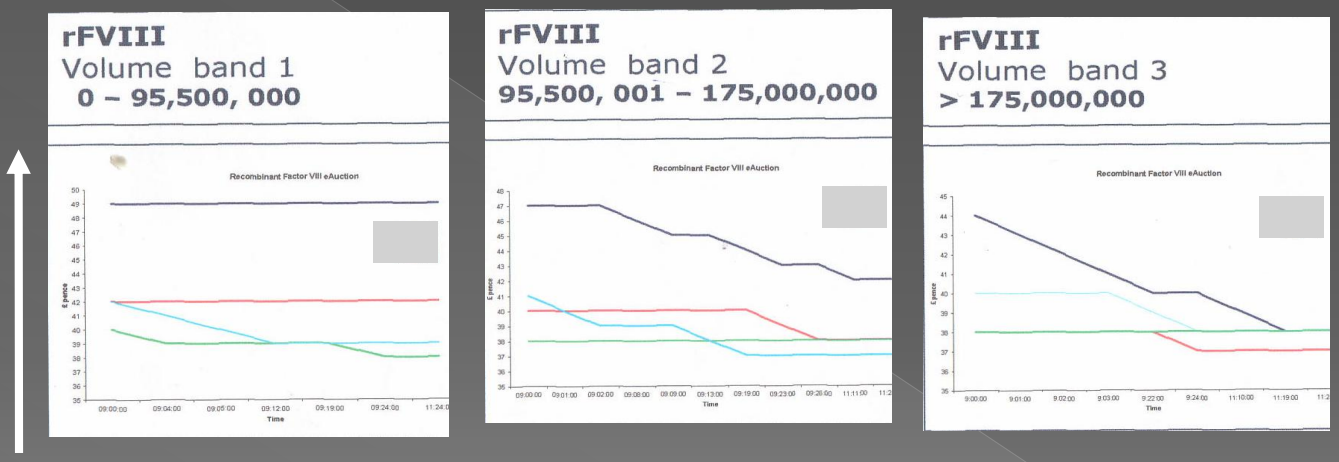
- Significant savings were made which were ploughed back into wider health care system
- All centres benefit from lower prices
- Forces centres to collaborate and share data which has other benefits
- Facilitated financial support from UK government for national database
- Offered formal setting for patient body to express views on choice of product

Potential disadvantages:

- In practice, focus is on cost rather than quality issues
- Patients need to be prepared to change products every few years
- Potential loss of choice:
  - consensus decision may conflict with local preference
  - companies might withdraw from UK market
  - future decisions may be left to managers
- Loss of profit to companies means less support available to wider haemophilia community
- Poor forecasting of volumes can result in penalty payments to companies if targets not met
- Success has drawn potentially unwelcome publicity to the high cost of haemophilia care
  - will a "cap" be placed on volume purchased in future?

E-auction

- The Recombinant Factor VIII eAuction proved to be the most competitive, and ran for 49 mins.



The eAuction was effective in almost doubling the saving

Areas of continuing controversy:

- Continuation of prophylaxis in adult patients
- Treatment of babies just after birth
- Dose of factor for immune tolerance
- Prophylaxis in patients with inhibitors
- Measuring outcome: e.g. quality of life, joint scores, use of ultrasound or MRI
- Best products for VWD and rare disorders

Conclusions:

- Equality of treatment is a just goal
- Competition can be a positive force in driving new developments
- Database is vital for predicting product demand
- National tenders can drive down price of products
- Patient organisations should have a say in product choice
- Production of detailed treatment guidelines is primarily the task of medical bodies
  - Positive influence in encouraging collaboration
  - Doctors bear legal responsibility for their decisions

Haemophilia treatment in Europe – an overview

Brian O'Mahony

Haemophilia treatment in Europe- An Overview

Brian O Mahony
Chief Executive, Irish Haemophilia Society
EHC Steering Group

Key Elements of National Care

- National Patient Registry
- Comprehensive care centre's
- Treatment Guidelines
- Prophylaxis for Children
- Immune Tolerance for Inhibitors
- Adequate amounts of Factor Concentrates with patient preferences a consideration
- Measurement of Outcomes
- **National Haemophilia Committee**

European Principles of Haemophilia Care

1. Haemophilia Co-ordinating Organisations with supporting local Organisations
2. National Haemophilia Patient Registry
3. Provision and Maintenance of Comprehensive Care Centres (CCCs) and Haemophilia Treatment Centres (HTCs)
4. **Partnership in the Delivery of Haemophilia Care**
5. Access to Safe and Effective Concentrates at Optimum Treatment Levels
6. Access to Home Treatment & Delivery
7. Access to Prophylactic Therapy
8. Access to Specialist Services and Emergency Care
9. Management of Inhibitors
10. Education and Research

Haemophilia treatment in Europe

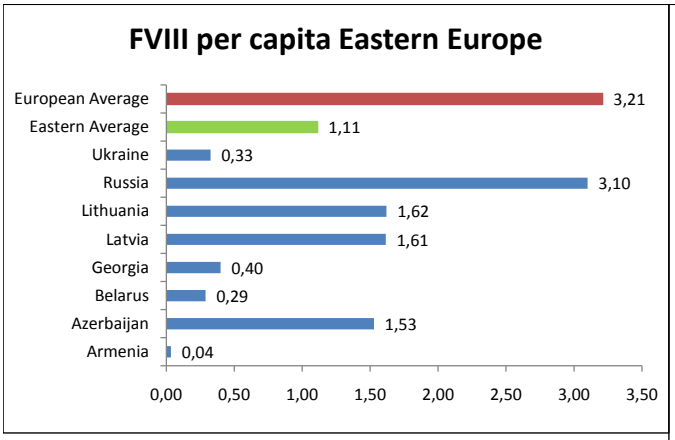
Access to treatment with Factor replacement therapy varies from:

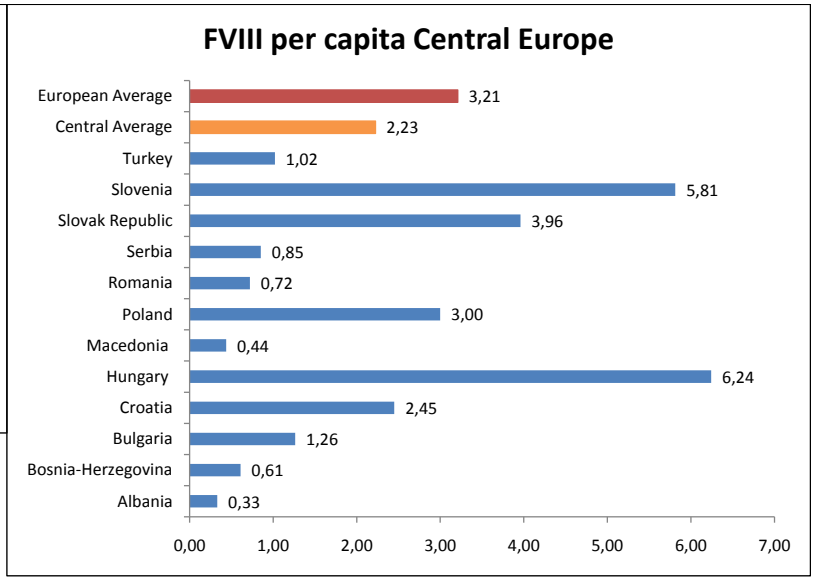
- No access to regular therapy to On-demand therapy to Prophylaxis
- Replacement therapy used varies from Plasma and Cryoprecipitate to Plasma derived Factor Concentrates to Recombinant factor Concentrate

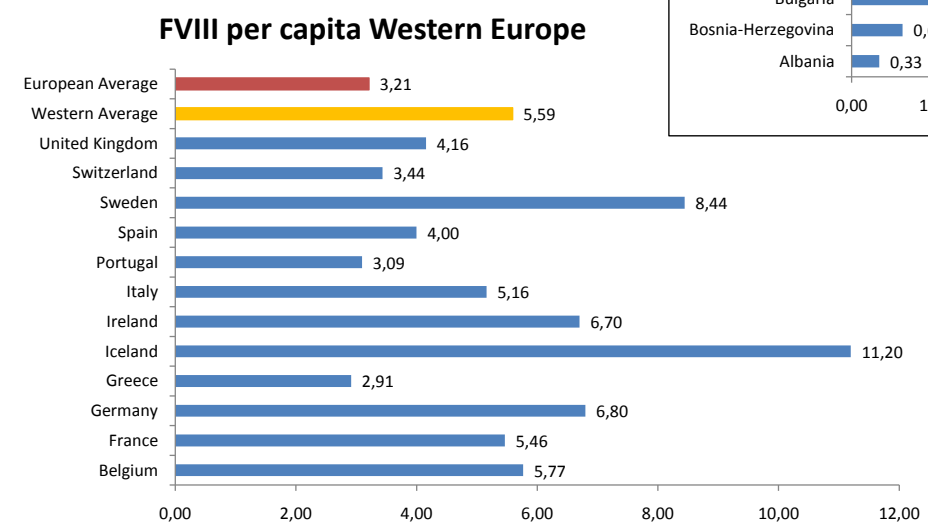
Factor Use relates to Economy

GNP	FVIII use	FIX use
>US$10,000	3.47	0.39
US$2 – 10,000	0.31	0.06
< US$ 2,000	0.02	0.001

WFH Global Survey 2007 data







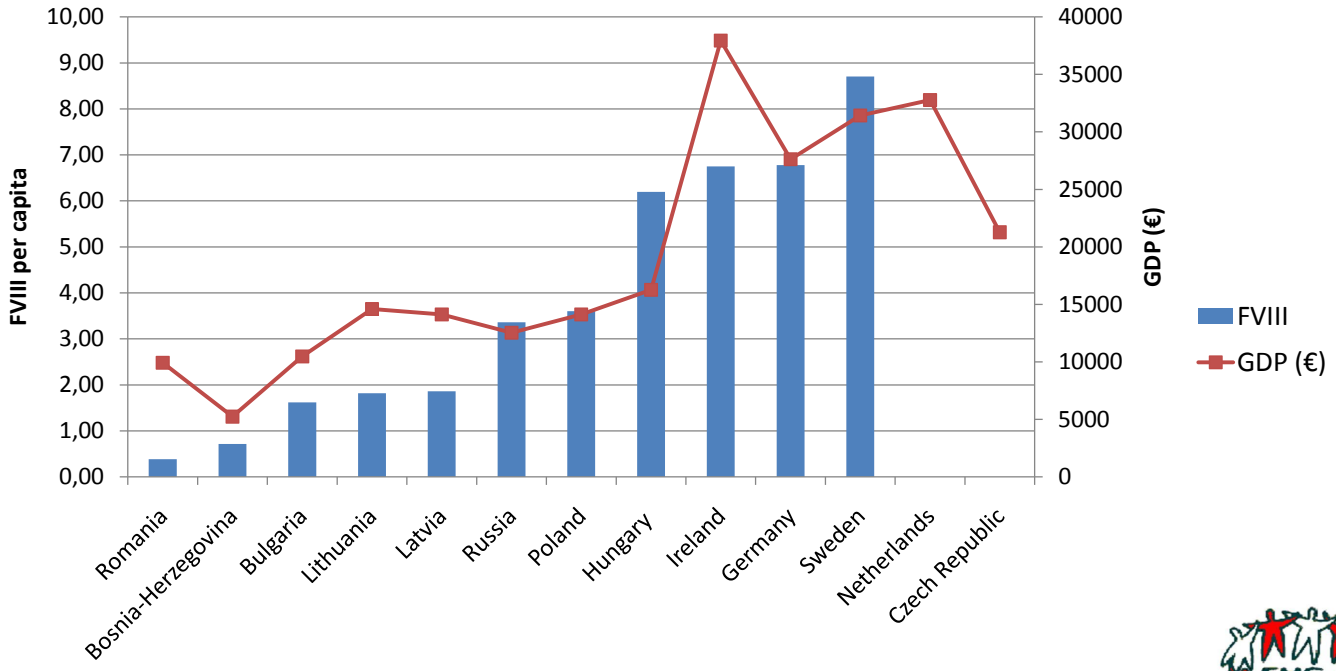
Region	
Eastern Average	1.11
Central Average	2.23
Western Average	5.59
European Average	3.21

2009 -13 Countries Surveyed

- Bosnia / Herzegovina
- Bulgaria
- Czech Republic
- Germany
- Hungary
- Ireland
- Latvia
- Lithuania
- Netherlands
- Poland
- Romania
- Russia
- Sweden

B O Mahony 2009

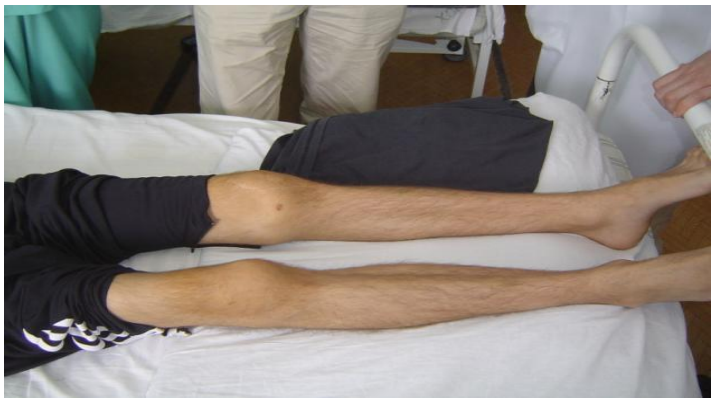
Concentrate Use per capita



B O Mahony 2009

Use Cryoprecipitate and/or Plasma

- Always; Romania
- Rarely: Bosnia
  Lithuania
  Russia



B O Mahony 2009

Use Plasma Derived and rarely Recombinant

- Sweden (17%)
- Germany
- Netherlands
- Hungary
- Czech Republic
- Latvia
- Lithuania
- Poland
- Russia

B O Mahony 2009

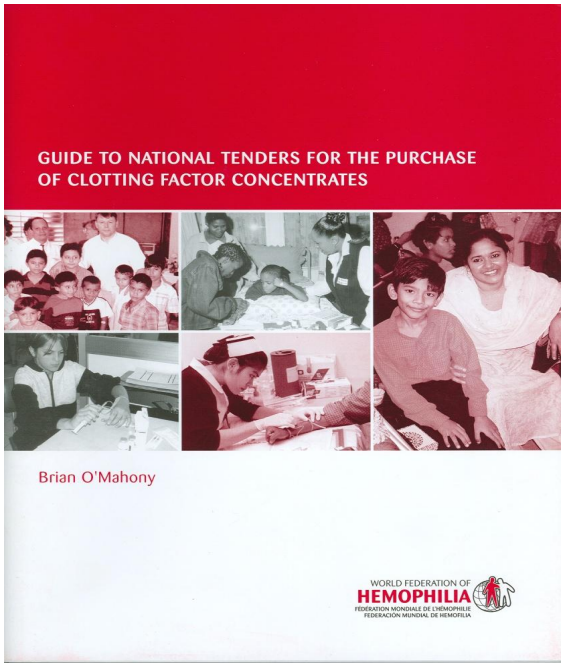
Russia –Increase in Factor VIII IU Per Capita

Since 2004, Total IU has increased from 32 to 463 million in 2008 (est.).

Source: Russian Hemophilia Society 1996-2007; 2008 est.

Use Recombinant and rarely Plasma Derived

- Ireland (100%)
- Sweden (83%)
- Germany (56%)
- Netherlands
- Hungary

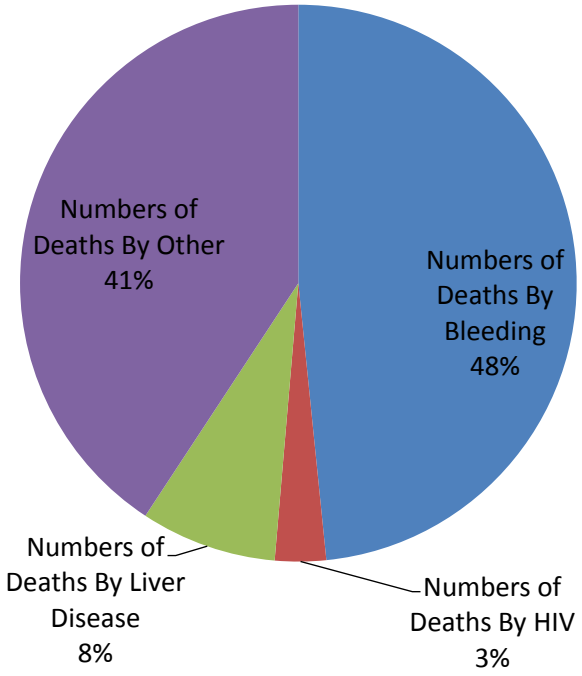


B O Mahony 2009

Comparison of Products used to treat Haemophilia and von Willebrands Disease

Country	Bosnia-Herzegovina	Bulgaria	Czech Republic	Hungary	Latvia	Lithuania	Netherlands	Poland	Romania	Russia	Germany	Ireland	Sweden
Haemophilia													
Plasma	Rarely	Never	Never	Never	Never	Rarely	Rarely	Never	Always	Rarely	Never	Never	Never
Cryoprecipitate	Rarely	Never	Never	Never	Never	Rarely	Never	Never	Rarely	Rarely	Never	Never	Never
Plasma-derived Factor Conc.	Always	Always	Always	Always	Always	Always	Always	Always	Rarely	Always	Always	Never	Rarely
Recombinant Factor Conc.	Rarely	Rarely	Rarely	Always	Never	Rarely	Always	Never	Rarely	Rarely	Always	Always	Always
Von Willebrand's													
Plasma	Never	Never	Never	Never	Never	Rarely	Rarely	Never	Rarely	Rarely	Never	Never	Never
Cryoprecipitate	Never	Never	Never	Never	Never	Rarely	Never	Never	Rarely	Rarely	Never	Never	Never
Plasma-derived Factor Conc.	Always	Always	Always	Always	Always	Rarely	Rarely	Always	Rarely	Always	Always	Always	Always
DDAVP	Never	Never	Rarely	Rarely	Always	Always	Always	Never	Rarely	Never	Always	Always	Always

Reported Deaths of PWH for Europe 2007

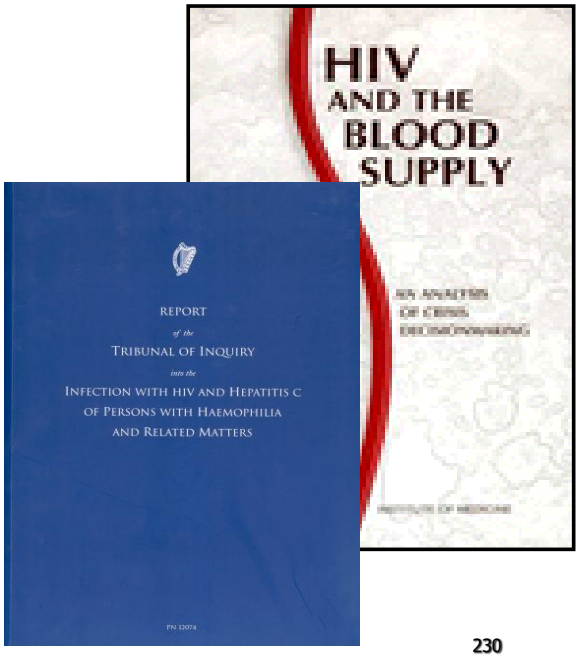


- Numbers of Deaths By Bleeding 196
- Numbers of Deaths By HIV 12
- Numbers of Deaths By Liver Disease 32
- Numbers of Deaths By Other 165

WFH Survey 2007

Economic Cost of Not providing safe Treatment in the past

- HIV
- Hepatitis A, B, C
- Cost of treatment
- Hospitalisation cost
- Cost of Inquiries
- Cost of Compensation



230

Factor Replacement Therapy

- **Countries with very good treatment improved incrementally:**
- Ireland FVIII use in 1997= 1.9iu/capita
  FVIII use in 2009 = 6.7 iu/capita
- Hungary FVIII use in 1994 = 0.7 iu/capita
  FVIII use in 2008 = 6.1 iu/capita
- Russia FVIII use in 2004 = 0.22 iu/capita
  FVIII use in 2008 = 3.3 iu/capita

B O Mahony 2009

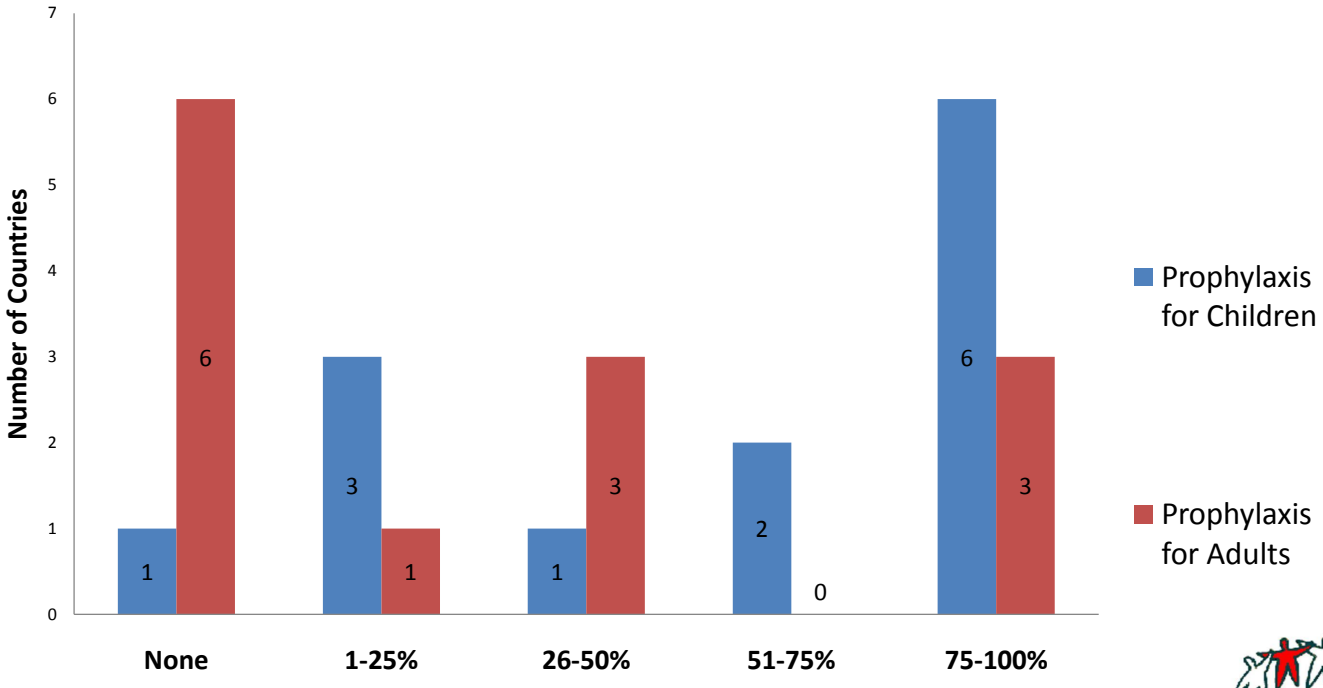
Home Treatment

Country	Bosnia-Herzegovina	Bulgaria	Czech Republic	Hungary	Latvia	Lithuania	Poland	Romania	Russia		Netherlands	Germany	Ireland	Sweden
Treatment delivered to the patient's home	**No Home Treatment**	**Unknown**	**No**	**No**	**No**	**No**	**No**	**No**	**No**		**Yes**	**Yes**	**Yes**	**Yes**
Percentage of PWH on home treatment	**None**	**Between 10 and 50%**	**Between 76 and 100%**	**Unknown**	**Between 51 and 75%**	**Between 76 and 100%**	**Between 51 and 75%**	**None**	**Between 51 and 75%**		**Between 76 and 100%**	**Between 76 and 100%**	**Between 76 and 100%**	**Between 76 and 100%**

None	1-9%	10-50%	51-75%	76-100%

B O Mahony 2009

Percentage of Patients on Prophylaxis



B O Mahony 2009

Prophylaxis - Incremental Cost can be calculated on bleeds avoided

- E.G. Germany
  - A person under 30 with on-demand Treatment has an average of 16.7 bleeds a year at a cost of **€85,451**
  - A person under 30 on prophylaxis has an average of 5.9 bleeds a year at a cost of **€157,972**
  - Effectiveness of the Treatment is the difference in bleeds avoided

    16.7 – 5.9= 10.8

  - Incremental Cost:

    $$\frac{\text{Cost Difference}}{\text{Difference in bleeds avoided}} = \textbf{€6,653}$$

B O Mahony 2009

Costs of an individual bleed

Financial

- Factor Replacement
  - e.g One patient with an Iliopsoas bleed received €150,000-€200,000 in treatment over 5 week period
- Medical Costs e.g. Hospital time
- Reduced Income – Less tax revenue
  - Possibly also for partners

Quality of life

- Individual bleed causes permanent damage
- Social Exclusion
- Stress for individual and family

B O Mahony 2009

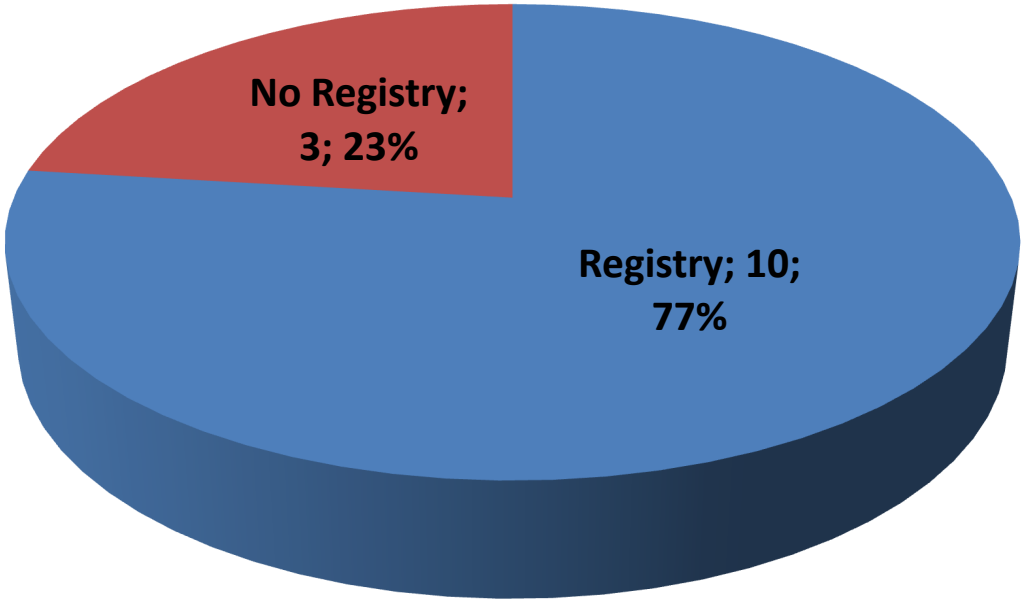
Cost effectiveness of prophylaxis

Published cost per QALY estimates of FVIII prophylaxis in children

Study	Cost per QALY estimate ($)
Miner 2009*	50,000
Miner 2002	65,000
Roosendahl 2007	300,000
Risebrough 2008	420,000
Lippert 2005	1.2m – 2.7m

* In Press

Have a National Haemophilia Patient Registry



B O Mahony 2009

What has the biggest impact on the quality of life for patients with bleeding disorders

1. **Quantity of product used.**

21%

2. **Access to comprehensive care at Hemophilia Treatment Centres.**

50%

3. **Age when treatment begins.**

23%

4. **Product choice.**

6%

Source: Proceedings of the 5th WFH Global Forum on Safety & Supply - September 2007

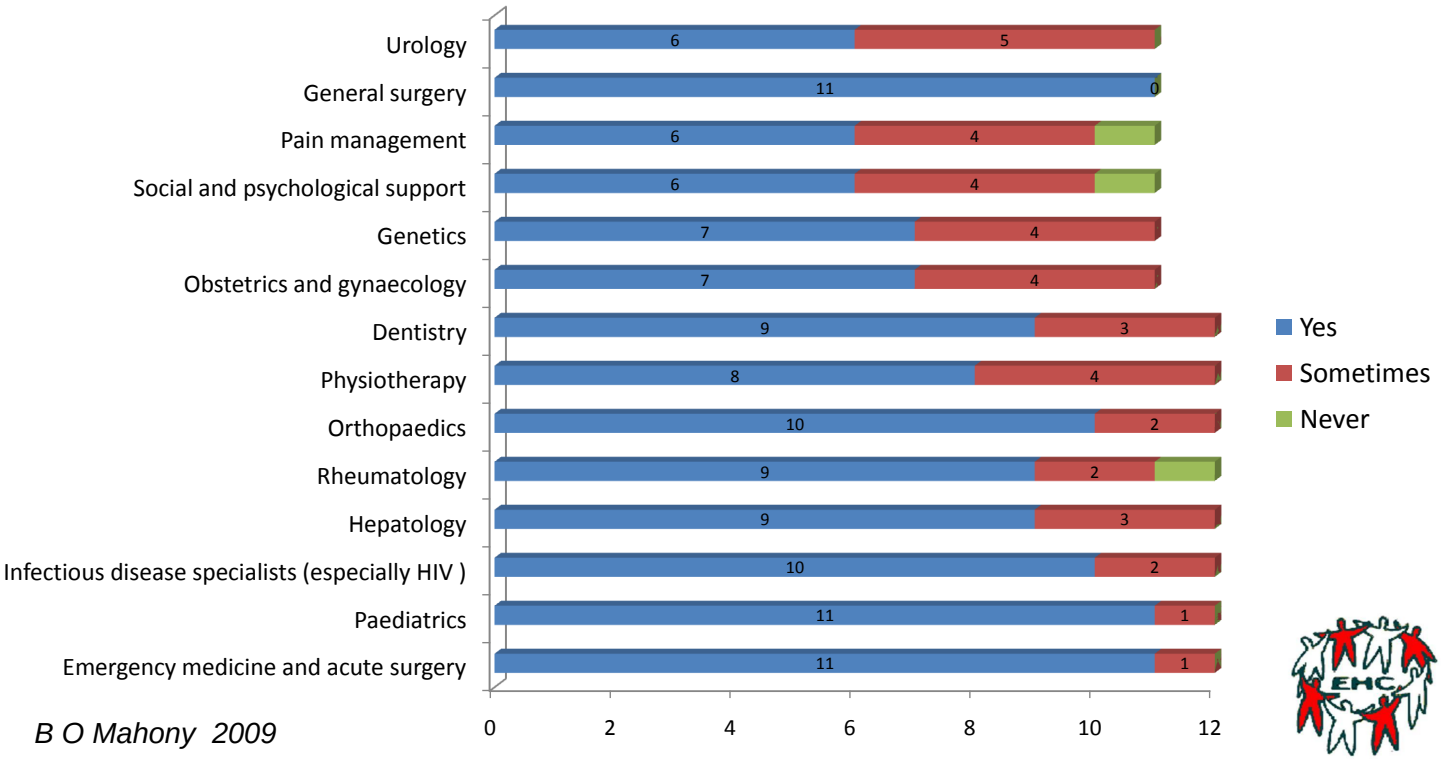
Comprehensive Care Centres (CCC's)

- **9/13 Countries have CCC's**
- 4 Countries do not have CCC's
  - Hungary
  - Bulgaria
  - Bosnia- Herzegovina
  - Lithuania
- Total CCC's Reported 31

Country	Bosnia-Herzegovina	Bulgaria	Czech Republic	Hungary	Latvia	Lithuania	Netherlands	Poland	Romania	Russia	Germany	Ireland	Sweden
Comprehensive Care Centres (CCCs)	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

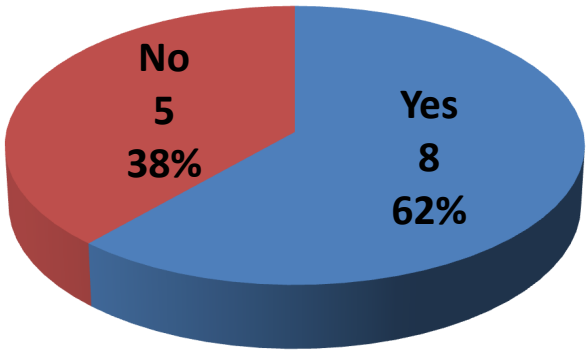
B O Mahony 2009

Availability of specialist services as a part of comprehensive care

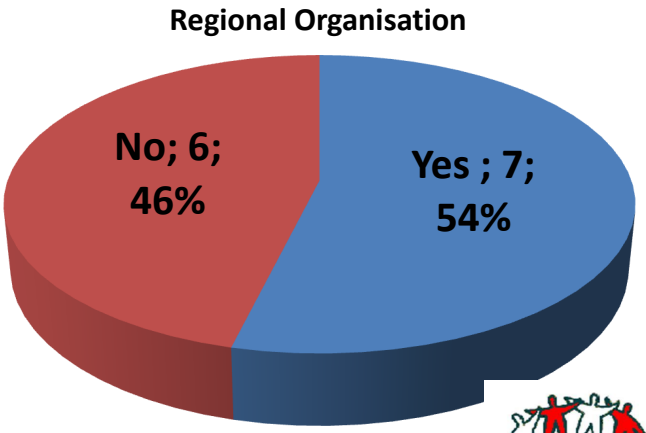


B O Mahony 2009

Have a central organization for haemophilia care?



National Organisation



B O Mahony 2009

Conclusions

- Great disparity in access to care and treatment from minimal to optimal within EU
- Treatment varies from struggle to survive to achieving full integration into society with excellent quality of life
- Treatment provided broadly in line with economy but some countries outperform and several significantly under perform

Conclusions (2)

- Home Treatment for Haemophilia a requirement in each country
- Prophylaxis for Children and Teenagers clearly the optimum therapy
- Treatment Guidelines as a resource for all member states – European Principles of Care
- Outcome measurements required - Economy

Conclusions (3)

- **National Haemophilia Committee's**
- Requirement for Formal Participation by Doctors and Patient Organisation's with Government in decisions on National Haemophilia care

  - Statutory Body (Ireland)
  - Haemophilia Alliance (UK)
  - Tender Commission (Ireland)

Rare bleeding disorders

Flora Peyvandi

RARE BLEEDING DISORDERS

Flora Peyvandi
Hemophilia and Thrombosis Center,
University of Milan

European Symposium on "Optimal Clinical Use of Blood Components"
April 24th-25th 2009
Wildbad Kreuth, Germany

- Rare disease: affects 1 out of 2,000 citizens Europe
- 30 million people have a rare disease in Europe

- Inherited coagulation deficiencies affect 65,000 people in Europe
- Rare Bleeding Disorders (RBDs) with a prevalence approx. 1:500,000 to 1:2,000,000 represent 3-5% of all the inherited coagulation deficiencies

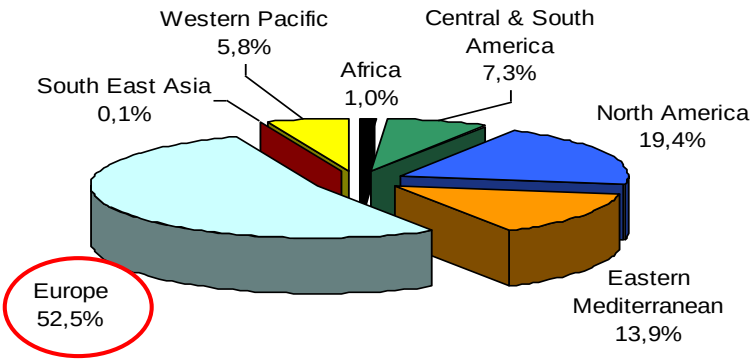
RARE BLEEDING DISORDERS (RBDs)

- Fibrinogen, FII, FV, FV+FVIII, FVII, FX, FXI, FXIII deficiencies are heritable abnormalities of haemostasis that may present significant difficulties in diagnosis and management
- Limited available data because very few clinical centres have the opportunity to see a significant number of patients

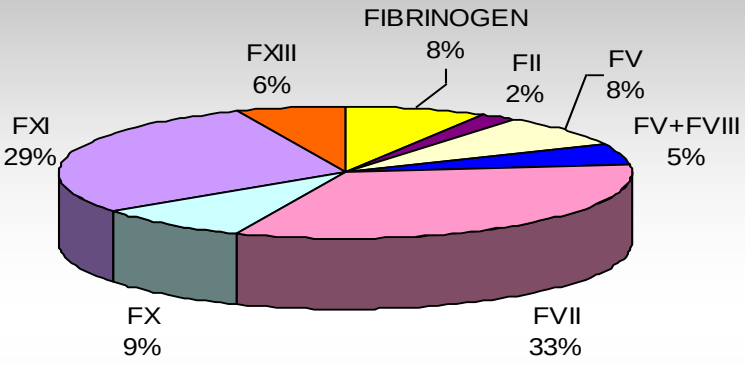
- The recent immigration of Middle East, African countries toward Europe has increased the number of patients in some European countries:
  - significant clinical problem
  - great demand for diagnosis and treatment
  - different economical investments within Europe

WORLD FEDERATION OF HEMOPHILIA GLOBAL SURVEY 2007

N of countries in 2007 survey	**105**	
% of world population covered	89	
N of people identified with HA and B	126.402	64%
N of people with VWD	51.367	26%
N of people with rare coagulation disorders	11.557	6%
N of people with platelet disorders	3.973	2%
N of people with unknown type of hemophilia or coagulation disorder	3.774	2%
Total	**197.073**	**100%**
N of countries using national registries	53	



GLOBAL FREQUENCY OF RBDs



Deficiency	RBDD survey	WFH survey
FIBRINOGEN	241	962
FII	55	208
FV	232	963
FV+FVIII	494	316
FVII	904	3976
FX	338	958
FXI	757	3565
FXIII	209	609
TOT	**3230**	**11557**

Data reported by RBD database (www.rbdd.org) and World Federation of Hemophilia (www.wfh.org)

	Deficiency	Frequency
1	FVII and FXI	33% and 29%
2	FX, fibrinogen, FV	8-9%
3	FXIII	6%
4	FII, FV+FVIII	2 and 5%

BLEEDING SYMPTOMS.1

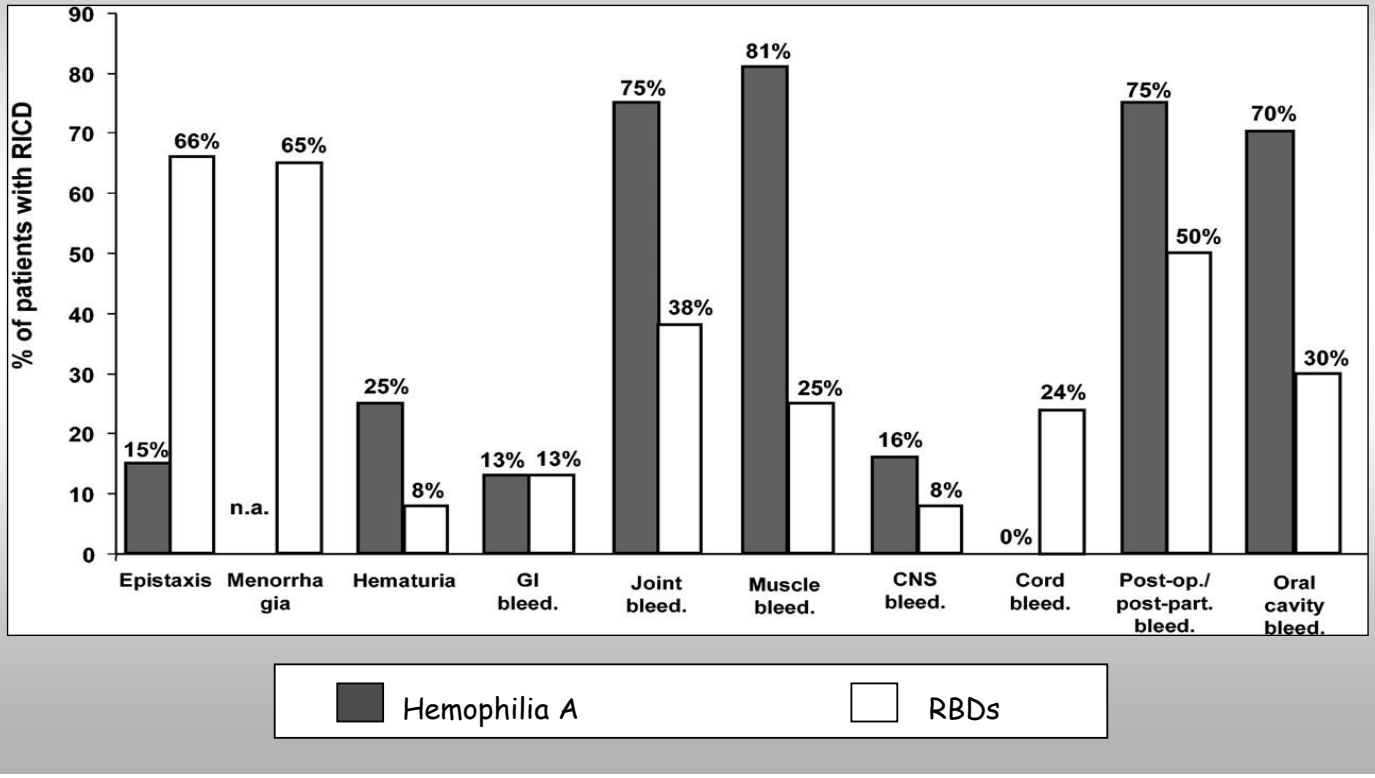
MILD-MODERATE:

- Epistaxis, menorrhagia, hematuria, oral tract bleeding, post-surgery bleedings

SEVERE:

- Life-threatening bleeding:
  - Central nervous system (CNS) bleeding
  - Gastrointestinal (GI) bleeding
  - Umbilical cord bleeding
- Disabling bleeding such as hemarthrosis and hematomas

BLEEDING SYMPTOMS.2



TREATMENT OF RBDs

- Reliable information about clinical management is often scarce
- Coagulation factor support may require the prescription of unlicensed treatment products that are not readily available

REPLACEMENT THERAPY:
- FFP
- cryoprecipitate
- prothrombin complex concentrates (PCC)
- single factor concentrates

NON-TRANSFUSIONAL TREATMENT:
- antifibrinolytic amino acids
- fibrin glue
- oestrogen-progesterone preparations
- desmopressin (DDAVP)

GENERAL PRINCIPLES OF REPLACEMENT THERAPY

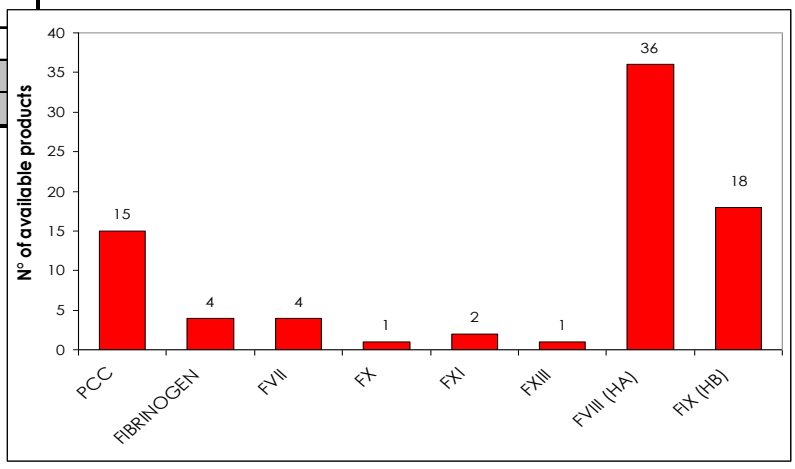
- The patient's personal and **family history** of bleeding are important guides for management
- **Replacement of the deficient factor** is the mainstay of treatment
- **Dosages** and **frequency** of treatment depend on
  - minimal haemostatic levels of the deficient factor
  - plasma half-life
  - type of bleeding episode
- **Safety** of the replacement material is an important principle of choice

REPLACEMENT THERAPY: FFP

- The backbone treatment is a single-donor **fresh-frozen plasma (FFP)**:
  - relatively inexpensive
  - containing all coagulation factors
  - widely available
- **Virus-inactivated FFP** preferable to plain FFP, but scarcely available

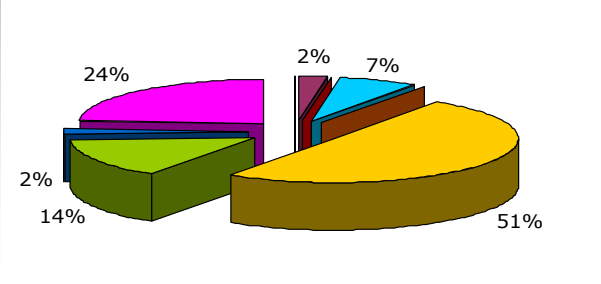
FACTOR CONCENTRATES

	n° products	Manufacturer
PCC	15	13
FIBRINOGEN	4	4
FVII	4	4
FX	1	1
FXI	2	2
FXIII	1	1
FVIII (HA)	36	23
FIX (HB)	18	15

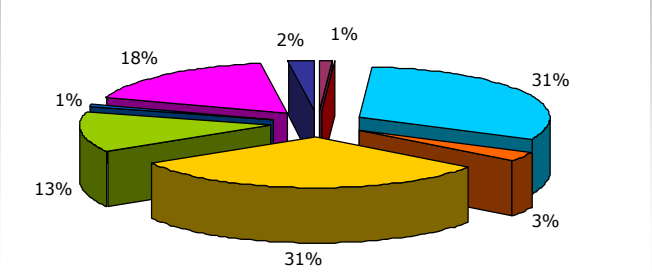


RBDs PRODUCTS DISTRIBUTION (RBDD): 67 CENTRES

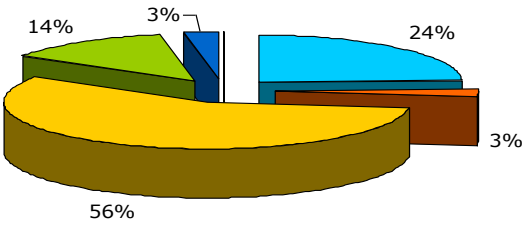
North- America: 13 Centres, 222 patients



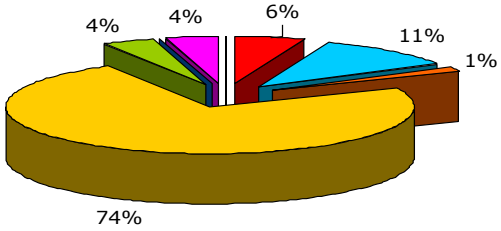
Europe: 33 Centres, 1309 patients



Central and South-America: 6 Centres, 277 pz



Asia and Africa: 15 Centres, 1461 patients



antifibrinolytics | blood | concentrate | FFP, cryo | DDAVP | PCC | platelets | rFVIIa | rFVIII

Since most of the data on RBDs comes from Europe:

- On March 2007, the EN-RBD project (University of Milan and other 9 European Centres, in association with an informatic partner (Alekos), was funded by the Public Health Executive Agency
- To develop a homogeneous on-line database to insert and manage data on clinical manifestation, phenotype, genotype, treatment and treatment-related complications

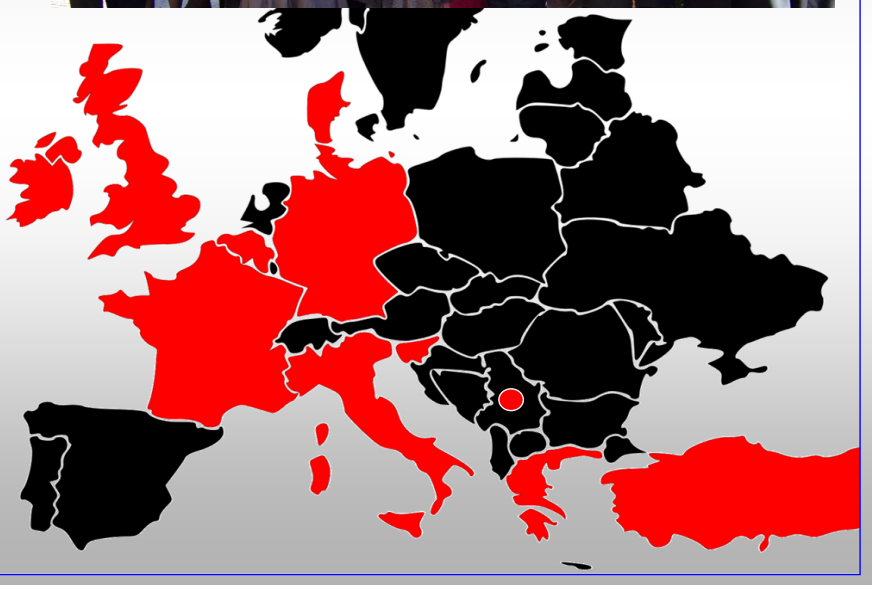
ne RBDD database was used as a starting platform in order to create the first European RBDs network

DATA COLLECTION and MANAGEMENT
- University of Milan, Italy

DATA COLLECTION
- Peerlinck Kathelijne, Belgium
- Jorgen Ingerslev, Denmark
- Florence Suzann, France
- Christoph Bidlingmaier, Germany
- Helen Pergantou, Greece
- Ruth Gilmore, Ireland
- Majda Benedik-Dolnicar, Slovenia
- Tiraje Celkan, Turkey
- Paul Giangrande, UK

NEW PARTNER
- Danijela Mikovic, Serbia

SET UP OF THE ON-LINE DATABASE
- Alekos, Milan, Italy, www.alekos.it



TREATMENT OF RBDs IN EUROPE

Products		Countries								
		Denmark	Germany	Greece	Ireland	Italy	Serbia	Slovenia	Turkey	UK
PCC	Beriplex (CSL Behring)	x								x
	FEIBA (Baxter)					x			x	
	HT DEFIX (SNBTS)									x
	Profilnine SD (Grifols)									x
	Prothromplex (Baxter)	x			x	x				x
	Uman Complex D.I. (Kedrion)					x				
fibrinogen	Haemocomplettan (CSL Behring)	x	x	x	x	x	x			x
FVII	Facteur VII (LFB)									x
	Factor VII (Bioproducts)									x
	Factor VII (Baxter)		x		x	x				x
	rFVIIa (NovoNordisk)	x	x	x	x	x	x	x	x	x
FX	Factor X (CSL Behring)	x	x	x		x				
FXI	Factor XI (Bioproducts)				x					x
	Hemoleven (LFB)		x	x						x
FXIII	Fibrogammin (CSL Behring)	x	x	x	x	x	x			x

Licensed products

TYPE OF TREATMENT

- On demand (treatment given to stop the bleeding)
- Prophylaxis
  - Primary (regular and continuous replacement therapy started after the first severe bleed and before the age of 2 years)
  - Secondary (continuously regular treatment in older patients who bleed with particularly high frequency)
  - Surgical (before and during surgical procedures)
  - Pregnancy/delivery

ON DEMAND TREATMENT

deficient factor	recommended trough levels	plasma half life	on demand
Fibrinogen	50-100 mg/dL	2-4 days	Cryoprecipitate (5-10 bags)
			Solvent/detergent (SD) treated plasma (15-30 mL/Kg)
			Fibrinogen concentrates (50-100 mg/Kg)
Prothrombin	20-30%	3-4 days	SD treated plasma (15-20 mL/Kg)
			FIX concentrates and prothrombin complex concentrates (PCC) (20-30 U/Kg)
Factor V	10-20%	36 hours	SD treated plasma (15-20 mL/Kg)
Factor V+VIII	10-15%	36 h for FV 10-14 h for FVIII	as for Factor V and hemophilia
Factor VII	10-15%	4-6 hours	FVII concentrates (30-40 U/Kg)
			PCC (20-30 U/Kg)
			Recombinant FVIIa (15-30 ug/Kg every 4-6 hours)
Factor X	10-20%	40-60 hours	SD treated plasma (10-20 mL/Kg)
			PCC (20-30 U/Kg)
Factor XI	15-20%	50 hours	SD treated plasma (15-20 mL/Kg)
			FXI concentrates (15-20 U/Kg)
Factor XIII	2-5%	9-12 days	Cryoprecipitate (2-3 bags)
			SD treated plasma (3 mL/Kg)
			FXIII concentrates (10-20U/Kg)

INDICATION FOR PROPHYLAXIS

- The clinical premises to the use of prophylaxis are represented by:
  - the frequency of bleeding
  - the risk of severe spontaneous bleeding
  - the risk of long-term disabilities associated to the occurrence of bleeding in a particular district of the body despite on-demand treatment (e.g., CNS, GI and joint bleedings)
- Based on the limited available data is hard to make a recommendation on the use of primary prophylaxis, except for severe FVII and FXIII deficiencies (Bolton-Maggs *et al.*, 2004)
- The secondary prophylaxis may be appropriate in cases where there has been potentially life threatening bleeding because of the risk of recurrence, e.g. CNS bleeding, as in afibrinogenemia, FX, FXIII and FVII deficiencies

PROPHYLAXIS

deficient factor	recommended trough levels	plasma half life	reported dose schedule for succesful long-term prophylaxis		
			product	dose	frequency
Fibrinogen	50-100 mg/dL	2-4 days	cryoprecipitate	1U	3 times/week
				3U	every 7-10 days
			fibrinogen concentrate	30-100 mg/Kg	every week
Prothrombin	20-30%	3-4 days	PCC	25-40 IU/Kg	once/week
Factor V	10-20%	36 hours	SD treated plasma	30 ml/Kg	twice/week
Factor V+VIII	10-15%	36 h for FV 10-14 h for FVIII	no data	no data	no data
Factor VII	10-15%	4-6 hours	FFP	10-15 ml/Kg	twice/week
			pdFVII	10-50 U/Kg	3 times/week
			rFVIIa	15-30 mcg/Kg	2-3 times/week
Factor X	10-20%	40-60 hours	PCC	30-40 U/Kg	2-3 times/week
Factor XI	15-20%	50 hours	no data	no data	no data
Factor XIII	2-5%	9-12 days	cryoprecipitate	2U	every 3 weeks
			SD treated plasma	15-20 ml/Kg	every 4-6 weeks
			FXIII concentrate	10 U/Kg	every 4-6 weeks

PREGNANCY/DELIVERY and SURGERY

deficient factor	pregnancy/delivery		surgery	
	minimum level	treatment	minimum level	treatment
Fibrinogen	>150 mg/dL	Successful pregnancy in afibrinogenaemia is impossible without fibrinogen replacement therapy	100 mg/dL	Fibrinogen concentrates (50-100 mg/Kg)
		No strong data to support routine post-partum fibrinogen prophylaxis beyond the first 1-2 days		Antifibrinolytic agents (dental extraction)
Prothrombin	> 25%	no data	20-40%	SD treated plasma (15-20 mL/Kg)
				PCC (20–30 IU/kg, higher doses for major surgery)
Factor V	15-25%	SD treated plasma (15-20 mL/Kg, until after delivery)	25%	SD treated plasma (15-20 mL/Kg)
Factor V+VIII	as for FV		as for FV	
Factor VII	>15-20%	Not required during pregnancy, unless there is a bleeding history with previous pregnancies	10-15%	FVII concentrates (30-40 mL/Kg)
		If FVII <20%, peripartum prophylaxis should be considered		PCC (20-30 U/Kg)
				Recombinant FVIIa (15-30 ug/Kg every 4-6 hours)
Factor X	10-20%	In severe FX deficiency and history of adverse outcome replacement therapy to cover delivery (up to 3 days) is indicated	10-20%	SD treated plasma (10-20 mL/Kg)
				PCC (20-30 U/Kg)
Factor XI	15-20%	FXI levels 15-70 u/dL, with no bleeding history , tranexamic acid for up to 3 days (first dose during labour)	15-20%	- Antifibrinolytic agents (3g/day) - FXI levels <15 U/dL: replacement therapy
		FXI levels <15 U/dL: replacement therapy should be considered at the onsent of labour		
Factor XIII	10%	FXIII concentrates: 250 IU/7 days in early period, 500 IU/7days after 23rd weeks)	5-10%	Cryoprecipitate (2-3 bags)
		Factor replacement should be given at delivery to maintain FXIII levels >20%		SD treated plasma (3 mL/Kg)
				FXIII concentrates (10-20 U/Kg)

CONCLUSIONS

- Treatment of patients affected with RBDs is very heterogenous in different EU countries due to different available products
- FFP is still used in 30% of EU countries
- However, virus inactivated FFP is not availble in most EU countries
- The PCCs and FVII concentrates are available in most EU countries
- The FXI concentrate is the less distributed product
- Fibrinogen and FXIII concentrates are available only in few countries in the world
- FV deficiency represents 10% of RBDs with no specific FV concentrate available

Rational quality management

Ernest Briët

Rational quality management

Ernest Briët MD
Sanquin Blood Supply Foundation Amsterdam

Conclusion: an EU concerted action

Quality systems:

a. Less, through harmonisation & integration
b. Covering chain from donor to patient
c. Evaluate their effect

Research program into:

a. Indications, triggers
b. Effects, side effects, costs & benefits
c. Compare alternatives w. components

Generic aims of quality management

Product

- Effective
- Safe
- Consistent
- Available
- ….

The medical intervention

- Well indicated
- Clinically effective & safe
- Cost effective
- ….

Sanquin

Quality framework transfusion service

EU guidelines
Nat'l laws & guidelines
GMP, GLP, GCP
EMEA & FDA
Nat'l competent authority
Audits:

- IGZ, RvA, CCKL, Lloyds, JACIE, NEDCORD Fact, ….
- FDA
- Accountant, Min of Health
- Internal audit system

Sanquin

EDQM Wildbad Kreuth April 24 2009

Cost & benefit

Quality framework hospitals

EU guidelines

Nat'l laws & guidelines

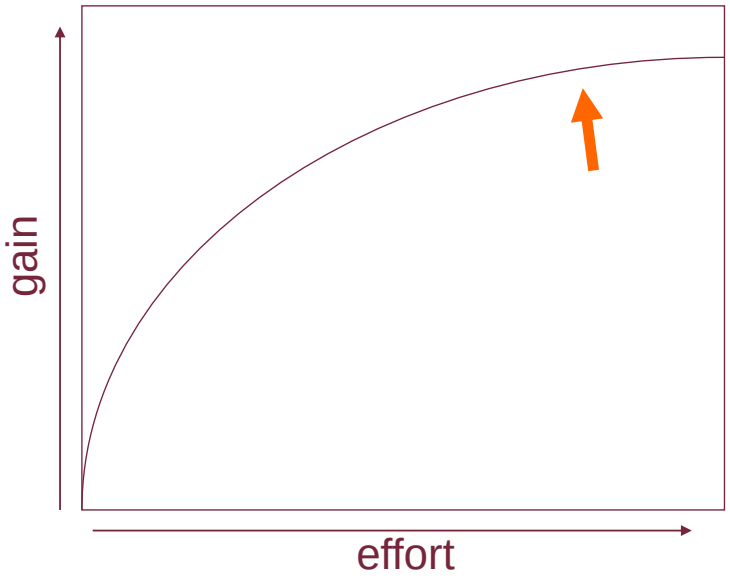
Nat'l competent authority

Audits:

- Nat'l Inst. Accr. H.C. "umbrella"
- Medical specialist training
- Medical specialist practice
- Insurance safety management
- Clin performance indicators
- Accountant
- HACCP, environment, …..

EDQM Wildbad Kreuth April 24 2009

Cost & benefit of Q-systems



Sanquin

Quality systems what to do

a. Less, through harmonisation & integration
b. Covering chain from donor to patient
c. Evaluate their effect

Sanquin

EDQM Wildbad Kreuth April 24 2009

Another perspective

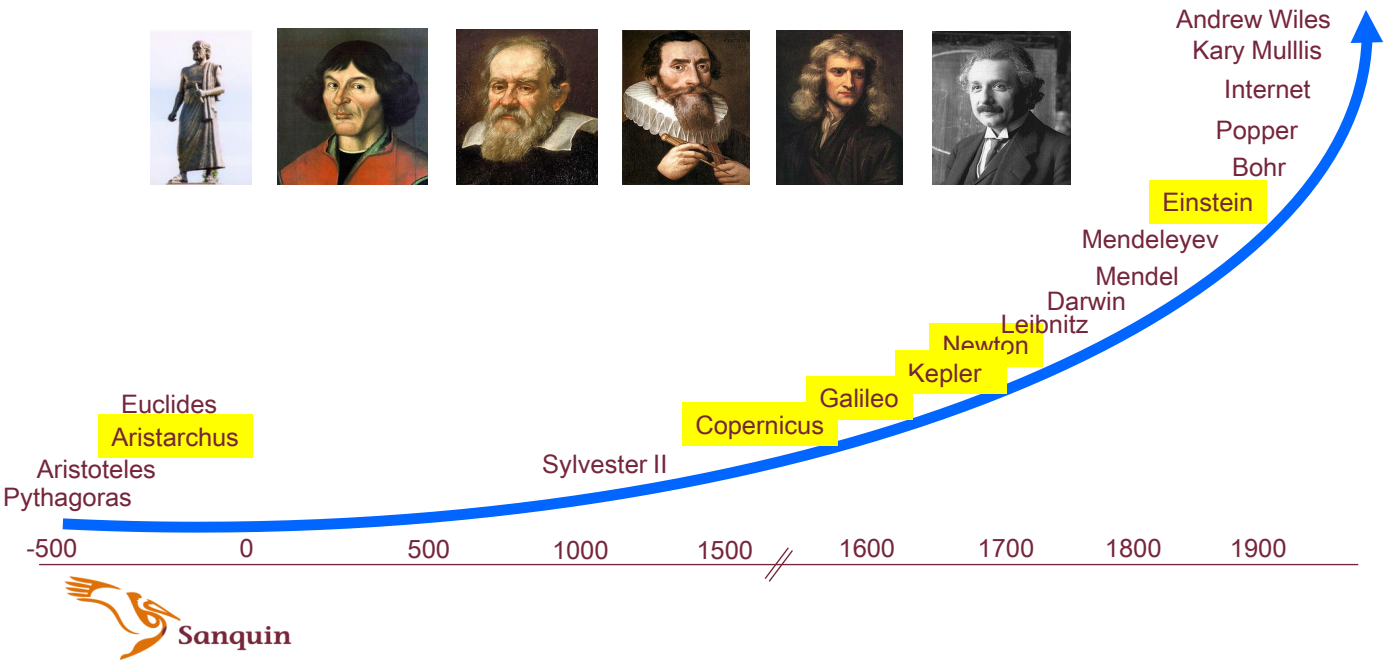
The main problem of transfusion medicine
Is the problem of clinical medicine

Clinical medicine has no scientific tradition

Compare:

- Physics
- Building bridges
- Clinical medicine

Physics: standing on the shoulders of giants



Pont du Gard aquaduct Nimes: ≈ 50 AD

Taag bridge in Alcántara 103 AD

Ponte vecchio Florence 1345

Iron bridge Telford UK 1779

Sanquin

Brooklin bridge NY 1883

Sanquin

Golden gate bridge San Francisco 1937

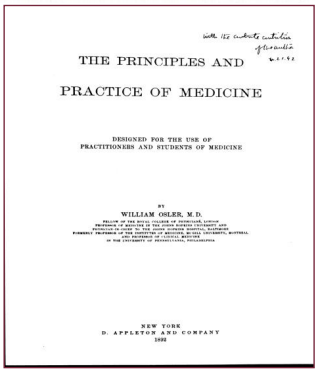
Akashi bridge Japan 1998

Viaduct Millau (Tarn) 2004

The history of clinical medicine

4000 years of blood letting

Mesopotamia
Egypt
Hippokrates
Galenus
Avicenna
Boerhaave
Cholera epidemic 1831
Osler … 1923


THE PRINCIPLES AND
PRACTICE OF MEDICINE
DESIGNED FOR THE USE OF
PRACTITIONERS AND STUDENTS OF MEDICINE
BY
WILLIAM OSLER, M.D.
NEW YORK
D. APPLETON AND COMPANY

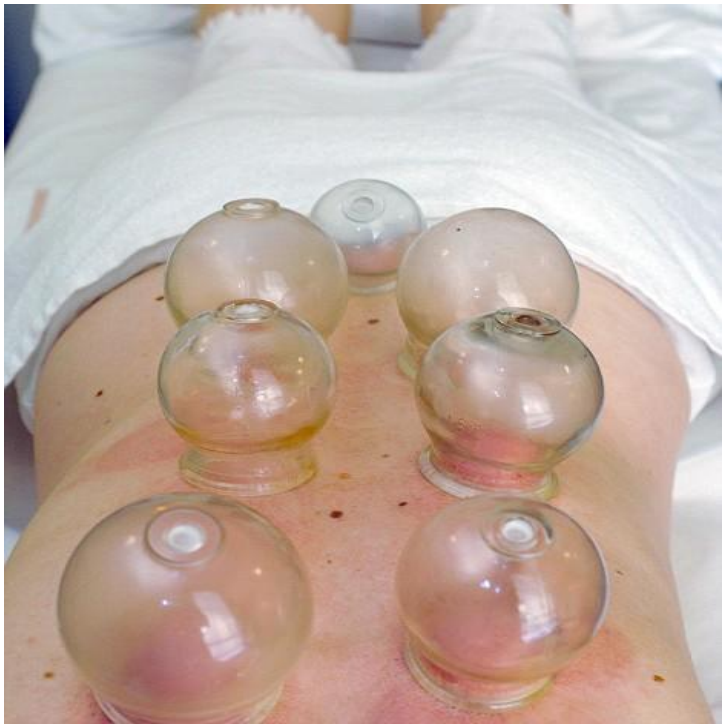
Sanquin

George Washington † (14 dec 1799)

2400 ml

Sanquin

Cupping



Sanquin

Hein 1 april 2009

Bed rest

Bed rest for tuberculosis 1950

Sanquin

Hein 1 april 2009

Diets

For peptic ulcer
For acute M.I.
For diabetes mellitus
…

Sanquin

Evidence based medicine 1992

Archie Cochrane
David Sackett
David Eddy
Gordon Guyatt




Sanquin

Clinical transfusion medicine

To fulfill the ambition of this conference:
Towards optimal clinical use of blood components

We need to fill the evidence base

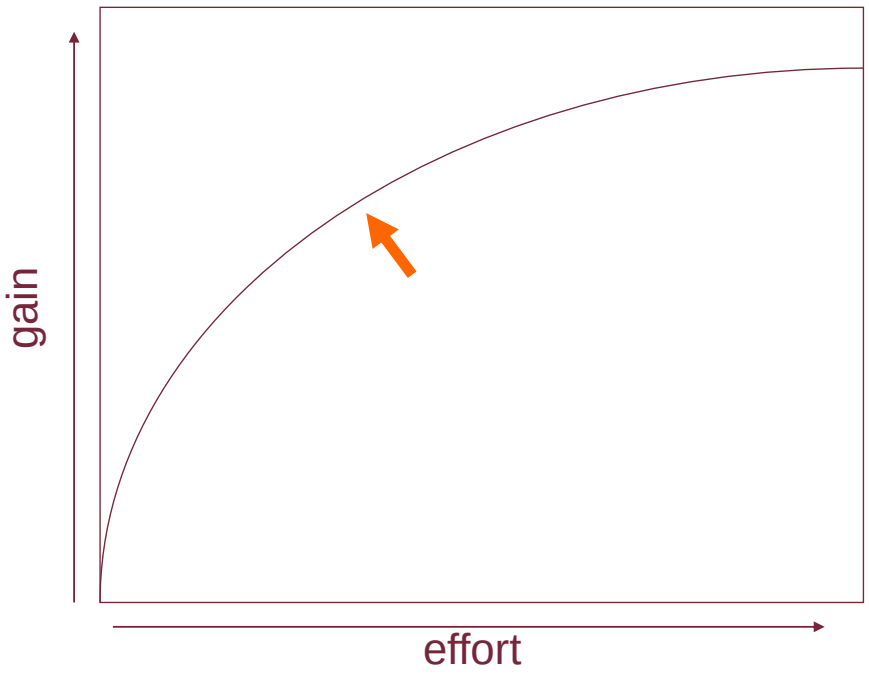
a. Indications, triggers

b. Effects, side effects, costs & benefits

c. Compare alternatives w. components

Sanquin

Clinical transfusion science



Sanquin

Conclusion: an EU concerted action

Quality systems:

a. Less, through harmonisation & integration

b. Covering chain from donor to patient

c. Evaluate their effect

Research program into:

a. Indications, triggers

b. Effects, side effects, costs & benefits

c. Compare alternatives w. components

Sanquin

Transfusion
QM --- Clinical Management

Wolfgang Korte

Transfusion
QM --- Clinical Management

1:NEED Indication

2:clinical haemovigilance

3:OUTCOME

Pat. Safety Critical Issues

country/organization specific

- Pat. Identification (permanent)
- Sample collection and at transfusion
- Human factor

Framework

- Local/Hospital Level - QM person
- Hospital manager responsibility
- National committee
- Workshops for implementation and improvement
- Training

- Standards
- Legislation / Regulation

- Documentation – Labelling - Pat. Id…..

Implementation clinical Champions

Continuous education ,-improvement
Documentation of indication, advices given…

National/international AE register

- Wording Production vs. Clinical context
- Centralized Production vs.Decentralized Application
- Efficacy - Outcome ? Surrogate?
- Minimal requirements (joint comm.)
- Prospective control of guidelines!
- Under - AND Overuse

Clinical TQM
everywhere at every time!
Apply general QM ALSO to Blood TF

- Part 1

- Process
- Chain
- “simple“
- Applicable everywhere

- Part 2

- Outcome
- Which relevant surrogates?
- also„simple“
- Haemovigilance as a tool?
- Applicable everywhere

Within the total qual. management
Within the general risk managenemnt

Different patient groups

Acute bleeding (therapy)

Peri/postoperative (prophylaxis)

Oncology („)

DIFFERENT OUTCOME MEASURANDS!
REGISTERS, Comparison between hospitals countries

QS national level, local level

- Legislation, guidance by the country
- Accreditation criteria

- Process mapping, critical control points
- QS of hospital as an umbrella

Introduction

- Needs of countries in European region vary based on the existing level of implementation of quality systems and availability of resources
- Need for better implementation and adherence to TQM
- Development of new knowledge
- Need for firm committment and support by government

Organisational Management

- Management must define and support responsibility at hospital level to implement quality system in clinical use (135)
- This quality system must be developed as integral part of the quality system in the hospital

Standards, National Guidelines and Legislation

- Standards for hospital accreditation and registration should include standards for clinical transfusion medicine
- To provide bench marking, at least at regional level and aim for Europe wide

Documentation

- Development of SOPs (139)
- Integrated hospital information and documentation system (140,79)
- System for Patient ID and labelling (100,139)
- Emphasize Patient transfusion records and traceability (ICT –based wherever possible)
- Strive for uniformity of documentation (103)

Education and Training

- Mechanism for training and ongoing CME for health professionals throughout the transfusion chain (136, 138, 148,105)
- Strive for comprehensive educational programmes across Europe (143)
- Incorporate QM in Use of blood in medical and nursing curricula (138)

Assessment

- Identify the critical control points in the transfusion chain
- Monitor appropriate outcomes (112) acknowledging differences between patient groups
- Institute clinical audit in hospitals, emphasizing the transfusion chain (103)

Development of knowledge

- Controlled studies (137)
- Sponsorship and support for these studies across Europe (145)
- Categorize patient groups aimed for specific outcome analysis (143,137)
- Support and expand work for evidence base for Transfusion Medicine and for translation into practice
- Cost-effectiveness analysis of procedures (e.g. compliance, over- and underuse)

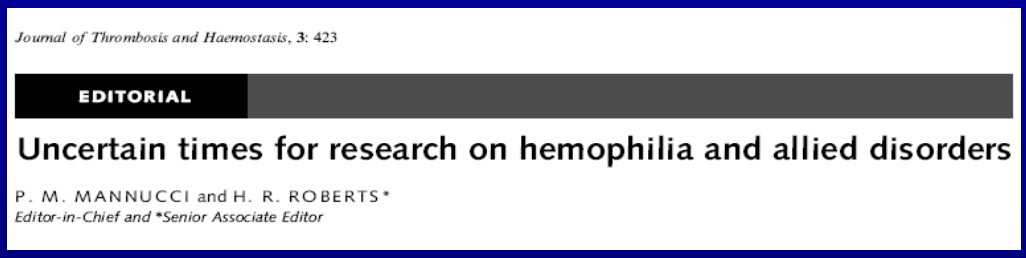
Education in Haemostasis

Jan Astermark

Education in Haemostasis

Jan Astermark, MD PhD Associate Professor,
Malmö, Sweden

Munich April 24, 2009



Journal of Thrombosis and Haemostasis, 3: 423

EDITORIAL

Uncertain times for research on hemophilia and allied disorders

P. M. MANNUCCI and H. R. ROBERTS*
*Editor-in-Chief and *Senior Associate Editor*

"Are we witnessing a dramatic decline in the number of young physicians interested in a clinical and research career in bleeding disorders?"

"...many young hematologist preceive the field of bleeding disorders as being too narrow. This may be overcome by making available training programs in thombosis..."

Munich April 24, 2009

Haemophilia (2005), 11, 433–437 DOI: 10.1111/j.1365-2516.2005.01130.x

RECOMMENDATIONS

Addressing current challenges in haemophilia care: consensus recommendations of a European Interdisciplinary Working Group

C. A. LUDLAM,* P. M. MANNUCCI† and W. G. POWDERLY‡ ON BEHALF OF THE EUROPEAN INTERDISCIPLINARY WORKING GROUP
*Department of Haematology, Royal Infirmary, Edinburgh, UK; †A. Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, and University of Milan, Milan, Italy; and ‡University College Dublin, Mater University Hospital, Dublin, Ireland

1. Developing the next generation of haemophilia specialist
2. Reducing the risk that emerging pathogens present to safe haemophilia care
3. Providing haemophilia care in an environment of cost constraint

Munich April 24, 2009

A survey of the Educational and Training Requirements for a T&H specialist in 10 European countries

- No specific requirements in 3 countries
- In the others - Full training required in internal medicine, hematology, pediatrics, anesthesiology, gynecology, clinical chemistry, neurology, immunology ***and/or*** transfusion medicine

Munich April 24, 2009

Scope of Role for a T&H specialist - A European survey (cont.)

- Coordination of haemophilia care / care of congenital coagulopathies / inherited and acquired bleeding disorders as well as thrombosis
- High variability depending on center organisation or on physician qualification
- In some cases also paediatric oncology / haematology

Training and Development to become a T&H specialist - A European survey (cont.)

- No specific training available in 6 out 10 countries
- Special training requested for 6-12 months in Dept for Coagulation Disorders for 6-12 months + 6-9 months in Clinical Chemistry and 6 months in haematology, transfusion medicine or angiology
- Special training requested for 12 months at an authorised center including 6 months of internal medicine & angiology, internal medicine & oncology / hematology or transfusion medicine

Brussels Meeting Outcome
2-4 February, 2005

Recommendations:

- **Developing the next generation of haemophilia specialists**
  - Recognised training programme and /or qualification in haemostasis and thrombosis
  - Expanded scope of role including thrombotic disorders and other chronic disorders of the blood that require multidisciplinary approach
  - Professional collaboration and co-ordination of care between large haemophilia treatment centres and smaller centres

The InterDiciplinary Working Group (IDWG)

Independent Group of about 45 Haemophilia specialists, supported and facilitated by Baxter BioScience Europe, working on initiatives supporting the harmonisation of haemophilia care across Europe

Group 1. The training of the next generation of haemophilia specialists
Group 2. The need to establish appropriate safety surveillance
Group 3. The delivery of haemophilia care in an environment of cost constraint

Purpose of a Curriculum in Thrombosis and Haemostasis

- There is no current consensus on the definition of specialist in haemostasis and thrombosis at the European level
- An aim to promote harmonization of the training and competences, both clinical and practical, for a specialist in the area within the European Community

Munich April 24, 2009

Haemophilia (2009), 15, 337–344 DOI: 10.1111/j.1365-2516.2008.01836.x

European Association for Haemophilia and Allied Disorders

European curriculum for thrombosis and haemostasis

J. ASTERMARK,* C. NEGRIER,† C. HERMANS,‡ P. A. HOLME,§ R. KLAMROTH,¶ P. KOTSI,** P. DE MOERLOOSE,†† J. PASI,‡‡ A. ROCINO,§§ M. VON DEPKA,¶¶ J. WINDYGA,*** C. A. LUDLAM††† and ON BEHALF OF THE INTERDISCIPLINARY WORKING GROUP IDWG

**Department for Coagulation Disorders, Malmö University Hospital, Malmö, Sweden; †Hôpital Edouard Herriot, CRTH Pavillon E, Lyon, France; ‡Haemostasis Department, Clinique Universitaires St Luc, Bruxelles, Belgium; §Section of Hematology, Medical Department, Rikshospitalet University Hospital, Oslo, Norway; ¶Vivantes Klinikum im Friedrichhain Klinik fuer Innere Medizin, Haemophiliazentrum, Berlin, Germany; **Haemophilia Center, Laikon General Hospital of Athens, Athens, Greece; ††Unité d' Hémostase, Hôpital Cantonal Département de Médecine Interne, Genève, Switzerland; ‡‡Centre for Haematology, Institute of Cell and Molecular Science Barts and the London Queen Mary's School of Medicine and Dentistry, London, UK; §§Ospedale San Giovanni Bosco, Centro Emofilia Divisione di Ematologia, Naples, Italy; ¶¶Werlhof Institute for Haemostasis & Thrombosis, Hannover, Germany; ***Department of Haemostasis and Thrombosis, Institute of Hematology and Blood Transfusion, Warsaw, Poland; and †††Department of Haemophilia and Thrombosis, Centre Royal Infirmary, Edinburgh, Scotland UK*

Munich April 24, 2009

European CV definitions

- **Awareness** - basic notion
- **Knowledge** - updated knowledge on epidemiology, physio-pathology, diagnosis, prognosis, clinical management and different therapeutic options
- **Competence -** In-depth knowledge and practical expertise in diagnosis, treatment and management of the patients in any phase of the disease, as well as in the research and teaching fields

European Curriculum of T&H

1. Role of T&H specialist
2. The practice of T&H
3. Bleeding and thromboembolic disorders
4. Plasma derived and recombinant therapeutic agents
5. Areas of consultative haemostasis
6. Transfusion medicine

1. Role of a H&T Specialist

- *A specialist in H&T will possess expertise in the diagnosis, assessment and treatment of patients with congenital and acquired bleeding and thrombotic disorders*
- *Depending upon the community's healthcare needs and the configuration of hospital services, the responsibilities will include many of the following*
  - Direct responsibility for the provision of a comprehensive care haemophilia service (including oversight of both the direct clinical care of patients and the diagnostic laboratory service)
  - Direct responsibility for the immediate care of patients with thrombotic disorders, especially the difficult ones
  - Provide a consultative service in the area of H&T to other medical, surgical and obstetric specialties
  - Responsibilities to oversee and advise on the general arrangements for service provision of haemostatic and thrombotic services to a wide range of hospital specialties and to the community
  - Provide leadership of a community anticoagulant service to ensure that patients receive an appropriate level of antithrombotic therapy
  - Quality control of laboratory and community based testing
  - Audit of the provision of care to individual patients
  - Research and teaching in the area of thrombosis and haemostasis to provide a high quality service

2. Practice of H&T

- *As a specialist in the area of haemostasis and thrombosis several general skills will be required and in many cases associated with a direct responsibility and management of a distinct laboratory service.*

- General Skills
- Diagnostic Procedures
- Adverse Events
- Clinical Trials

3. Bleeding and Thromboembolic Disorders

- Principles and mechanisms of haemostasis
- Platelets disorders
- Inherited Bleeding disorders
- Acquired Bleeding disorders
- Thrombotic disorders

4. Plasma Derived & Recombinant Therapeutic Agents

- *All specialists in thrombosis and haemostasis should possess a high expertice level in the area of factor concentrates and replacement therapy including a historical perspective in the use of these agents and national regulations*

5. Areas of Consultative Haemostasis

A specialist will have to serve as consultant to other specialists to prevent bleeding and thrombotic complications in association with various interventions as well as to manage patients with an established haemostatic disorder

Areas of consultation:

- Gynaecology / obstetrics
- Intensive care
- Oncology & other haematological diseases
- Neurology
- Nephrology
- Forensics
- Infectious diseases & Gastroenterology
- Cardiology & Cardiovascular surgery
- General & Orthopaedic surgery
- Traumatology

6. Transfusion Medicine

- *A close collaboration with specialists in transfusion medicin should be established and a specialist in T&H should acquire knowledge in:*

  Blood donation / blood products

  Transfusion transmissible infections

  Therapeutic procedures
  (incl. apheresis and immunoadsorption)

  Administration of transfusions

  Adverse transfusion reactions

Concluding Remarks

- T & H is an emerging well-defined sub-specialty
- Recruitment of young physicians to the field of T & H are important to secure quality of care in the future
- Recognised training programmes with high credibility are warranted and should be supported by European Associations – adopted by EAHAD

Munich April 24, 2009

The use of blood components and patient characteristics

Cees L. van der Poel

Sanquin

The use of blood components and patient characteristics

Cees L. van der Poel, MD, PhD
Secretary Medical Affairs Sanquin
Ass. Prof. Epidemiology, Univ. Utrecht

European Symposium on the Optimal Use of Blood Components, Wildbat Kreuth
24-25 april 2009

edqm
European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

DEPARTMENT OF BIOLOGICAL STANDARDISATION, OMCL NETWORK & HEALTHCARE (DBO)

MEEF/md

Working document, with no legally binding status, intended exclusively for the addressees and their associates, under the responsibility of the addressees (listed opposite). Level 1
English /Anglais

PA/PH/TS-GPUQA (07) 10

Strasbourg, July 2007

EUROPEAN COMMITTEE (PARTIAL AGREEMENT) ON BLOOD TRANSFUSION

The collection, testing and use of blood and blood products in Europe in 2004

Draft report

Authors : C. van der Poel, M. Janssen, B. Borkent-Raven

EDQM Responsible Scientific Administrator : M.-E. Behr-Gross

Definitions….definitions…..

Directive 2002/98/EC, Annex II, requests Member States of the European Union to report annually on the blood establishment's activity. This request includes data with similar definitions also asked for in this questionnaire (questions. 1.1 + 1.2.1, 2.1-5, 3.1-5, 4.1-2, 7.1 + 8.3.1, 7.2 + 8.3.2, and 12.2).

Definitions and data requested on confirmatory testing and NAT testing of for infectious diseases (tables 7 + 8) are congruent with those requested by the "Guideline on epidemiological data on blood transmissible infections" by the EMEA (EMEA/CPMP/BWP/3794/03).

Definitions and data requested on haemovigilance (table 12) are congruent with those requested by Directive 2005/61/EC.

A process has started to harmonise with WHO, as of 2005 questionnaire, revisions and additions were made to adapt a WHO draft questionnaire on selected indicators.

Sanquin

Trend Analysis on the Collection, Testing and Use of blood components in Europe 2001 - 2005

edqm European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

TTA TRANSFUSION TECHNOLOGY ASSESSMENT

UMC Universitair Medisch Centrum Utrecht

Julius Centrum

Sanquin

Materials and methods

Testing for a trend for a specific country

(≥ 4 data points)

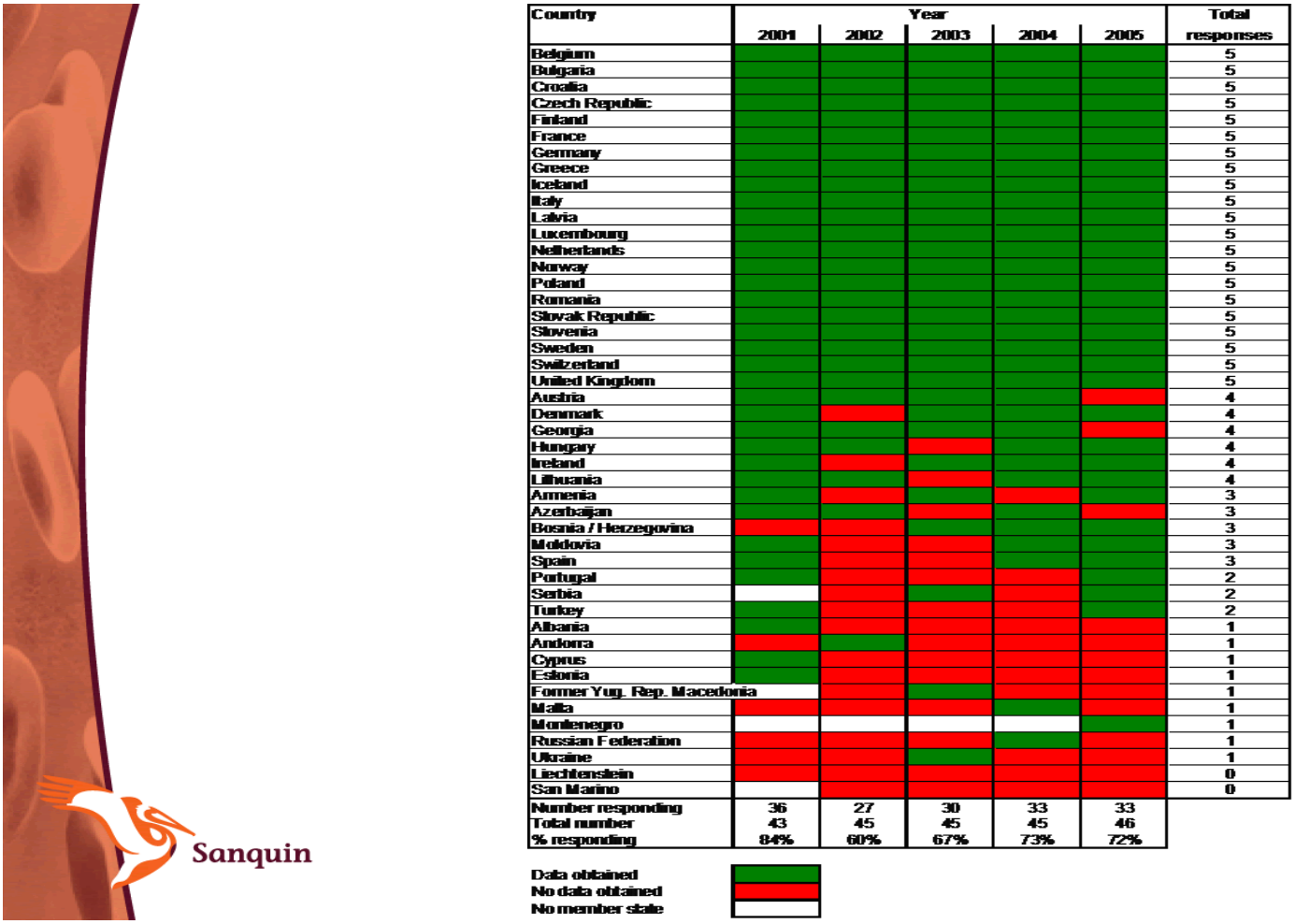
Nonparametric Mann-Kendall test for trend

Parametric test for trend (linear regression)

Testing for global trends

Linear Mixed Model

Sanquin

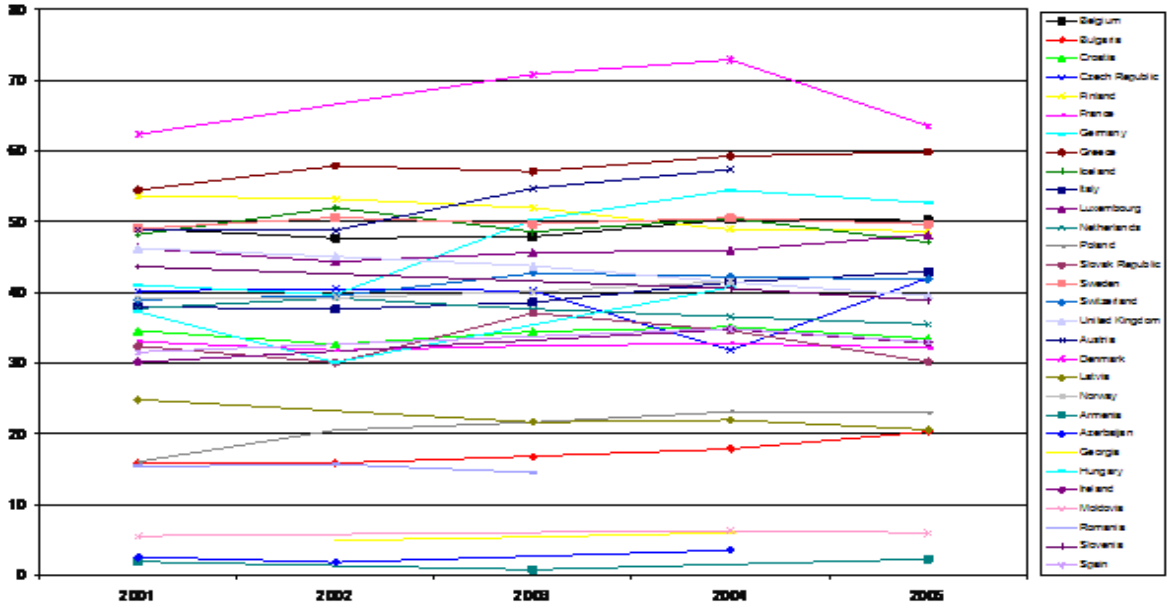


Country	Year					Total responses
	2001	2002	2003	2004	2005	
Belgium						5
Bulgaria						5
Croatia						5
Czech Republic						5
Finland						5
France						5
Germany						5
Greece						5
Iceland						5
Italy						5
Latvia						5
Luxembourg						5
Netherlands						5
Norway						5
Poland						5
Romania						5
Slovak Republic						5
Slovenia						5
Sweden						5
Switzerland						5
United Kingdom						5
Austria						4
Denmark						4
Georgia						4
Hungary						4
Ireland						4
Lithuania						4
Armenia						3
Azerbaijan						3
Bosnia / Herzegovina						3
Moldovia						3
Spain						3
Portugal						2
Serbia						2
Turkey						2
Albania						1
Andorra						1
Cyprus						1
Estonia						1
Former Yug. Rep. Macedonia						1
Malta						1
Montenegro						1
Russian Federation						1
Ukraine						1
Liechtenstein						0
San Marino						0
Number responding	36	27	30	33	33	
Total number	43	45	45	45	46	
% responding	84%	60%	67%	73%	72%	

Data obtained
No data obtained
No member state

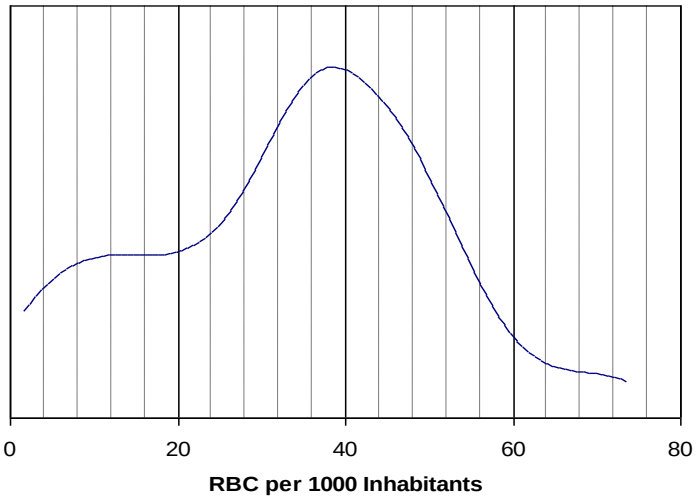
Sanquin

RBC units per 1000 inhabitants delivered



Sanquin

RBC units per 1000 inhabitants delivered



Mean = 34

Median= 37

Sanquin

RBC units per 1000 inhabitants delivered

There are 8 out of the 21 countries with four or more entries that show a significant trend.

Of these eight there are five upward and three downward trends (Bulgaria(+), Greece(+), Italy(+), Poland(+), Norway(+), Finland(-), Netherlands(-), United Kingdom(-)).

There is a statistically significant global increase of 0,38 RBC units per 1000 inhabitants (p-value of 0,02, 95% CI 0,05-0,71).

Sanquin

2005 Ranking RBC use / 1000 inhabitants	
Denmark	63,5
Greece	59,9
Germany	52,6
Belgium	50,2
Sweden	49,6
Finland	48,7
Luxembourg	48,1
Iceland	47,1
Italy	42,9
Czech Republic	42,0
Switzerland	41,8
United Kingdom	39,5
Slovenia	38,9
Netherlands	35,5
Portugal	34,0
Croatia	33,5
Spain	33,0
Ireland	32,9
France	32,1
Serbia	31,3
Slovak Republic	30,2
Latvia	20,6
Bulgaria	20,3
Moldovia	6,0
Armenia	2,3

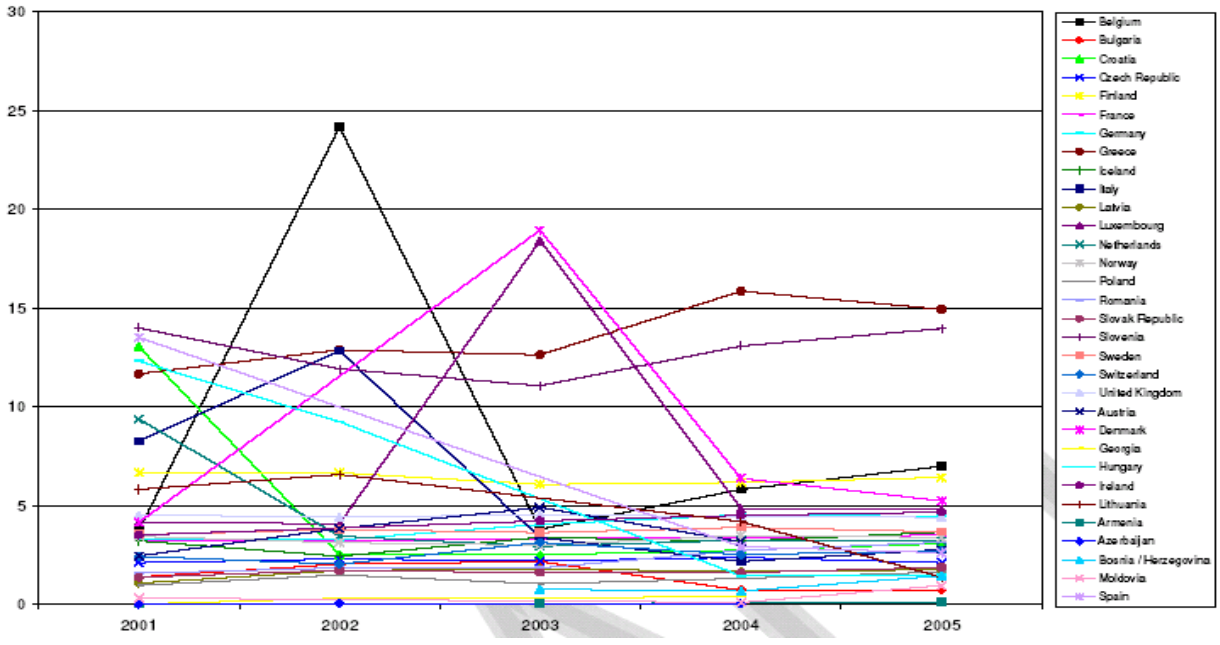
Sanquin

RBC use per 1000 inhabitants 2001 - 2003	
USA	48,8
Australia	28,0
England	44,9
Denmark	54,1

Sanquin

Cobain, Vamvakas, Wells, Titlestad, Transfusion Med 2007

Platelet adult doses per 1000 inhabitants delivered



Sanquin

Platelet adult doses per 1000 inhabitants delivered

There are 3 out of the 27 countries with four or more entries that show a significant trend.

All of these are upward trends (France, Romania, Ireland).

There is also a statistically significant general trend (p-value of 0.02) of -0,27 platelet units per year (95% CI -0,50-0,048).

Sanquin

2005 Ranking Platelets / 1000 inhabitants	
Greece	14,95
Slovenia	13,96
Belgium	6,98
Finland	6,42
Denmark	5,23
Luxembourg	4,79
Ireland	4,66
Germany	4,45
United Kingdom	4,39
Sweden	3,67
Iceland	3,66
France	3,50
Norway	3,39
Netherlands	3,19
Romania	3,13
Croatia	3,06
Italy	2,75
Switzerland	2,69
Spain	2,61
Czech Republic	2,10
Turkey	1,95
Slovak Republic	1,87
Portugal	1,74
Latvia	1,74
Serbia	1,69
Hungary	1,46
Bosnia / Herzegovina	1,43
Lithuania	1,35
Moldovia	0,94
Bulgaria	0,70

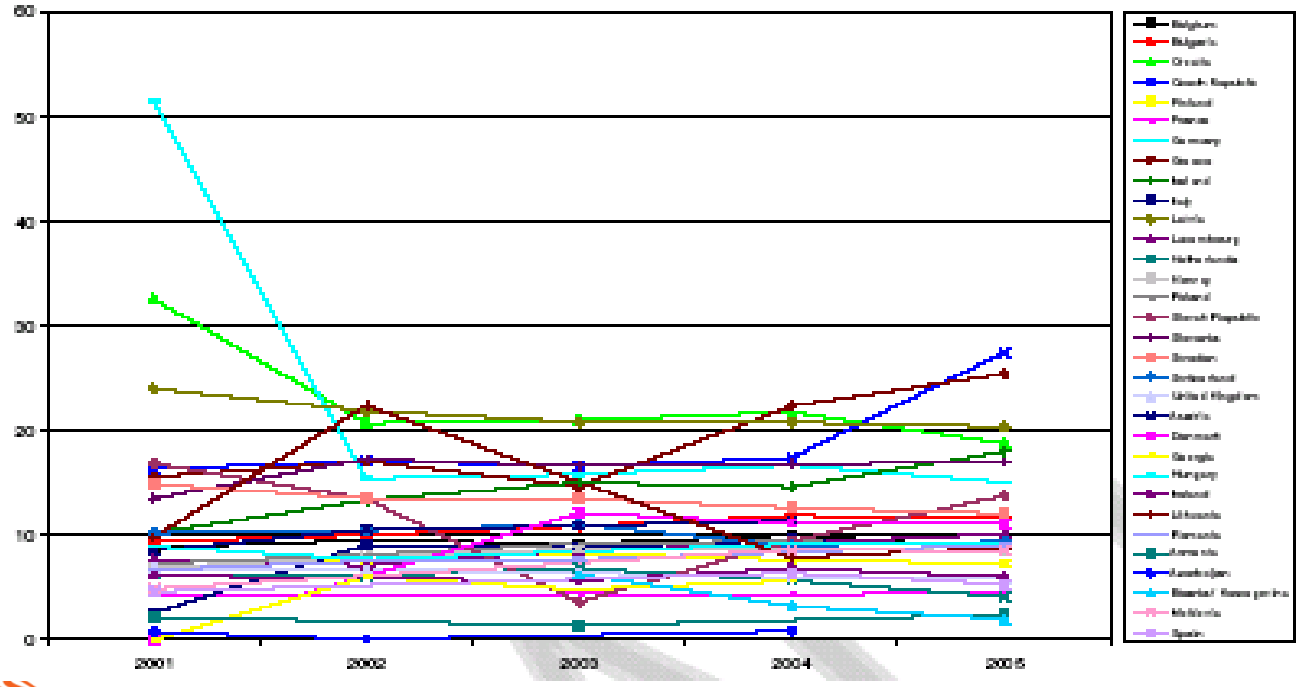
Sanquin

Platelet use per 1000 inhabitants 2001 - 2003	
USA	5,9
Australia	3,0
England	2,0
Denmark	4,7

Sanquin

Cobain, Vamvakas, Wells, Titlestad, Transfusion Med 2007

FFP per 1000 inhabitants delivered



Sanquin

FFP per 1000 inhabitants delivered

There are 10 out of the 27 countries with four or more entries that show a significant trend.

Of these ten there are seven upward (Bulgaria(+), Czech Republic(+), France(+), Iceland(+), Luxembourg(+), Austria(+), Romania(+)), and three downward trends (Latvia(-), Sweden(-), United Kingdom(-)).

There is no statistically significant global trend.

However, when the first observation from Germany is discarded, there is near significant increasing trend of 0,29 FFP units per year (95% CI -0,03-0,61).

Sanquin

2005 Ranking FFP / 1000 inhabitants	
Czech Republic	27,5
Greece	25,5
Latvia	20,4
Croatia	18,8
Iceland	18,0
Slovenia	17,0
Serbia	15,6
Germany	15,1
Slovak Republic	13,8
Sweden	12,1
Bulgaria	11,6
Denmark	11,1
Luxembourg	10,2
Switzerland	9,5
Hungary	9,2
Italy	9,1
Romania	9,1
Belgium	8,8
Lithuania	8,8
Norway	8,5
Moldovia	8,5
Finland	7,3
Ireland	6,0
United Kingdom	5,8
Turkey	5,6
Spain	5,3
France	4,5
Netherlands	4,2
Armenia	2,4
Bosnia / Herzegovina	2,0
Portugal	0,2

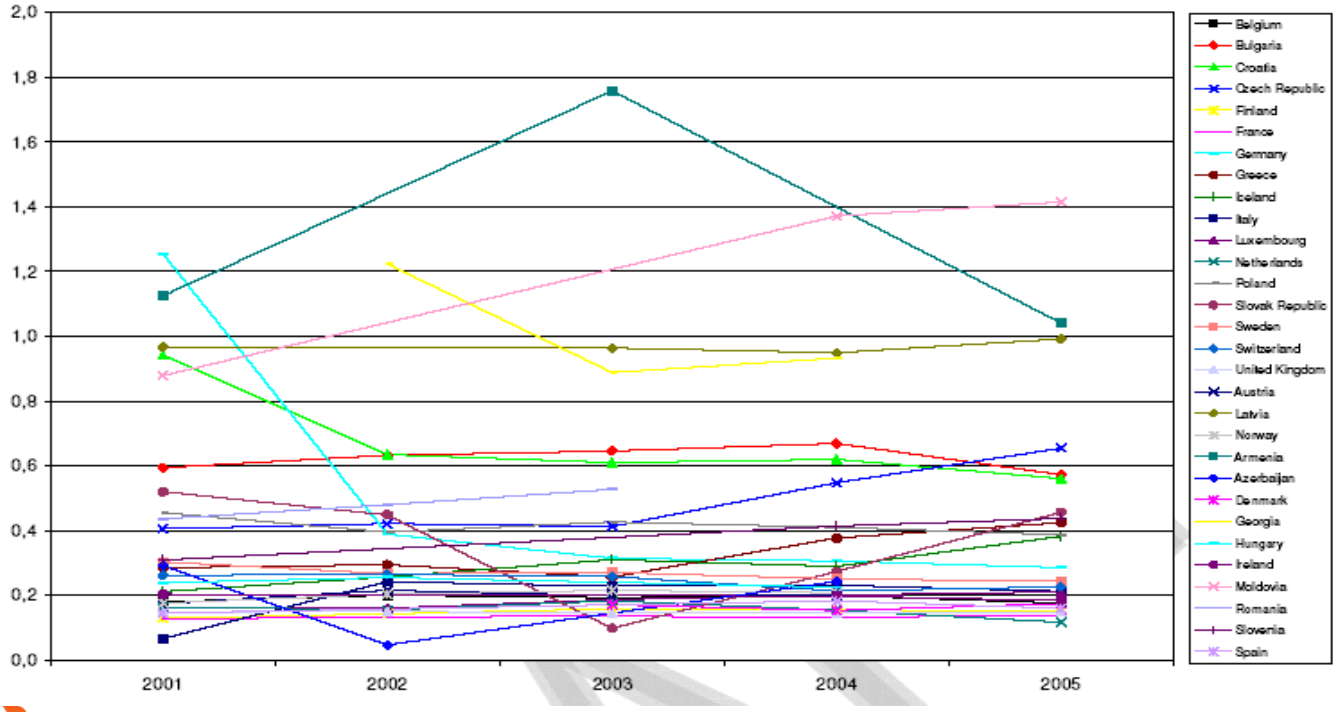
Sanquin

FFP use per 1000 inhabitants 2001 - 2003	
USA	13,8
Australia	5,3
England	5,9
Denmark	5,2

Sanquin

Cobain, Vamvakas, Wells, Titlestad, Transfusion Med 2007

FFP / RBC Ratio



Sanquin

FFP / RBC Ratio

There are 6 out of the 20 countries with four or more entries that show a significant trend.

Of these six there are three upward and three downward trends (Czech Republic(+), Iceland(+), Luxembourg(+), Croatia(-), Germany(-), Sweden(-)).

There is no statistically significant general trend.

Sanquin

Conclusions Trend Analysis CoE surveys 2001 - 2005

- RBC use
  - upward trend, 0,38 Units /1000 inh. / yr
  - % whole blood use downward trend, 24% / yr
  - use below 20 / 1000 inh. / yr may indicate shortage of supply
- Platelet use
  - upward trend 0,27 Units / 1000 inh. / yr
- FFP use
  - large differences in use / 1000 inh. / yr
  - upward trend 0,29 Units / 1000 inh. / yr
  - FFP / RBC ratio, no trend, if >1 may indicate over-use

Sanquin

PROTON study
PROfiel Transfusie Ontvangers

Universitair Medisch Centrum
Utrecht

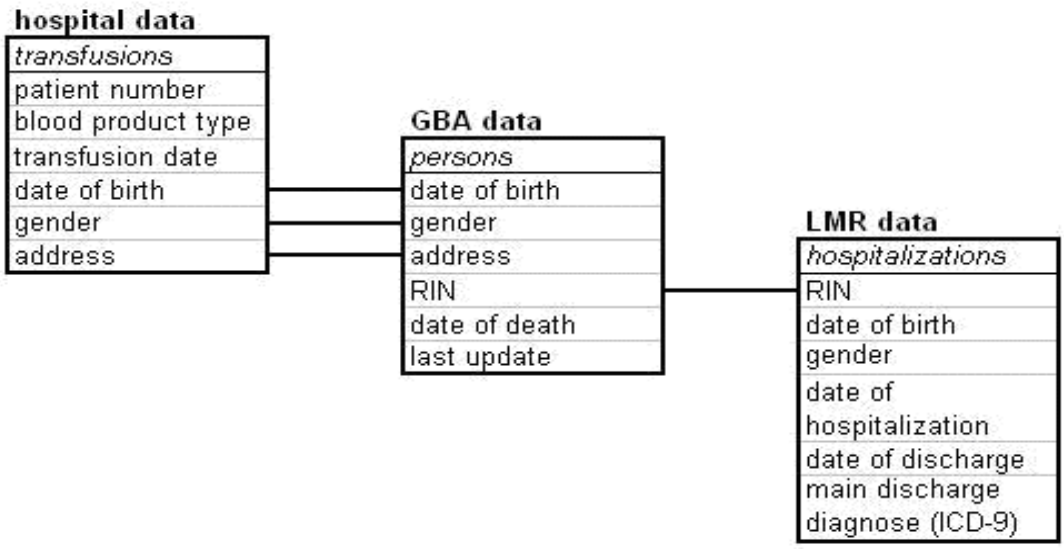
Julius Centrum

Sanquin

hospital number	category	years of follow-up	# patients in dataset	# BPT in dataset	mean BPT per recipient	% BPT linked to GBA	% BPT linked to diagnosis
1	academic	12.0	30,091	370,296	12.3	94%	98%
2	academic	12.0	32,694	317,701	9.7	94%	95%
3	academic	11.0	28,342	285,189	10.1	87%	82%
4	academic	10.3	24,191	193,559	8.0	93%	97%
5	cancer	12.0	7,227	59,909	8.3	94%	89%
subtotal	academic		122,545	1,226,654	10.0	92%	93%
6	general	11.2	23,283	163,888	7.0	92%	83%
7	general	12.0	19,195	142,441	7.4	96%	87%
8	general	8.2	15,330	96,023	6.3	93%	89%
9	general	12.0	14,812	93,424	6.3	92%	78%
10	general	8.7	12,233	90,731	7.4	89%	74%
11	general	12.0	13,770	75,854	5.5	95%	88%
12	general	12.0	11,867	66,234	5.6	91%	89%
13	general	12.0	7,667	46,605	6.1	83%	72%
14	general	12.0	7,338	41,368	5.6	94%	92%
15	general	12.0	6,965	33,140	4.8	94%	79%
16	general	7.9	4,349	23,115	5.3	94%	91%
17	general	4.6	2,458	12,393	5.0	95%	70%
18	general	2.5	1,743	7,403	4.2	93%	32%
19	general	1.7	718	3,871	5.4	98%	86%
subtotal	general		141,728	896,490	6.3	92%	83%
total			**264,273**	**2,123,144**	**8.0**	**92%**	**89%**

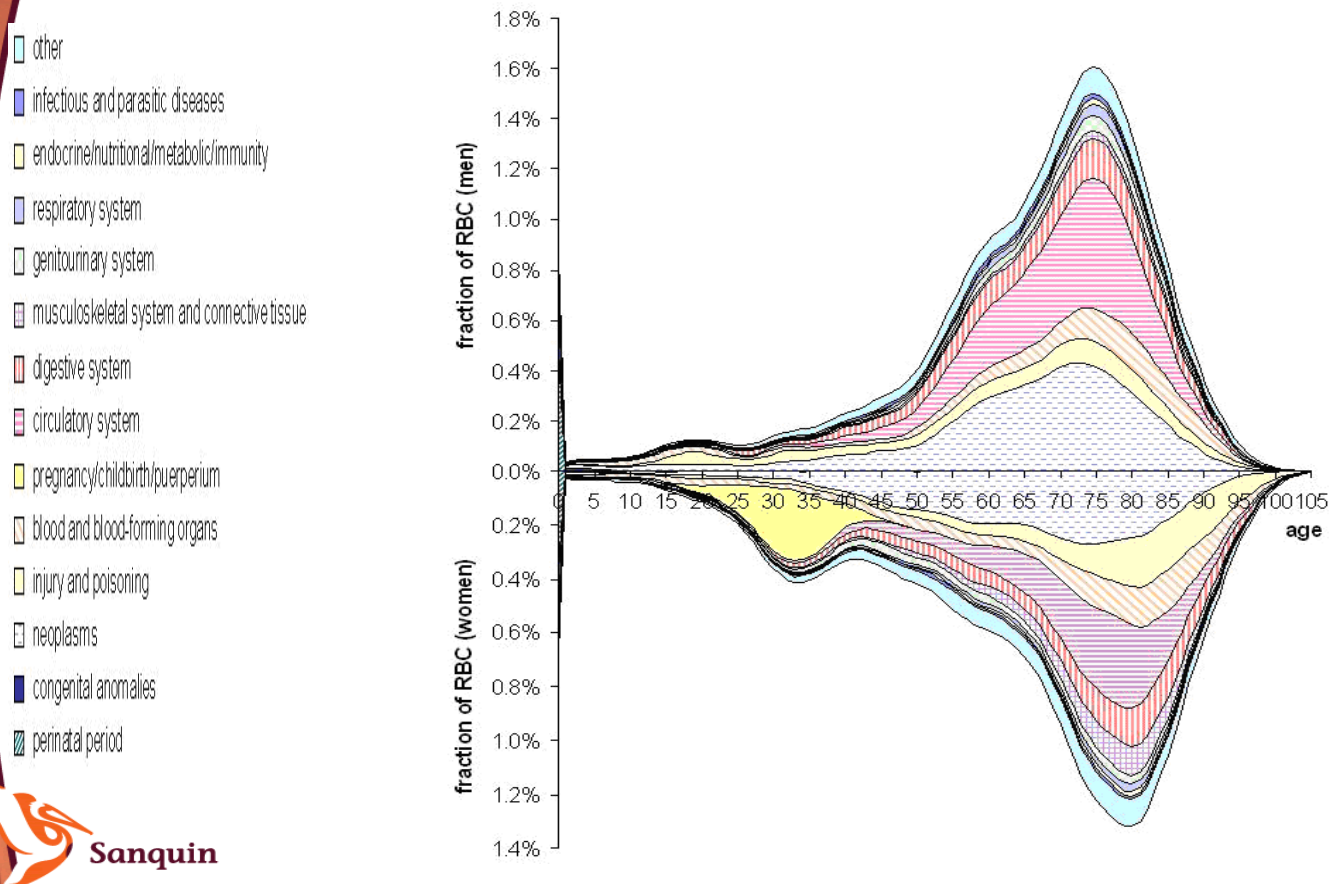
Sanquin

PROTON study
Mining transfusions from 1995 – 2006



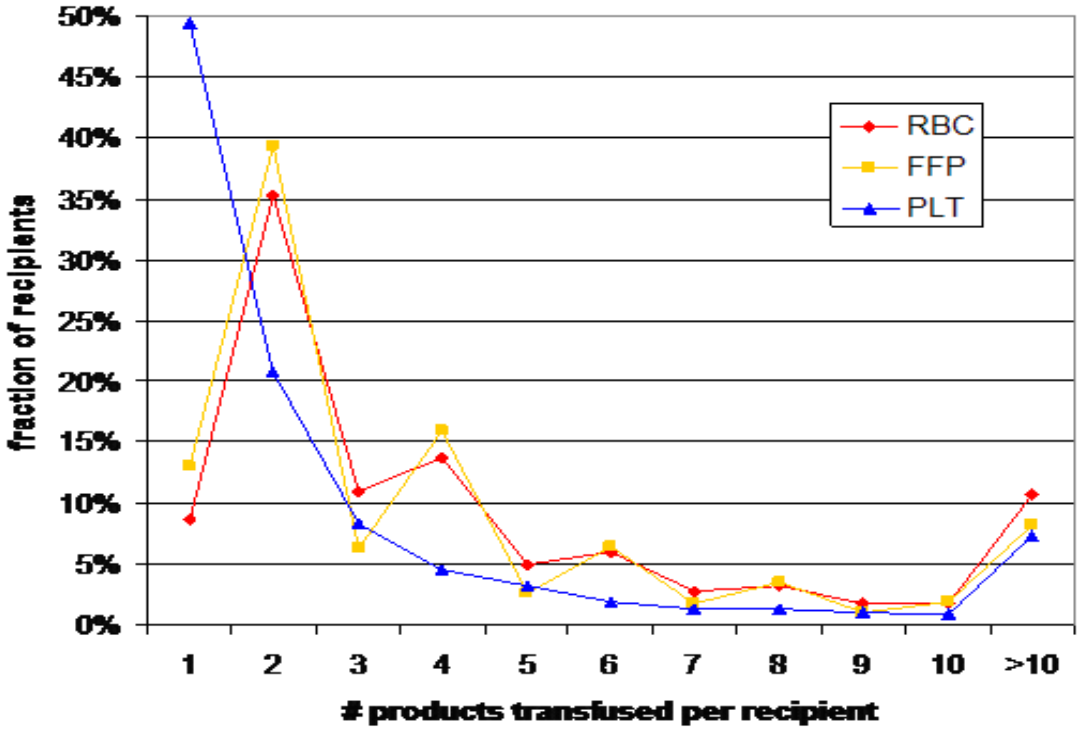
Sanquin

Borkent-Raven B, in preparation

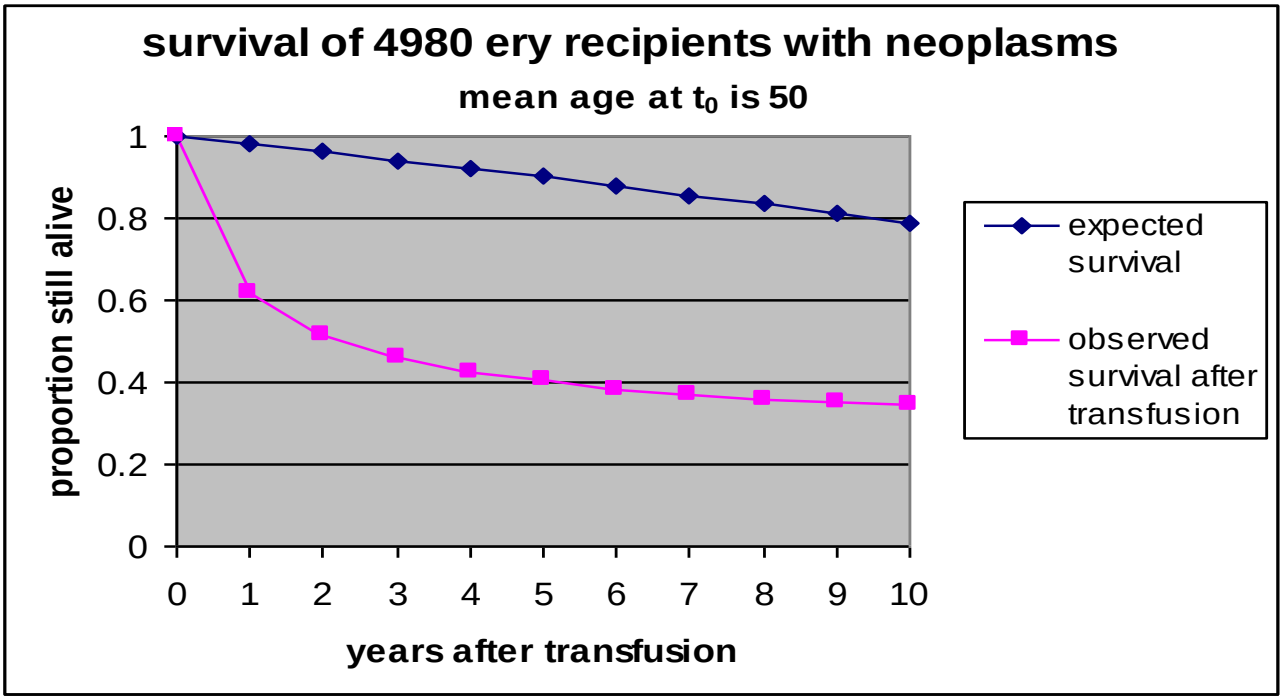


Sanquin

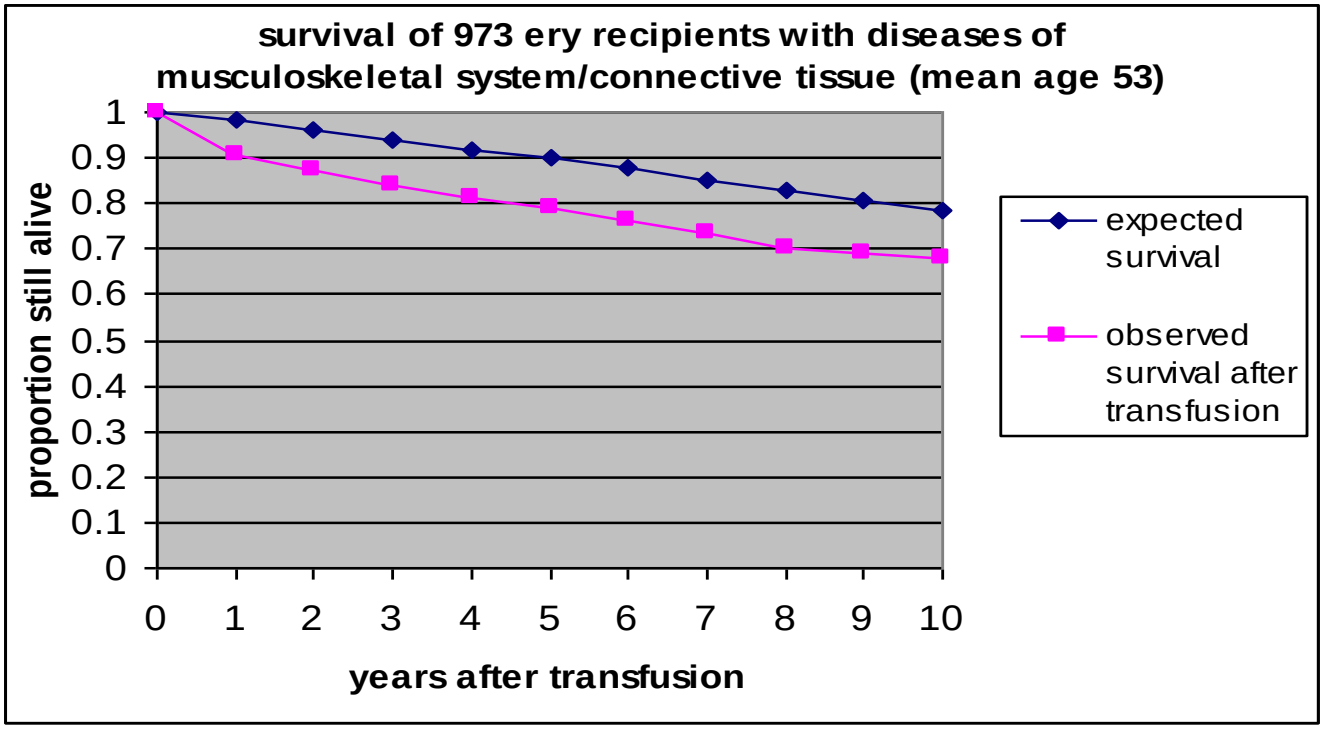
Numbers of products per patient



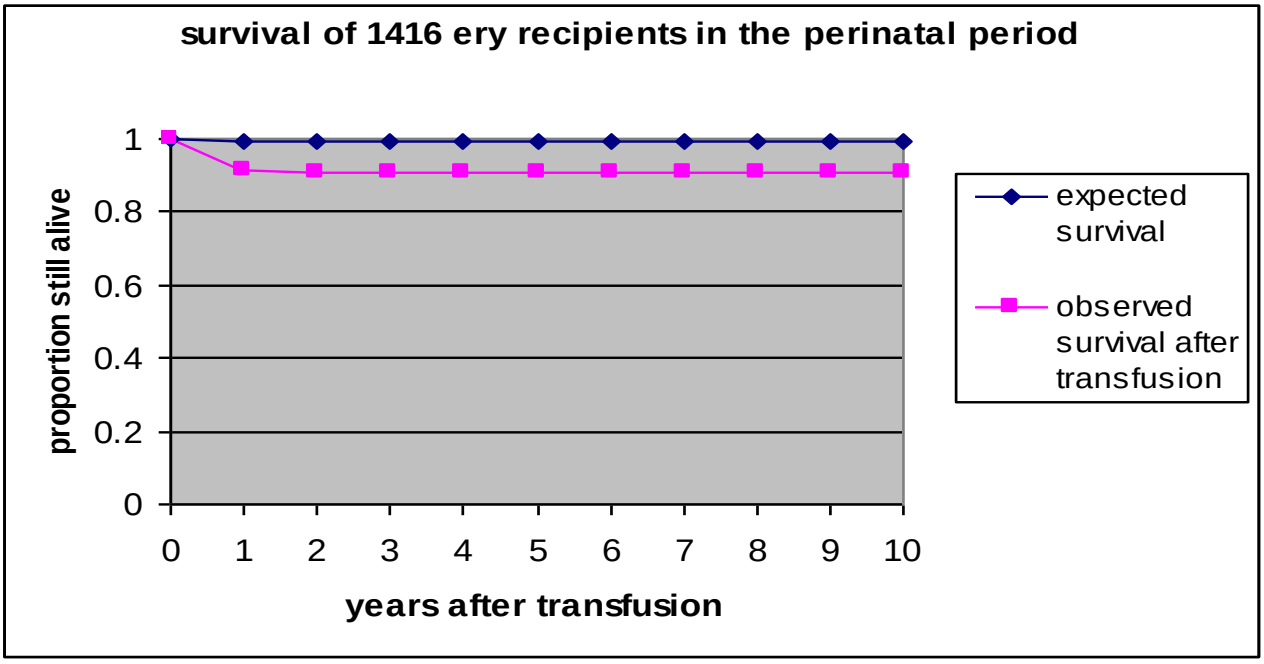
Sanquin



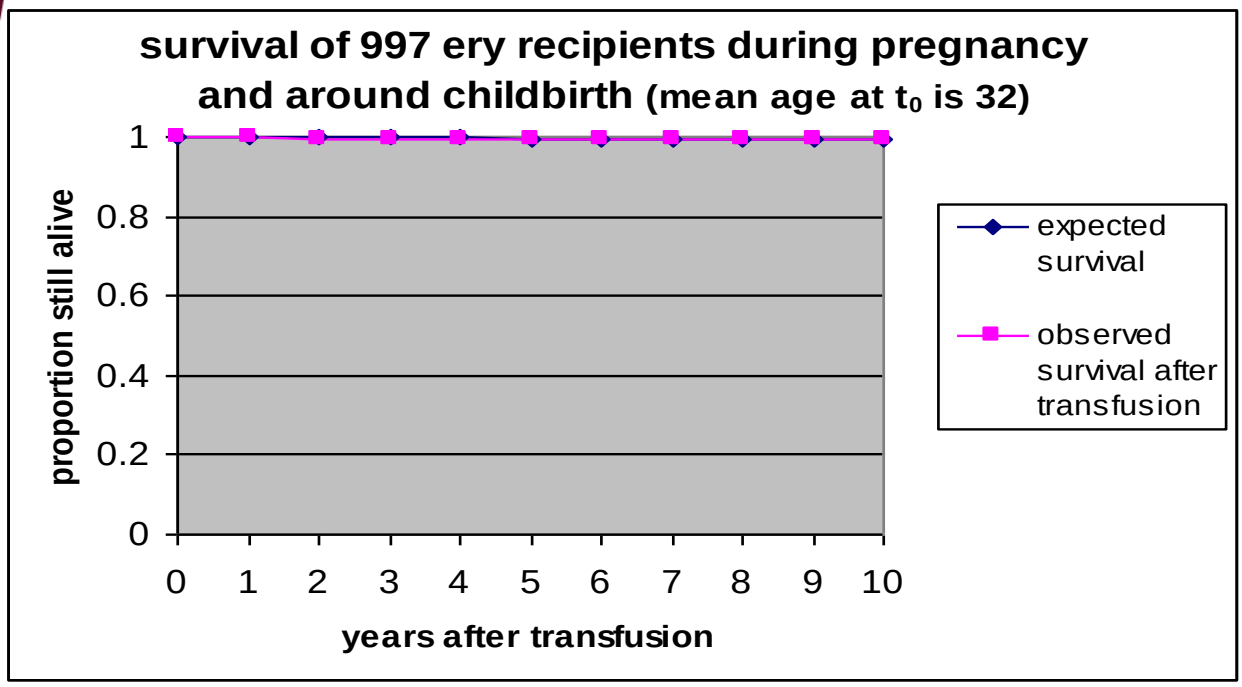
Sanquin



Sanquin

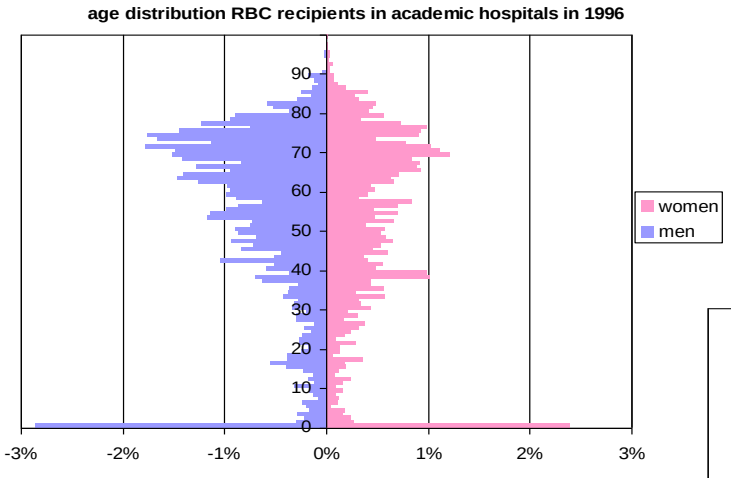


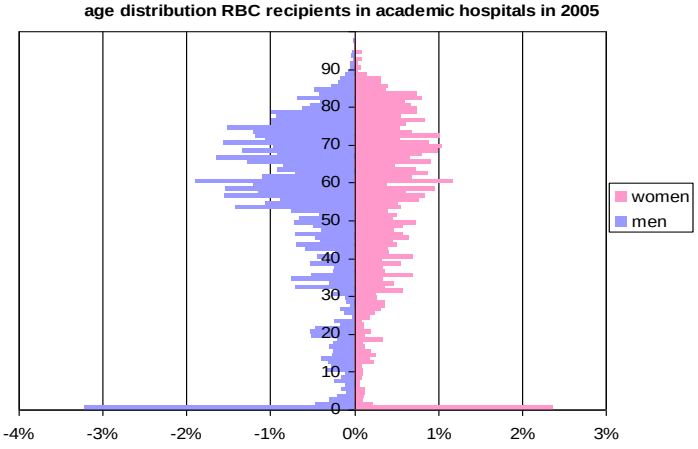
Sanquin



Sanquin

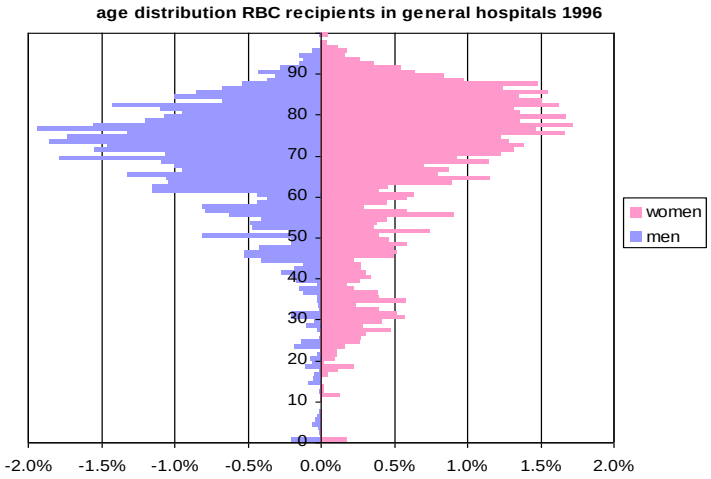
Age distribution RBC recipients in academic hospitals

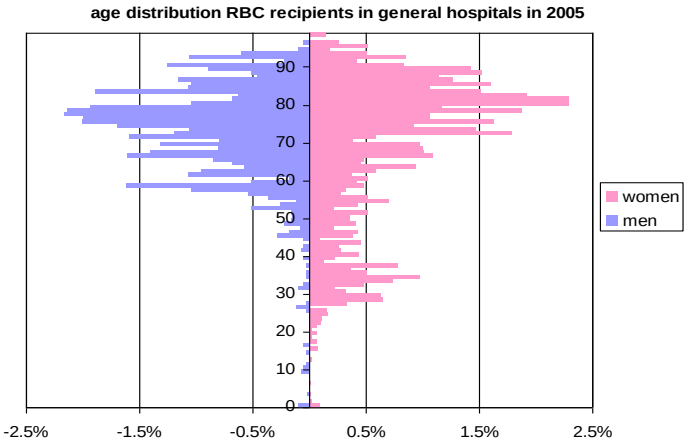




Sanquin

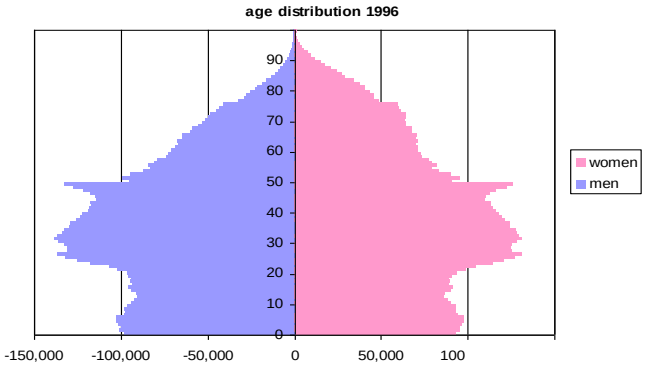
Age distribution RBC recipients in peripheral hospitals

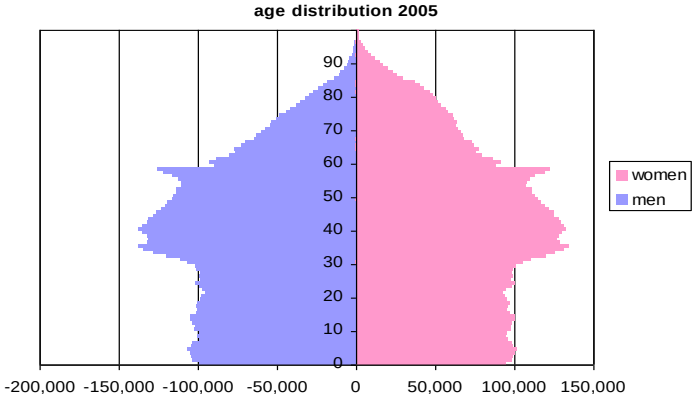




Sanquin

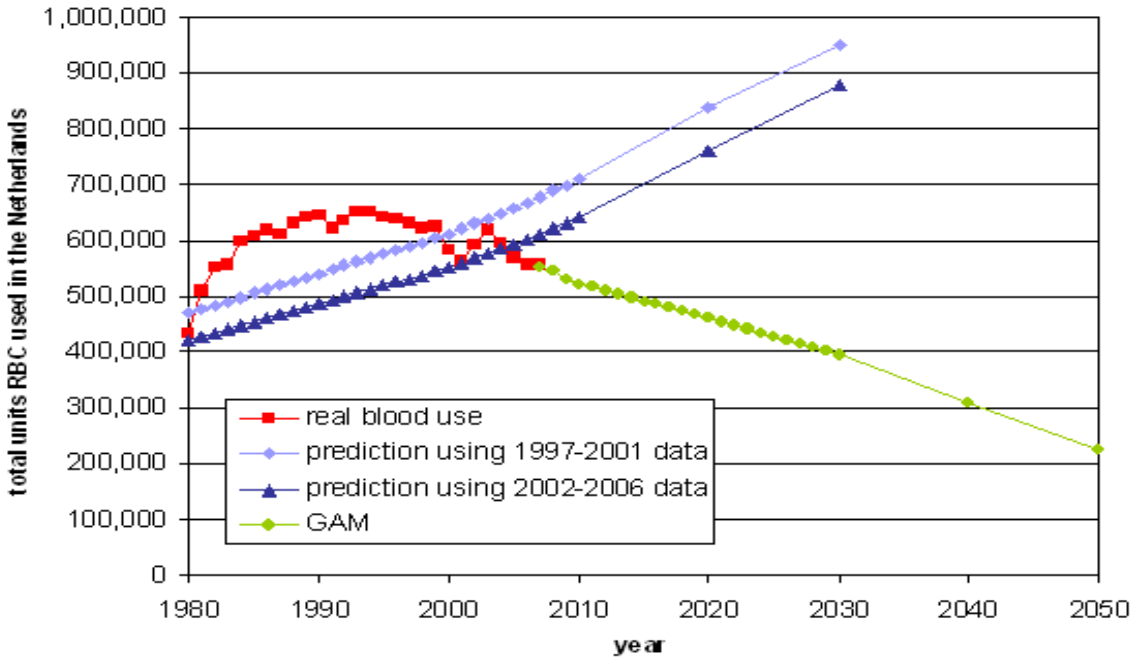
Age distribution Netherlands population





Sanquin

PROTON study and prediction of blood use Generalized Additive Modeling



Sanquin

Overall conclusions blood use in Europe 2001-2005

- RBC use
  - upward trend, 0,38 Units /1000 inh. / yr
  - use below 20 / 1000 inh. / yr may indicate shortage of supply
- Platelet use
  - upward trend 0,27 Units / 1000 inh. / yr
- FFP use
  - large differences in use / 1000 inh. / yr
  - upward trend 0,29 Units / 1000 inh. / yr
  - FFP / RBC ratio >1 may indicate over-use

Sanquin

Overall conclusions blood use in The Netherlands 1995 - 2006

- RBC and FFP: 2 units may be the “therapeutic dose”
- RBC Transfusions per se do not appear to negatively affect recipient survival
- Demand has decreased significantly since 1996
- Demographic developments may increase demand but medical developments lowering demand may be stronger

Sanquin

Transfusion Technology Assessment UMCU / Sanquin

- Dr. C.L. van der Poel (Julius UMCU, Sanquin)
- Ir. M.P. Janssen (Julius UMCU, Sanquin)
- Drs. B. Borkent (Julius UMCU, ZONMW)
- Prof. B.A. van Hout (Julius UMCU)
- Prof. G. J. Bonsel (Erasmus, R’dam)
- Dr. W.M. Schaasberg (CBS, Den Haag)
- Dr. M. Kretschmar (Cib / RIVM, Julius UMCU)
- Dr. A. de Wit (Cib / RIVM, Julius UMCU)

Sanquin

Efficacy of transfusion services in term of outcome

Constantina Politis

Efficacy of transfusion services in terms of outcome

Haemovigilance, epidemiological and economic aspects

Constantina Politis

Athens, Hellas

Introduction

Parameters on efficacy in terms of outcome

Haemovigilance, Epidemiological

& Economic aspects

including cost-effectiveness and cost expenditures

to improve budgeting and monitoring BTS costs

within an appropriate healthcare quality system should be registered and evaluated

Agenda

- The efficacy of transfusion of therapeutic blood components and associated side effects from the haemovigilance point of view
- Monitoring blood usage in Greece

  Guidelines / Recommendations

  The model of thalassaemia and of a cardiosurgery centre
- Product pricing and the challenges of the optimal costing model correlating with clinical efficacy in terms of outcome

Definitions

Efficacy – the degree to which a therapeutic outcome of transfusion or a probability of benefit to individuals in a defined population from a medical technology is achieved under rigorously controlled and monitored circumstances

Examples

- Randomised clinical trials;
- Implementation of a new technology for a given medical problem

The Kreuth Initiative 1999

Definitions

Outcome – any result or consequence that stems for exposure to a casual factor such as preventive or therapeutic health care intervention

- Primary endpoint - (evaluating a technology)
- Intermediate – (short-term significance)
- Ultimate - (a long-term significance)

- Quality of life endpoint – (a consequence of the use of a health care intervention that affects the patients' physical/social/psychological functioning

The Kreuth Initiative 1999

The dual power of blood

Euripides 2500 BC

Haemovigilance aspects

Haemovigilance represents one of the most reliable (and, in Europe, legally- imposed) quality systems demonstrating among other things

the efficacy of laboratory and clinical transfusion medicine in terms of associated adverse reactions and adverse events

which may have an impact in the immediate, short-term or long-term outcome of transfusion.

Errors

•Errors in the administrative practices related to transfusion

(eg recipient identification and compatibility testing) may result in ABO mismatch and consequently have a serious impact on the mortality and the morbidity of transfusion

•Blood transmitted viral or bacterial infection may raise serious doubts about blood safety.

Viral vs non-infection safety

Considering the low prevalence of TTIs, it is possible that optimization of blood transfusion services may be more cost-effective in terms of health gain and cost-benefit, than additional blood screening strategies.

EU

Directive 2002/98/EC

Emphasis on the quality, safety and efficacy requirements of blood products to be used for therapeutic purposes

Directive 2005/61/EU

Imposes on member states common notification formats for serious ARs/AEs

	Important information	
Outcome	Complete recovery Minor sequelae Serious sequelae Death	No. of issued units No. of transfused units No. of recipients

Council of Europe, WHO and ISBT, IHN

Cooperation in developing common definitions of ARs/AEs and in harmonizing reporting practices may facilitate benchmarking and allow comparisons

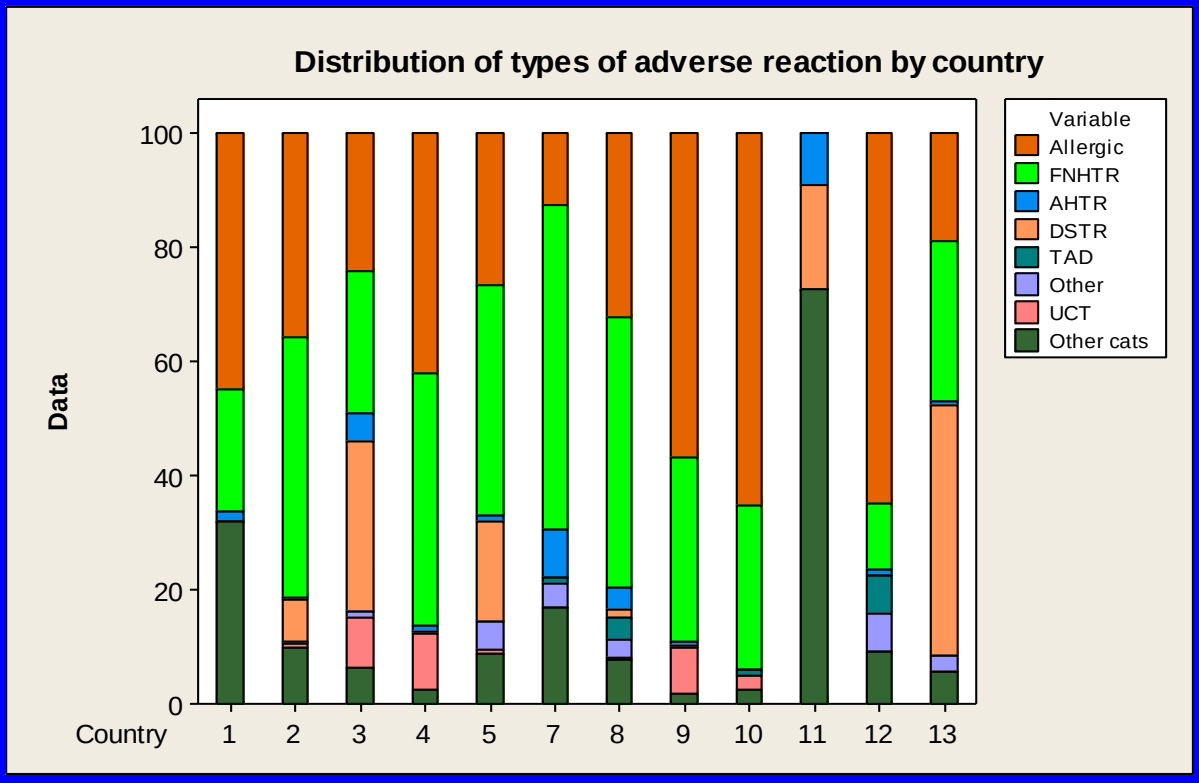
Surveillance of Total Adverse Reactions/ Events (STARE)
The International Haemovigilance Network Database
Pilot study: first results (2006-2007)

The Working Group

C. Politis, J. Jorgensen, C. Richardson,

P. Robillard, J. Wiersum

Data from 12 countries 2007
14,391,424 units issued



STARE pilot study, 2007

The risk of transfusion

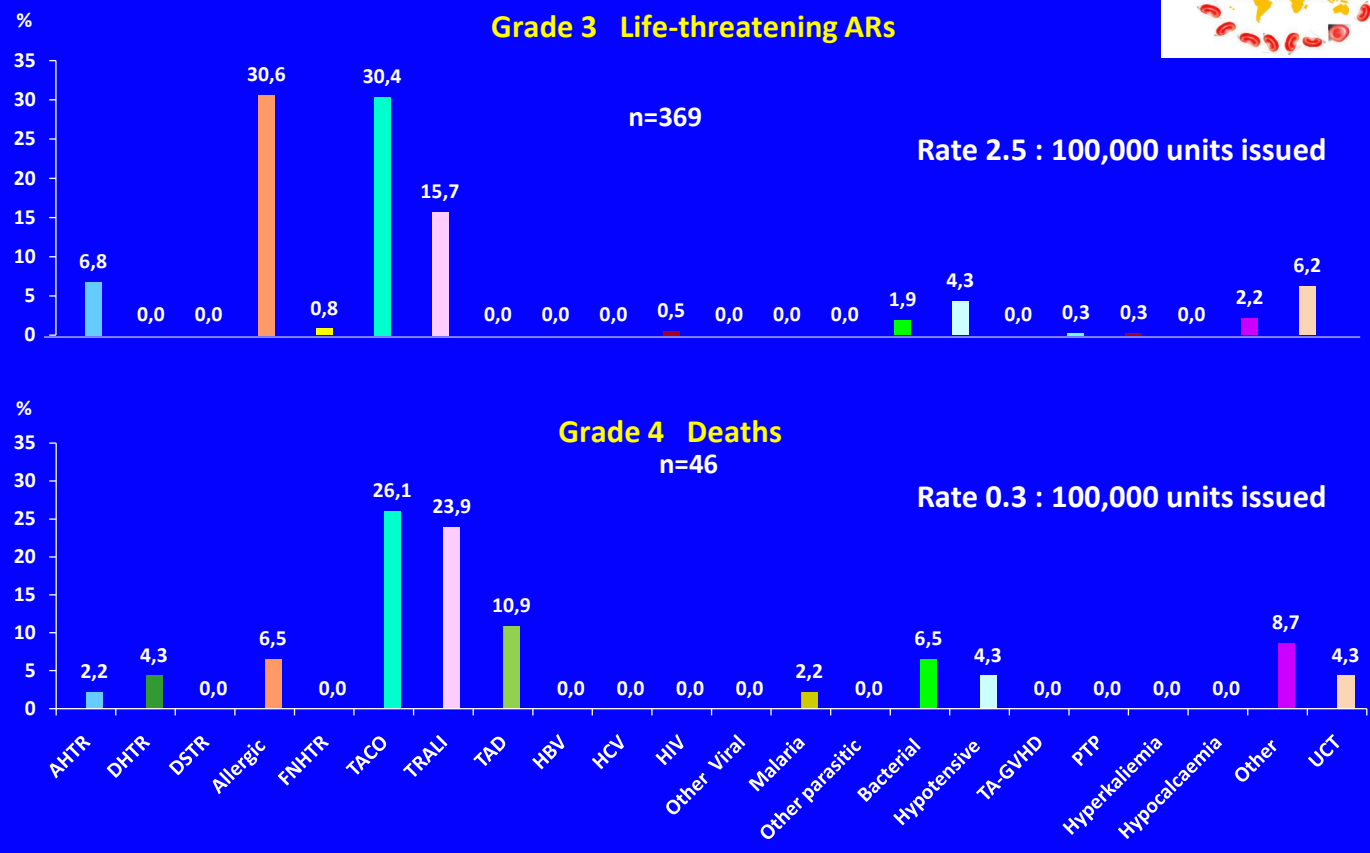
13,142 total ARs in patients per 14,391,424 units issued

(rate 91 : 100,000)

Analysis by severity (rates)

Grade 1	Non-severe	62: 100,000
Grade 2	Severe	18: 100,000
Grade 3	Life-threatening	2.5: 100,000
Grade 4	Deaths	0.3: 100,000

Rates vary among countries

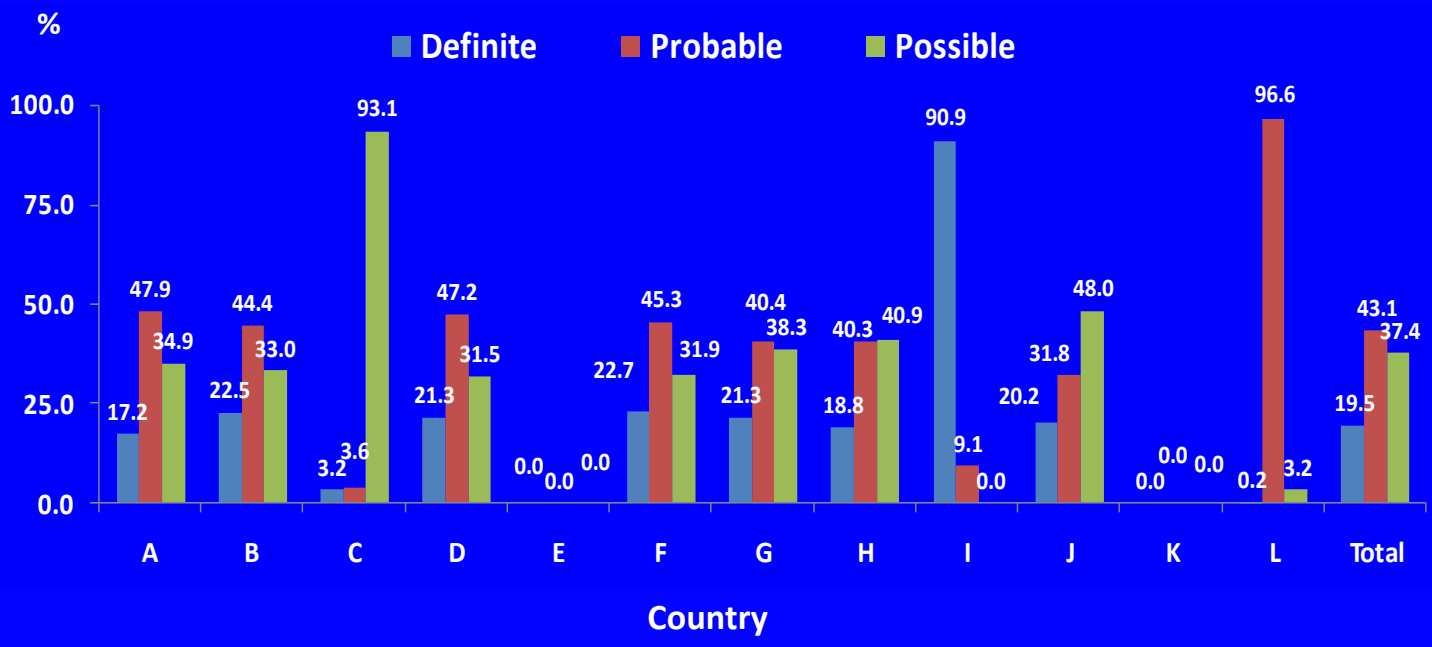


STARE pilot study, 2007
IBCT (n=172)

Data from 11 countries — **IBCT with reaction n=37 (21%)**

~~Site of primary error~~	~~%~~	
Blood unit (wrong label)	0	
Patient Sample	5.4	
Compatibility	5.4	
Transfusion		
Wrong patient	*0*	
Wrong label	*5.4*	*rate 0.25: 100,000 issued units*
ABO incompatibility	*83.6*	*rate 0.93: 100,000 issued units*

Imputability of adverse reactions by country - 2007



Conclusions

- Incidence of total ARs varies between countries
  - Reporting of ARs varies
  - Estimation of imputability varies
  - Transfusion practices vary
- Compliance to international definitions is not optimal
- There is a need to develop meaningful standardized definitions for adverse transfusion events (errors and near misses)

Hellas
Strategies for the optimal use of blood

Ministerial Res. 1132 / 2000, Law 3402/05

It is the responsibility of the Hospital Transfusion Committee to operate quality management system for optimal clinical blood usage and avoidance of ARs/AEs and to develop SOPs.

National protocols for safety/quality/inventory management be developed by the NBC Transfusion Committee

Currently

- National data on issued (but not used) components
- Haemovigilance - 85%; Traceability - 95%;
- TTIs surveillance - 100%
- Data on thallassaemia – 100%

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΜΕΤΑΓΓΙΣΙΟΘΕΡΑΠΕΙΑΣ

ΦΡΕΣΚΟ ΚΑΤΕΨΥΓΜΕΝΟ ΠΛΑΣΜΑ FFP (Fresh Frozen Plasma)

ΠΡΟΕΛΕΥΣΗ
Αποχωρίζεται από 1 μονάδα ολικού αίματος και συντηρείται στους -20˚έως -30 ˚C μέχρι ένα έτος, για την διατήρηση των ασταθών παραγόντων πήξεως V,VIII.

ΟΓΚΟΣ ΜΙΑΣ ΜΟΝΑΔΑΣ 150 - 300 ml

ΠΕΡΙΕΚΤΙΚΟΤΗΤΑ
Περιεκτικότητα ανά 200 ml:

Ινωδογόνο	400	mg	Citrate	4	mmol
Παράγοντας VIII	140	units	Lactate	1	mmol
Sodium	35	mmol	Hydrogenion	12	nmol
Glycose	4	mmol	Λευκωματίνη	7	gr
Potassium	1	mmol	Ph	7.2 - 7.4	

ΕΝΔΕΙΞΕΙΣ ΜΕΤΑΓΓΙΣΗΣ ΚΑΤΕΨΥΓΜΕΝΟΥ ΠΛΑΣΜΑΤΟΣ
Το FFP πρέπει να χρησιμοποιείται μόνον για την θεραπεία αιμορραγικών επεισοδίων και για την προετοιμασία ασθενών για εγχείρηση όταν υπάρχει γνωστή αιμορραγική διάθεση ή βρίσκονται υπό θεραπεία με κουμαρινικά αντιπηκτικά.

ΑΠΟΛΥΤΕΣ ΕΝΔΕΙΞΕΙΣ ΜΕΤΑΓΓΙΣΗΣ ΚΑΤΕΨΥΓΜΕΝΟΥ ΠΛΑΣΜΑΤΟΣ
1. Αντικατάσταση ενός παράγοντα πήξεως όταν δεν είναι διαθέσιμος σε συμπυκνωμένη μορφή.
2. Αιμορραγική διάθεση λόγω έλλειψης πολλών παραγόντων πήξεως.
3. Αιμορραγική διάθεση από κουμαρινικά (Warfarin) .
4. Θεραπεία Οξείας διάχυτης ενδαγγειακής πήξης .
5. Θεραπεία Θρομβωτικής θρομβοπενικής πορφύρας

ΜΕΤΑΓΓΙΣΗ ΚΑΤΕΨΥΓΜΕΝΟΥ ΠΛΑΣΜΑΤΟΣ ΚΑΤΑ ΠΕΡΙΠΤΩΣΗ
Πρέπει να συνυπάρχει αιμορραγία και διαταραχή της πήξης
1. Μαζική μετάγγιση. (Μετάγγιση 8-10 μονάδων Ερυθρών δεν προκαλεί συνήθως προβλήματα αιμόστασης εξ αραιώσεως.)
2. Ηπατική ανεπάρκεια με αιμορραγική διάθεση με INR >2 ή PT>1.5 φορές της φ.τ.
3. Εγχείρηση καρδιοαναπνευστικής παράκαμψης (εξωσωματική κυκλοφορία)

ΑΔΙΚΑΙΟΛΟΓΗΤΗ ΜΕΤΑΓΓΙΣΗ ΠΛΑΣΜΑΤΟΣ
1 Υποογκαιμία
2 Υπολευκωματιναιμία (όχι σε τιμές λευκωματίνης άνω των 2 gr/dl)
3 Έλλειψη ανοσοσφαιρινών
4 Ως παράγων παρεντερικής θρέψης

Στις περιπτώσεις αυτές προτείνονται ασφαλέστερες και πιο αποτελεσματικές εναλλακτικές θεραπείες όπως με κρυσταλλοειδή, κολλοειδή, λευκωματίνη, ενδοφλέβια ανοσοσφαιρίνη, παρεντερική διατροφή.

ΔΟΣΟΛΟΓΙΑ
10-20 ml/Kg Βάρους σώματος ανάλογα με την κλινική κατάσταση και τα αποτελέσματα του PT και PTT . Σε αιμορραγία από υπερβολική δόση Warfarin χορηγούμε 5-8ml /Kg Β.Σ.

ΤΡΟΠΟΣ ΧΟΡΗΓΗΣΗΣ
Χορηγείται με απλή συσκευή μετάγγισης, σε ρυθμό που επιτρέπει η κλινική κατάσταση του ασθενούς, ποτέ όμως σε χρόνο μεγαλύτερο από 4 ώρες.

ΚΙΝΔΥΝΟΙ ΑΠΟ ΤΗΝ ΜΕΤΑΓΓΙΣΗ ΠΛΑΣΜΑΤΟΣ
1. Μετάδοση ιογενών λοιμώξεων όπως HIV, HBV, HCV, HTLV κ.λ.π.
2. Υπερφόρτωση κυκλοφορίας
3. Σοβαρές αναφυλακτικές αντιδράσεις
4. Αιμολυτική αντίδραση από αντισώματα του δότη έναντι ερυθρών του λήπτη.

ΑΚΑΤΑΛΛΗΛΟ ΓΙΑ ΜΕΤΑΓΓΙΣΗ ΠΛΑΣΜΑ
1. Περιεχόμενο ασκού θολό , αιματηρό, χολερυθρινικό.
2. Παραμονή εκτός ψυγείου περισσότερο από 4 ώρες.

ΣΥΜΒΑΤΟΤΗΤΑ
Δεν χρειάζεται διασταύρωση . Χορηγείται πλάσμα ομάδας συμβατής ως προς τα αντισώματα αντι-Α και αντι-Β, σύμφωνα με τον πίνακα. Η Συμβατότητα ως προς το σύστημα Rhesus πρέπει να λαμβάνεται υπ΄όψιν σε Rhesus αρνητικές νεαρές γυναίκες.

ΟΜΑΔΑ ΑΣΘΕΝΟΥΣ	ΟΜΑΔΑ ΠΛΑΣΜΑΤΟΣ ΤΟΥ ΑΣΚΟΥ ΠΟΥ ΜΕΤΑΓΓΙΖΟΥΜΕ
O	O ή A ή B ή AB
A	A ή AB
B	B ή AB
AB	AB

Η ΧΟΡΗΓΗΣΗ ΜΗ ΚΑΤΕΨΥΓΜΕΝΟΥ ΠΛΑΣΜΑΤΟΣ (ΚΟΙΝΟΥ ΠΛΑΣΜΑΤΟΣ) ΔΕΝ ΕΧΕΙ ΚΑΜΜΙΑ ΕΝΔΕΙΞΗ

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΜΕΤΑΓΓΙΣΙΟΘΕΡΑΠΕΙΑΣ

Guidelines for the use of FFP, 1999

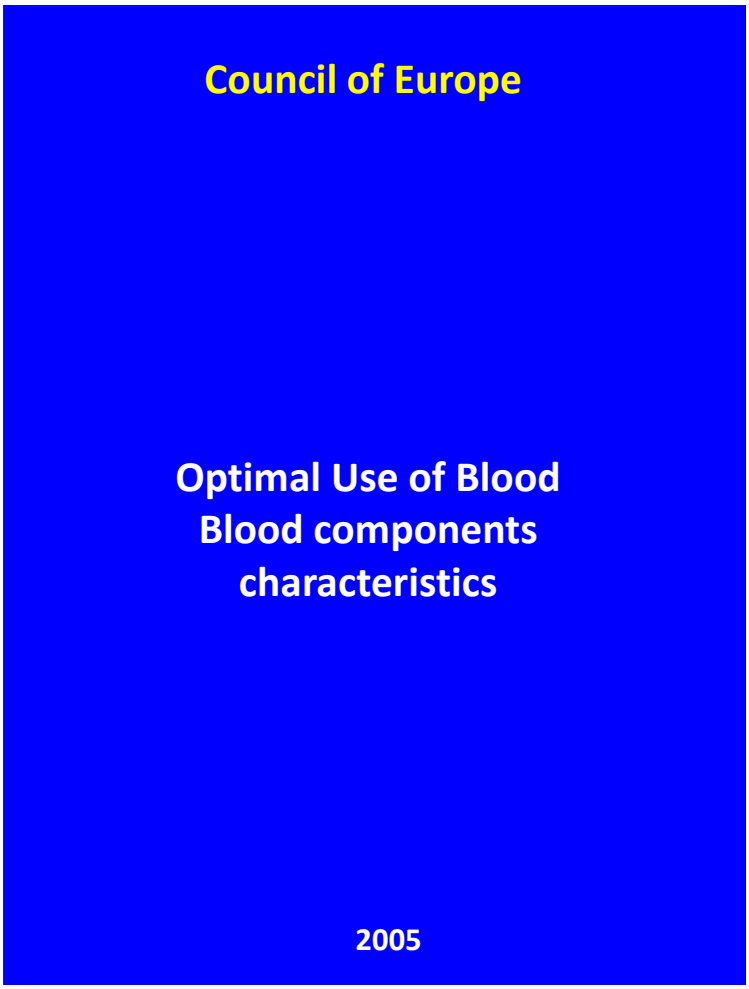
- Production-Properties
- Recommendations-definite indications
- Conditional uses-Special indications
- Inappropriate use (no justification)
- Dosage-application
- Side effects
- Compatibility
- Common plasma is not indicated

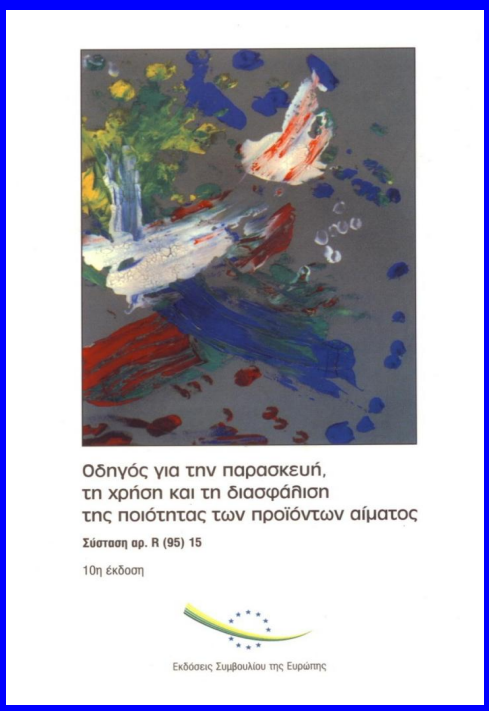
Hellenic Blood Transfusion Society

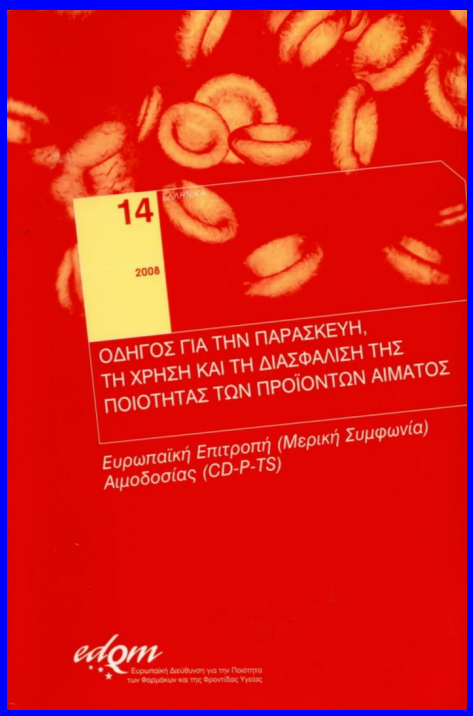
Guidelines for safe blood transfusion, 2003-2005

-Ordering blood products
-Sampling of blood and patient' s ID
-Transfer of blood sample in the blood bank
-Transfer of cross matched blood bag from the blood bank to the clinic
-Safety measures prior to transfusion
-The procedure of transfusion management of an adverse reaction
-Empty blood bags return in the blood bank irrespectively of outcome of transfusion
- The role of the hospital transfusion committee is underlined

SKAE





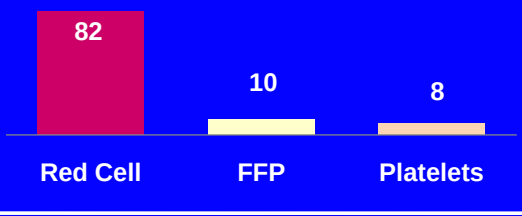


Hellas

Issued blood components per ‰ inhabitants

Component	2003	2004	2005	2006	2007	Trend	2007/bed
RBCs	56.6	59.3	57.5	59	55	Stable	9.3
FFP	14.7	22.4	21	32	29	+3.82	4.8
RBC/FFP	*3.8*	*2.6*	*2.7*	*1.8*	*1.9*	*-0.46*	*1.9*
WB-Pts	11	13.7	12.5	12.3	12.8	Stable	2.2
Aph-Pts	1.7	2.2	2.4	2.8	1.7	Stable	0.28

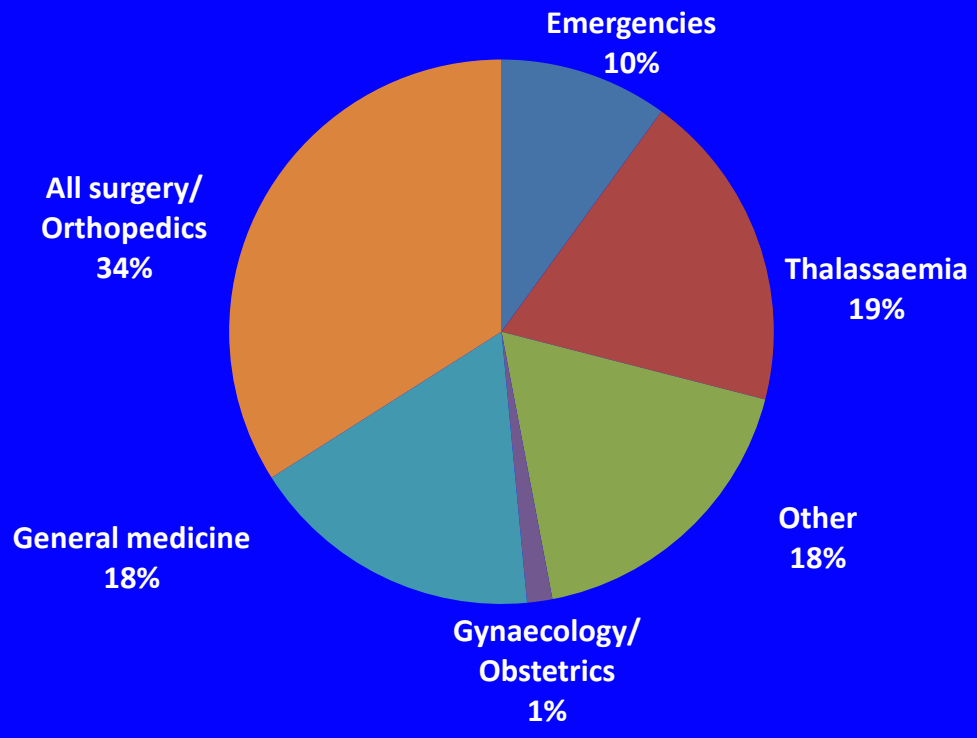
Total ARs (%)



Rate of ARs per 100,000 issued components

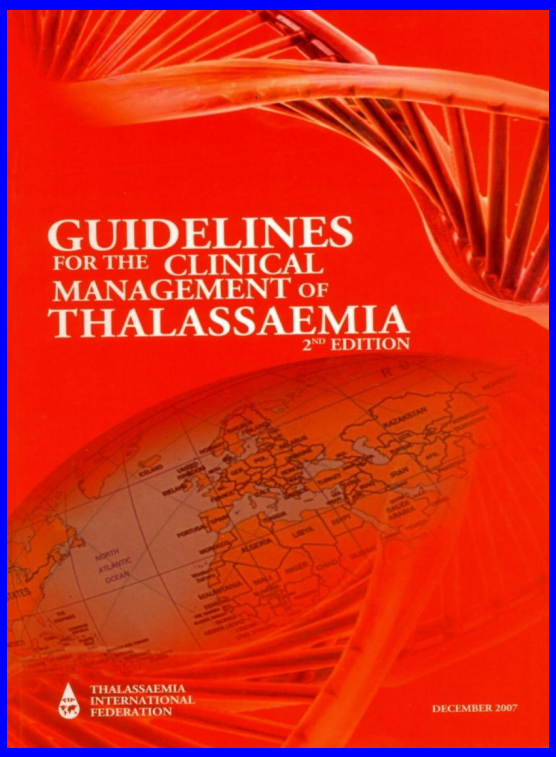
	2003	2004	2005	2006	2007	Trend
Total	117	96.6	91	123.5	116.5	2.6
Serious	5.6	6.5	4.3	8.5	7	0.5

Issued blood components for patients with index conditions, 1997-2007



SKAE

The global approach



Transfusion

- Acquisition and preparation of safe blood
- Standardized protocol for transfusion
- Genotyping the patients blood group
- Prevention of transmission of infectious diseases
- and other transfusion associated complications

Iron chelation and other therapies

Continuous education

Psychological support

Management protocol

What to transfuse

Red cell concentrates, one week fresh (one week old if stored in CDPA-1 and two weeks old if in additive solutions) leukodepleted, plasma protein free, phenotyped and compatible with matched donor blood for 3 or more red cell antigenic systems
(Irradiated and HLA typed when appropriate)

TIF, 2007

Transfusion treatment

Indices for evaluation	Optimal values
Pre-transfusion Hb	Not below 9.5 g/dl
Target increase Hb	Not above 15.0 g/dl
Mean Hb	Varies with regimen≅12
Mean rate of Hb fall	1% of post-transfusion Hb/day
Transfusion efficacy	Not below 67%
Apparent blood volume	Not above 1.5 x normal
Red cell consumption	Not above 250 ml/kg/year (ideally 180 mL)
Transfusion interval	Varies with centre
Date for next transfusion	

A Short Guide to the Management of Thalassaemia, WHO working group and TIF 2007

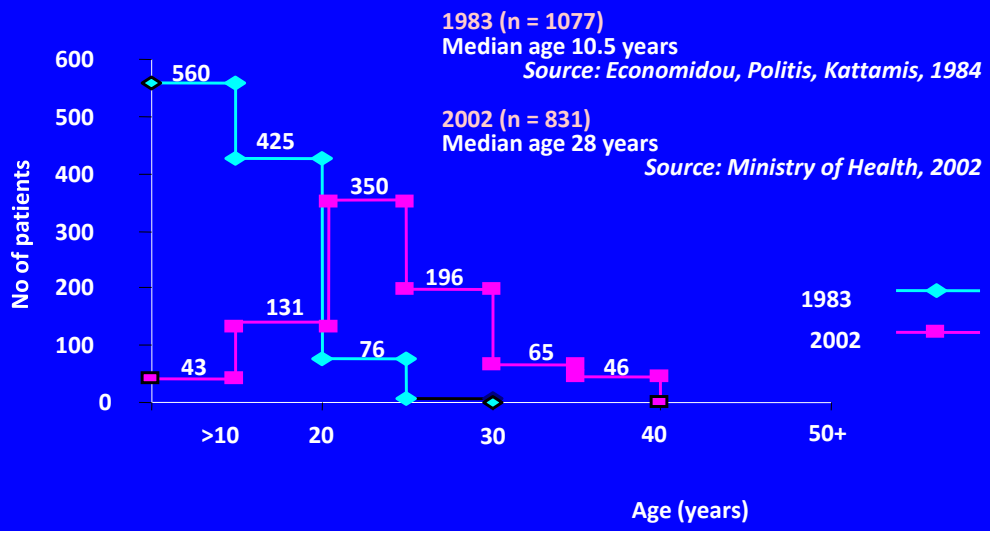
Hellas
Efficacy of transfusion in thalassaemia

- Patient's survival
- Social integration
- High quality of life

2002

Patients	2786
Mean pre-transfusion Hb	9.5 g/dl
Mean blood consumption	9635 ml/year

Mean transfusion interval (days): 18 (range 9-32)



Cost-effectiveness of transfusion in thalassaemia, 2005

The impact on BTS

- Specialized staff
- Increased resources (reagents, materials, work hours)
- Management of seasonal shortages of blood, allo/auto-immunization, rare blood groups
- Haemovigilance, treatment of adverse reactions
- Continuous education

Cost of transfusion vs chelation per year in 2,850 patients

One unit of RCCs	340 €
(phenotyped, leukodepleted, NAT tested)	
Total	40,120,000 €

Cost of iron chelation therapy

Total	16,000,000 €

Optimising blood use in CV surgery

The Onasseion 15-years study in children and adults

Perioperative algorithm

- Treatment of concomitant anaemia / thrombocytopemia
- Haematological / haemostatic vigilance
- Screening for irregular antibodies
- Strict transfusion criteria, use of SDPs, cell-savers
- Improving anaesthetic/ surgical techniques
- Heparin "antidotes", rFVIIa, cryo, fibrinogen, fibrinolysis inhibitors

Results

1st – 2nd period	Blood Use decreased
2nd - 3rd period	Increasing blood requirements

Attributing factors: advanced age, surgical procedure/ type / complexity, "redo" operations and heart transplantations after VAD – application

E. Melissari et al, ESCVS, 2008

Economic Aspects

Tetradrachm
404 BC

One euro
2002 AC

Manufacturing direct costs incurred in two Blood Centres

Cost of one blood unit in € : analysis per Item, 2004

Capital costs are not included

Item	Crete		Athens	
Personnel*	49.10	22	39.90	14
Medical	19.64		17.12	
Nursing	13.75		12.77	
Technicians	10.31		8.63	
Other	5.40	%	1.37	%
Reagents	132.80	65	179.10	72
Materials	26.80	13	34.70	14
Total cost	208.70	100	253.70	100

* Includes blood collection, processing, testing, maintenance and storage

Politis et al. Delphi, 2005

Kanavos, Yfantopoulos, Vandoros, Politis Int J. Tech.Ass. Health Care 22:3 (2006)

Total cost per blood unit (year 2004)
Vein to vein

Activity Based Costing	Crete (basic costs)	Athens (basic + additional costs)
Recruitment (advertising)	1.16	1.16
Collection	9.88	9.88
Processing and testing	208.70	253.70*
Maintenance	0.11	0.11
Transportation	1.46	1.46
Indirect cost	42.10	42.10
Total	263.41	308.41
Compatibility and transfusion materials	33	33
Gross total	296.40	347.60

* Includes leukodepletion and NAT testing (HCV-RNA/ HIV-RNA/ HBV-DNA), MB-FFP

The price of blood in Europe

Country	Central pricing?	Price for blood products?	Price per blood unit €
France	Yes	Yes	168
Romania	No	Yes	11 notional (from 1999)
Greece	No	No	220 real cost*
Portugal	Yes	Yes	112
Bosnia Herzegovina	No	Yes	0.30 per ml
Moldova	Yes	Yes	?
FYROM	No	Yes	22-51; real cost 63

* €226 with additional processing and testing (NAT etc)

Council of Europe study: The economics of blood, Delphi, Hellas 2005

Lifetime cost of transfusion related illnesses

Illness	Source	Country	Risk/10^6	Cost
• HIV/AIDS	Gold 1996	Canada	1	$87,290
• Hepatitis B	Dusheiko 1995	UK	16	$19,141
• Hepatitis C	Dusheiko 1995	UK	10	$15,621
• Fatal hemolytic Reaction	Sonnenberg 1996	USA	1.67	$36,936
• Non-fatal hemolytic reaction	Sonnenberg 1996	USA	52.6	$136
• Febrile reaction	Gibis 1997	Canada	1/100	$90
• Iron chelation in thalassaemia	Politis 2005	Hellas	100%	€ 16 millions per year

Conclusions

- The price of blood should correspond to associated manufacturing cost
- In Hellas and elsewhere the cost of blood is very high
- Reagents represent the highest cost followed by labour
- There is a need to control costs and restrain expenditures in conjunction with guarantees of sufficiency and quality.

Future plans

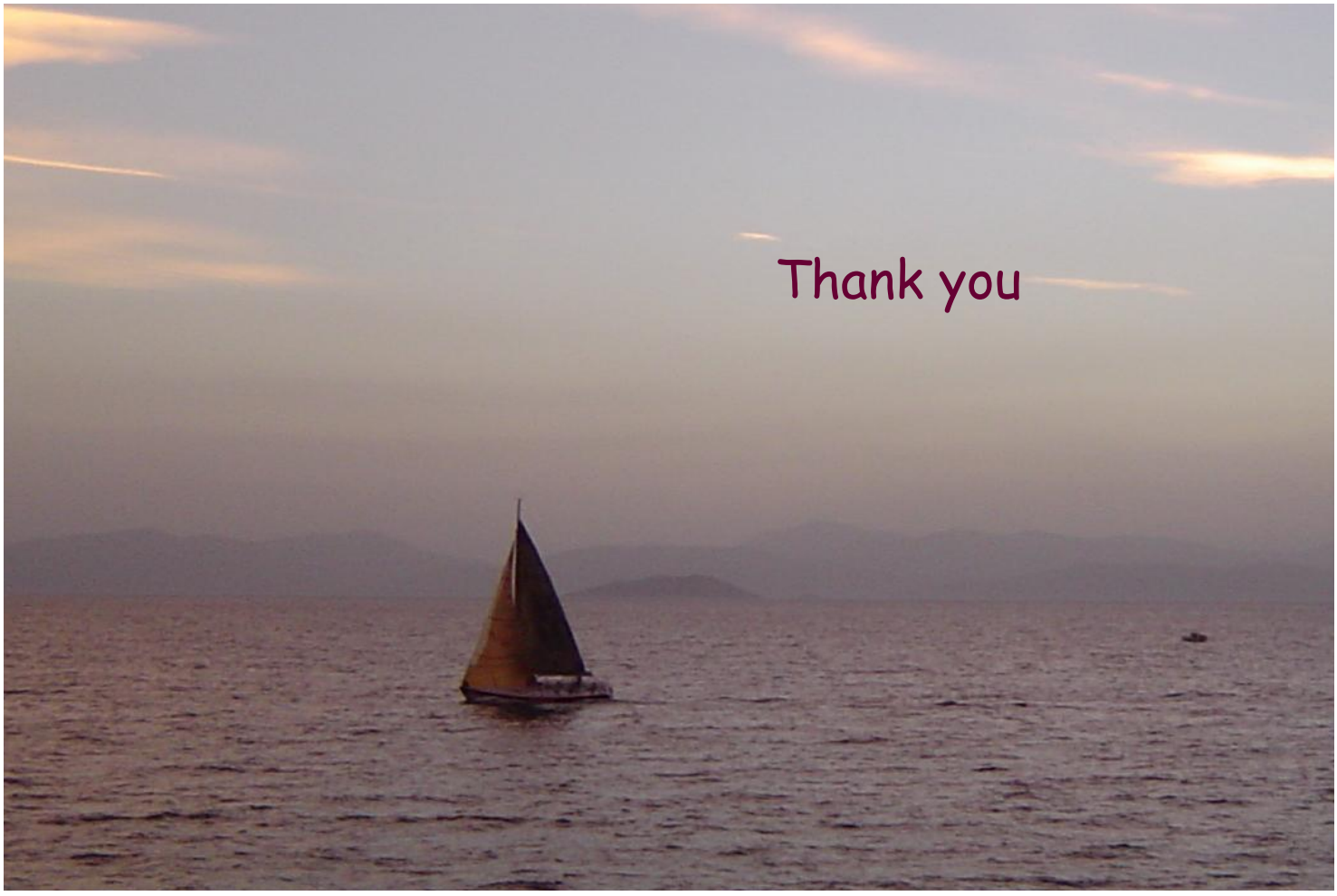
Estimating non-manufacturing costs

Haemovigilance

Traceability

Look back procedures

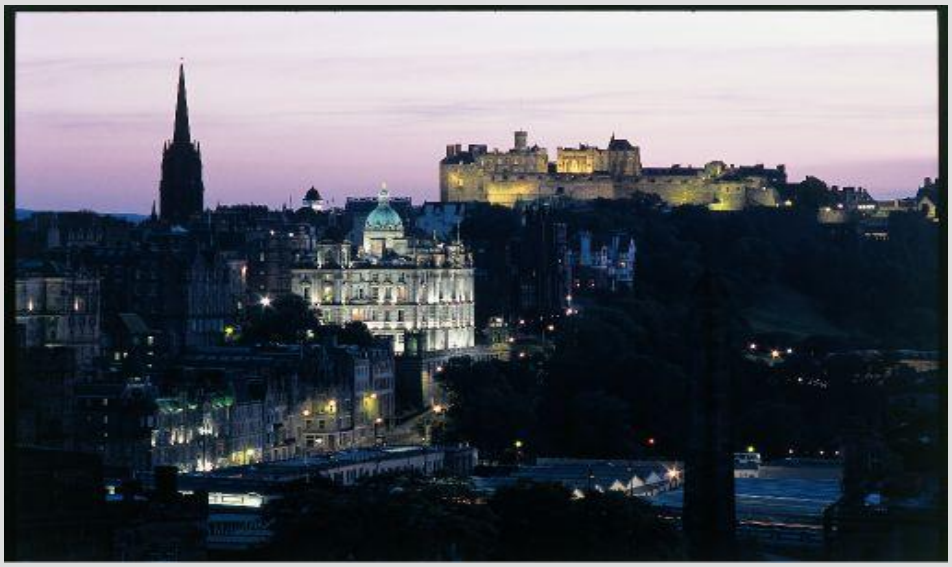
Other



HTA – Clinical and cost effectiveness of thromboelastography / thromboelastometry

Alastair Nimmo

HTA - Clinical and cost effectiveness of thromboelastography / thromboelastometry



Dr Alastair Nimmo
Dept of Anaesthesia, Critical Care & Pain Medicine
Royal Infirmary of Edinburgh, Scotland

www.nhshealthquality.org

Royal Infirmary of Edinburgh

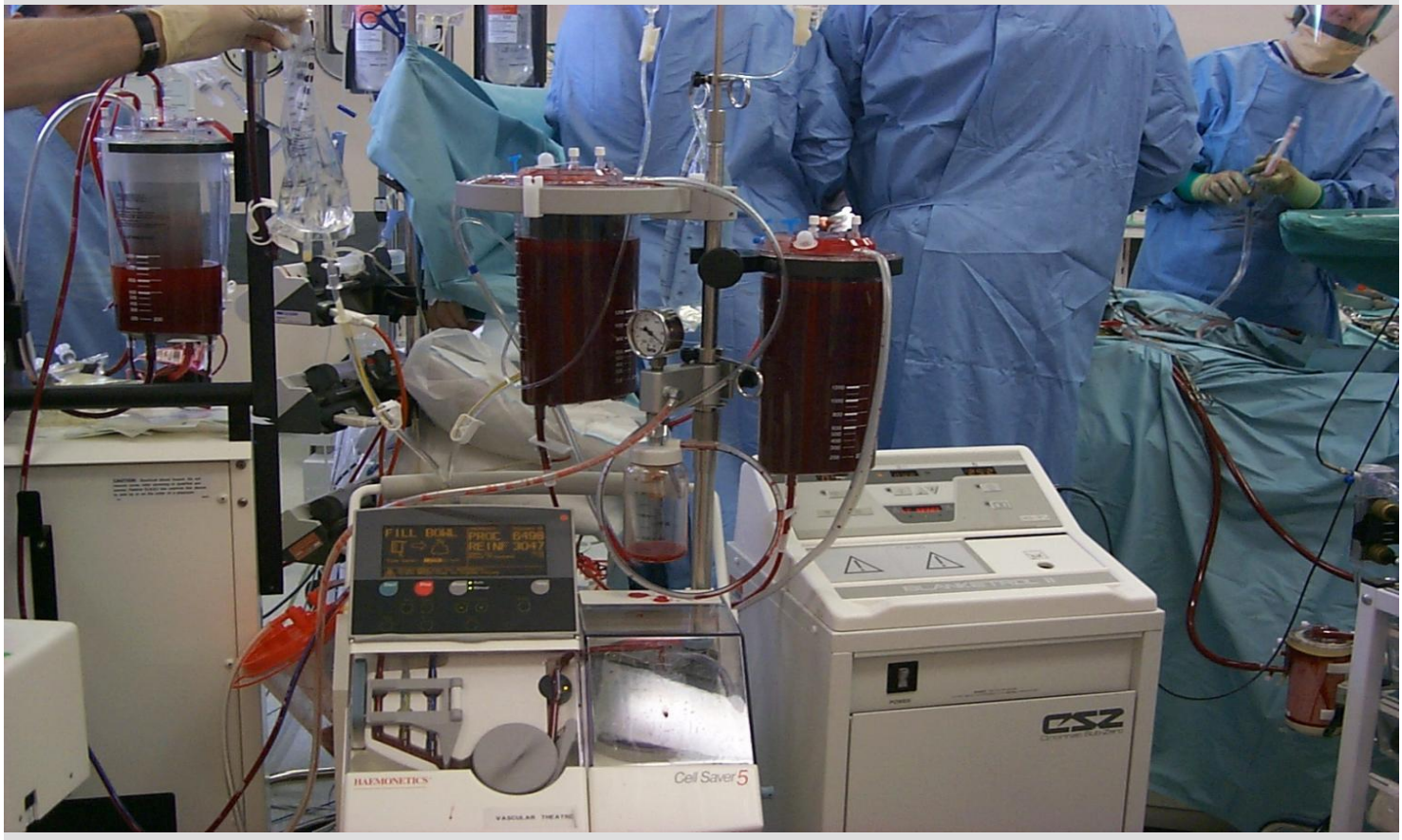
900 adult beds

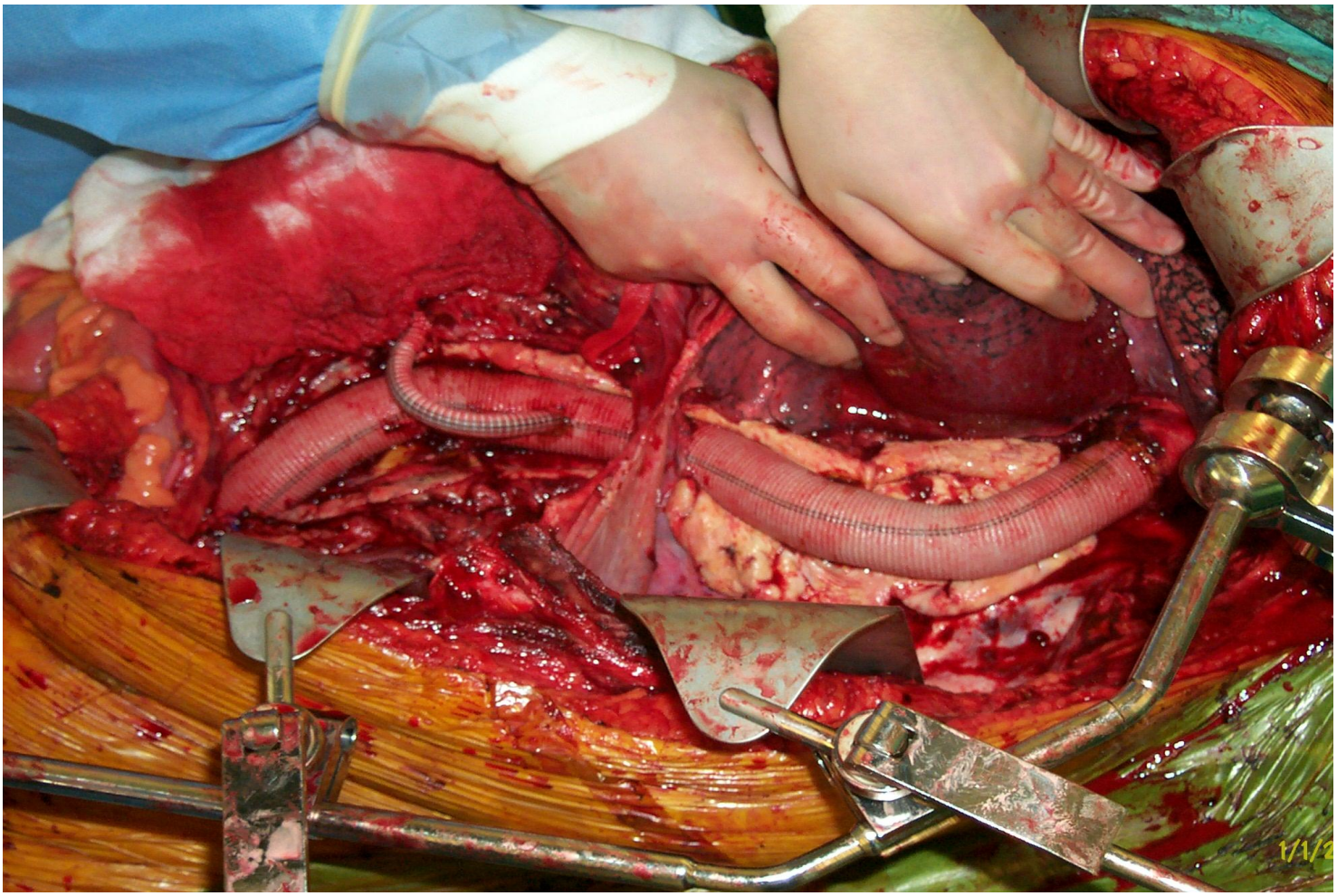
Scottish centre for

- thoraco-abdominal aortic aneurysm surgery
- liver and pancreas transplants

Regional centre for

- vascular surgery
- hepatobiliary surgery; renal transplants
- major trauma
- cardiac & thoracic surgery





HTA on thromboelastography / thromboelastometry

- Background
- Aim of the HTA
- Methods
- Conclusions
- Recommendations
- Implementation

Thromboelastography / thromboelastometry

- “viscoelastic” test of whole blood coagulation
- usually a point-of-care test → rapid results
- provides information on onset of coagulation, development of clot strength, maximum clot strength and clot lysis
- permits rapid identification / quantification of: - thrombocytopenia / (platelet dysfunction) - low fibrinogen / impaired fibrin polymerisation - low coagulation factor levels - heparin effect

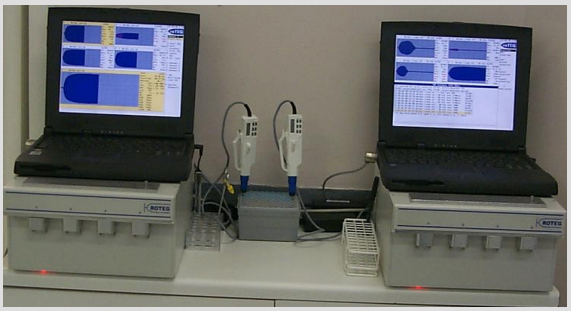
Thromboelastography / thromboelastometry

- “viscoelastic” test of whole blood coagulation
- usually a point-of-care test → rapid results
- provides information on onset of coagulation, development of clot strength, maximum clot strength and clot lysis
- permits rapid identification / quantification of: - thrombocytopenia / (platelet dysfunction) - low fibrinogen / impaired fibrin polymerisation - low coagulation factor levels - heparin effect

Thromboelastography / thromboelastometry

- Two analysers based on the same principle from two different companies

TEG® Haemoscope, Niles, Illinois, USA

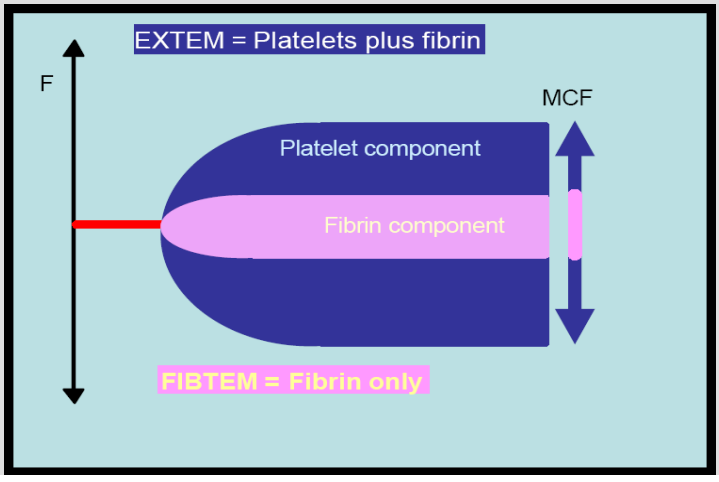


ROTEM® Pentapharm, Munich, Germany

Thromboelastography / thromboelastometry

- Different tests are performed by adding different reagents to the blood sample e.g. heparinase to reverse the effect of heparin

An inhibitor of platelet aggregation is added to permit a low fibrinogen level to be distinguished from thrombocytopenia (FIBTEM or Functional Fibrinogen test).



Aim

To report on “the clinical and cost effectiveness of using thromboelastography and thromboelastometry analysers (both abbreviated to TE hereafter) compared with standard laboratory tests/assays (SLTs) and clinical discretion (CD) alone, to improve the diagnosis and subsequent management of **patients experiencing unexplained blood loss during or after surgery.”**

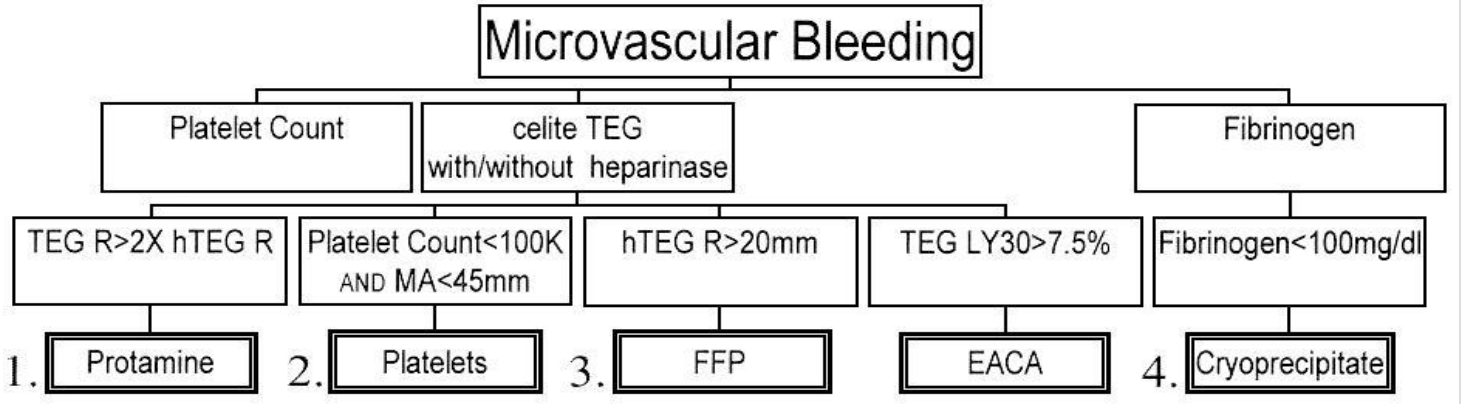
Methods

- A **Systematic Review** of the literature considered the clinical benefits of TE
- An **Economic Model** of the cost effectiveness of TE in cardiac surgery and liver transplant surgery was developed by the York Health Economics Consortium
- A **Budget Impact Analysis** of applicability of the research findings to NHS Scotland
- **Sensitivity Analysis –** different assumptions
- **Expert advisory group / expert reviewers / consultation report**

Clinical effectiveness - cardiac

RCT - Complex cardiac surgery

Shore-Lesserson L. Anesth Analg 1999; 88:312-319



	FFP	Platelets
SLTs	31%	29 %
TE and SLTs	8 %	13 %

Clinical effectiveness - cardiac

RCT – cardiac surgery, mostly complex

Royston D. British Journal of Anaesthesia 2001; 86:575-8

Heparinase TEG® test only.

No attempt made to distinguish between reduce amplitude of trace caused by low fibrinogen and reduced amplitude caused by thrombocytopenia

	FFP or platelets
Standard management	33 %
TE	17 %

Clinical effectiveness - cardiac

Study with historical controls

Anderson L. Transfus Med 2006; 16:31-9

ROTEM® tests including FIBTEM®.1000 patients

Blood product use recorded for 6 months before introduction of TE and 6 months after.

No change in staff or Hb transfusion triggers. Increased complex surgery in the second period.

	Red cells	FFP	Platelets
Before TE	60 %	17 %	16 %
TE	53 %	12 %	11 %

These figures were used in the cost effectiveness analysis

Cost effectiveness - cardiac

Economic model

Increased cost of testing with TE

Decreased cost of blood components

Assumed cost of testing per patient

SLTs	TE
£20	£77
€25	€87

Assumed cost of blood components

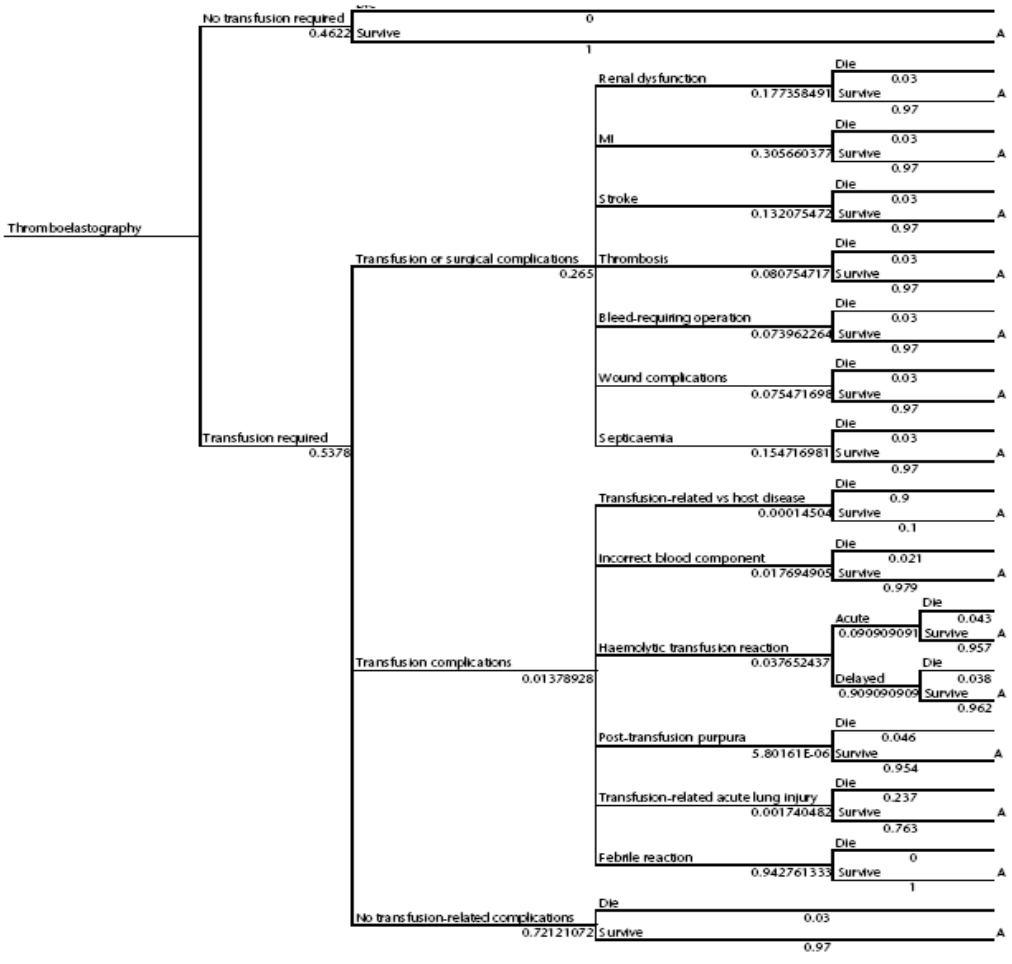
Red cells	FFP	Platelets
£122	£31	£202
€137	€35	€227

Cost effectiveness - cardiac

Economic model

Cost of increased complications in transfused patients over 1 month / 1 year after surgery.

- transfusion-transmitted infections
  rare
- transfusion complications e.g.
  incorrect blood component, TRALI
  uncommon
- transfusion-associated increased mortality and morbidity e.g. postoperative infection ?



Cost effectiveness - cardiac

Table 5-5 Total costs per patient (2005/2006 prices) at 1 month and at 1 year by cost category in cardiac surgery

Cost category	Cost for TE	Cost for SLTs	Incremental cost*
Costs of tests performed	£76.83	£20.00	£56.83
Pre-operative costs of transfusion	£11.55	£12.93	-£1.38
Peri-operative costs of transfusion	£3.33	£3.73	-£0.40
Blood products transfused	£91.40	£163.81	-£72.41
Costs of hospitalisation non-related to complications	£664.32	£743.56	-£79.24
Costs of hospitalisation related to complications/infections at 1 month	£211.37	£240.36	-£28.99
Costs of healthcare related to complications/infections between months 1 to 12	£125.06	£140.12	-£15.06
Total			
Costs at 1 month	£1,058.80	£1,184.40	-£125.60
Costs at 1 year	£1,183.86	£1,324.52	-£140.66

* Cost of TE minus cost of SLTs

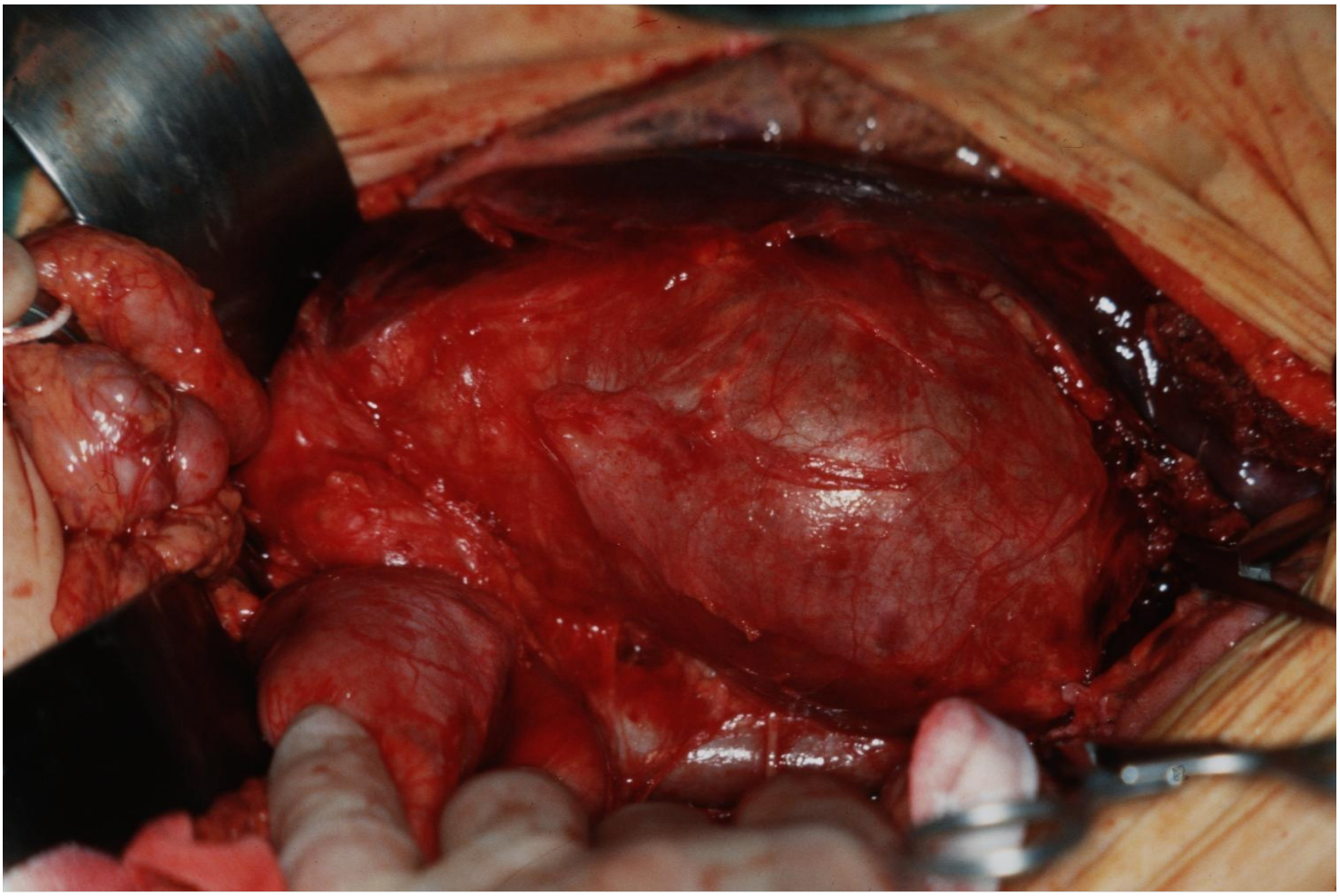
Recommendations & implementation

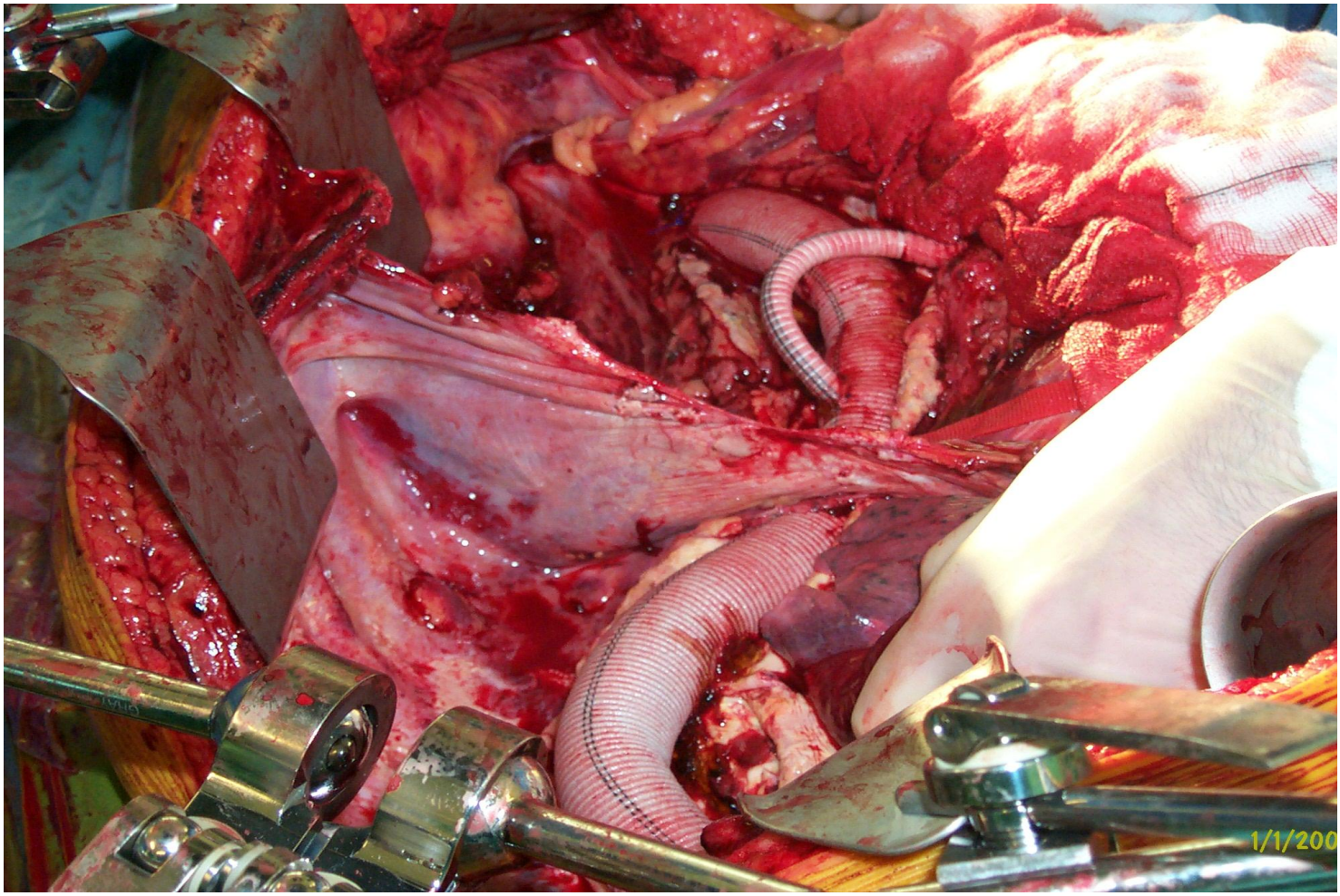
1. *The use of TE is recommended in cardiac and liver transplant surgery.*

Most cardiac and liver transplant units in the UK were already using TE. TE analysers have been purchased by several cardiac units since the report was published.

Recommendations & implementation

2. *There is no published robust, controlled clinical data to support the use of TE in other major surgery associated with a high blood loss.*





Recommendations & implementation

2. *There is no published robust, controlled clinical data to support the use of TE in other major surgery associated with a high blood loss. However... Observational evidence supports using TE in such surgical areas.*

   Increasing use of TE in major vascular surgery, trauma, obstetric haemorrhage.

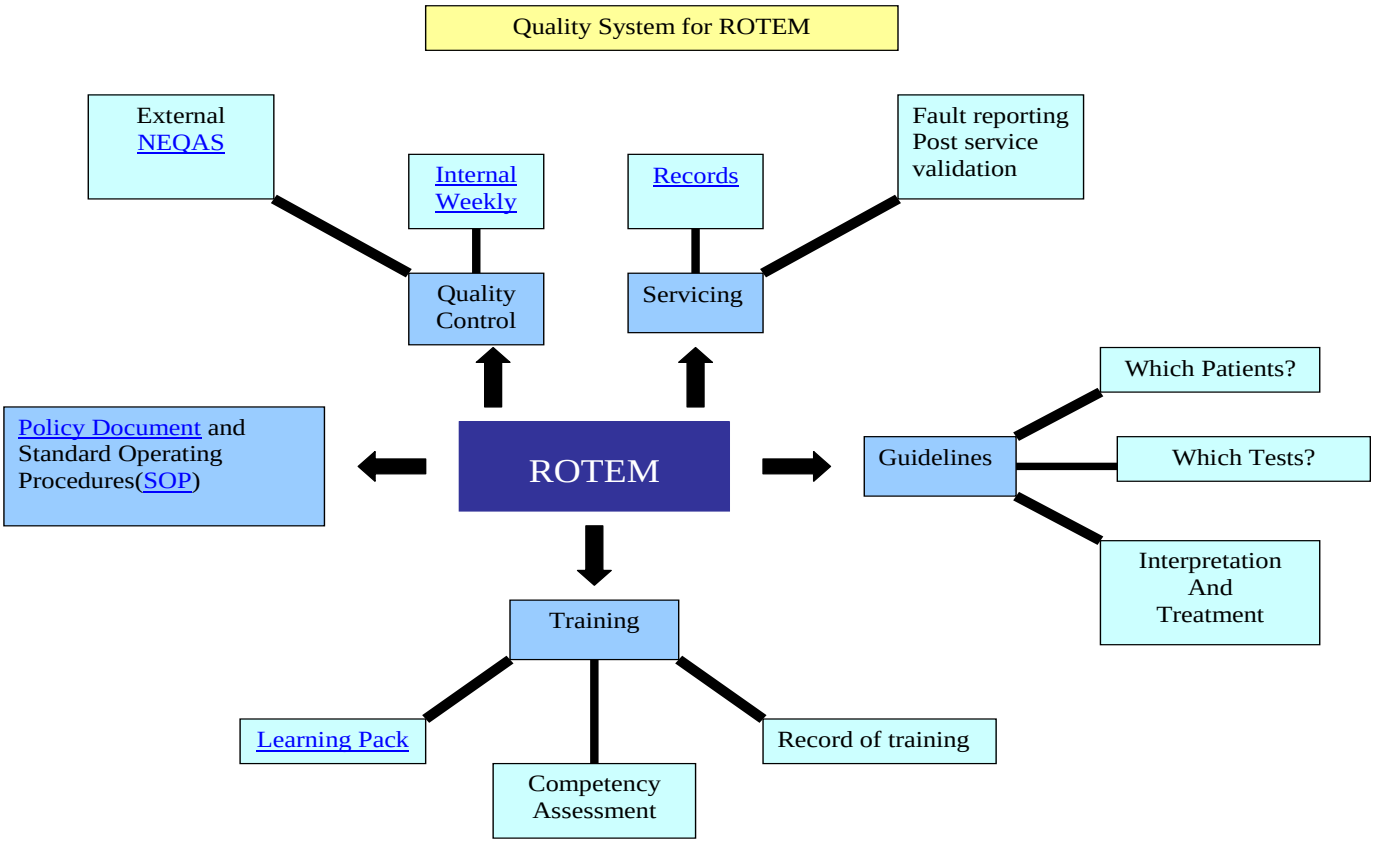
Recommendations & implementation

3. *Research data from controlled studies would be beneficial to strengthen the evidence base in surgery other than cardiac and liver but it is recognised that such studies may be difficult to conduct because of the emergency nature of many of the interventions and the small patient numbers.*

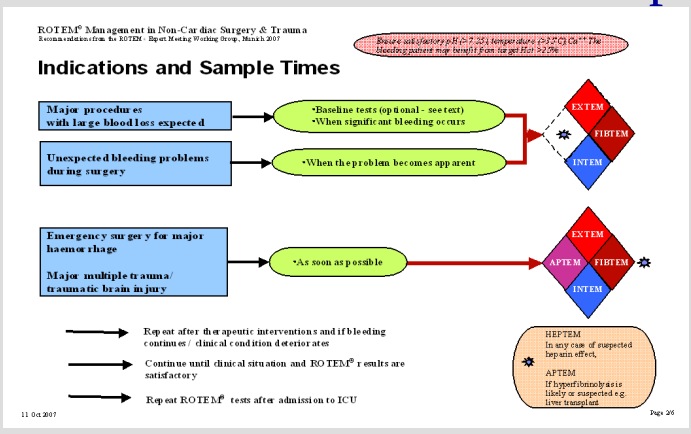
Recommendations & implementation

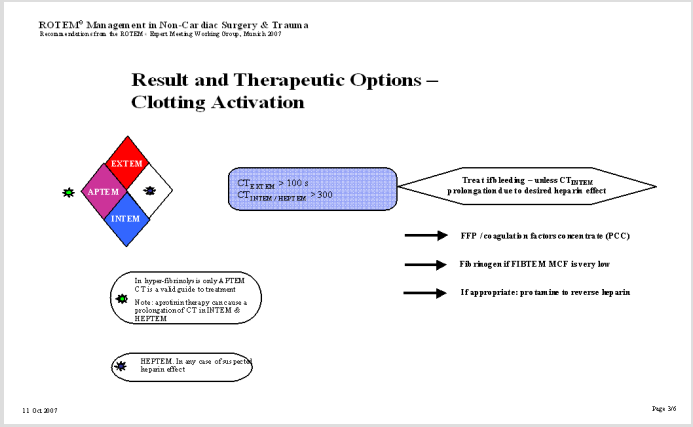
Six other recommendations including the need for training, quality control, protocols

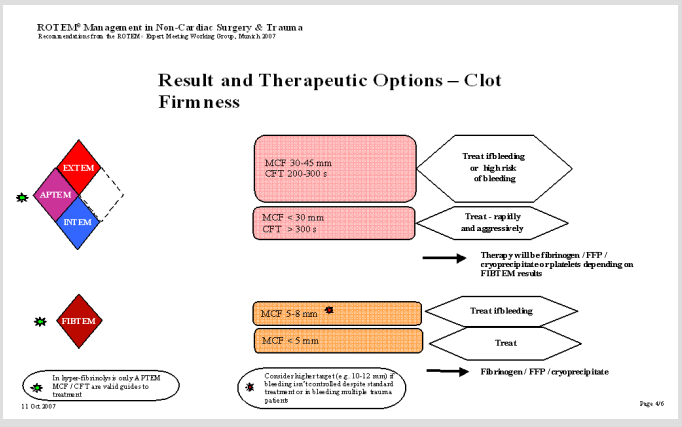
www.nhshealthquality.org

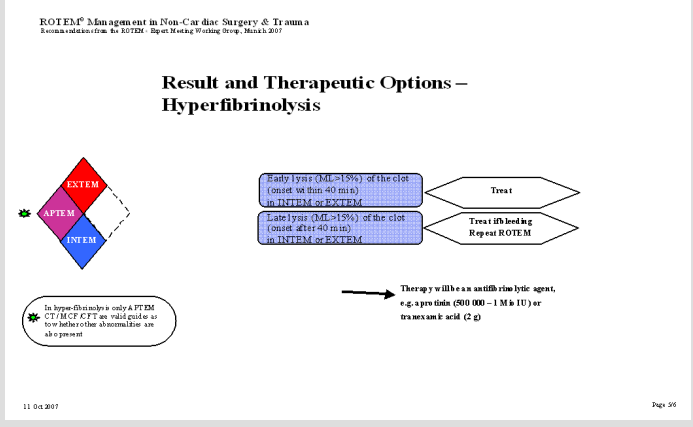


Guidelines on interpretation & treatment

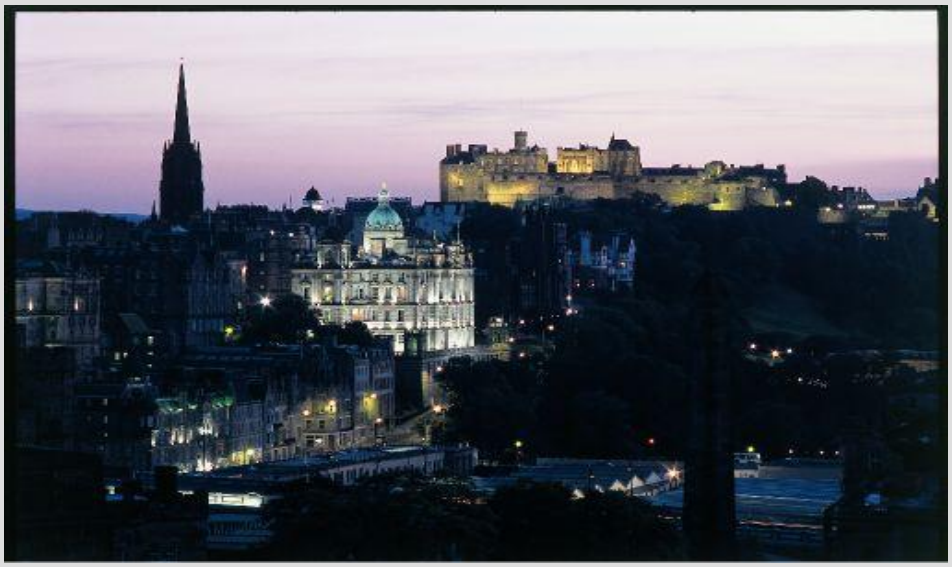








Clinical and cost effectiveness of thromboelastography / thromboelastometry



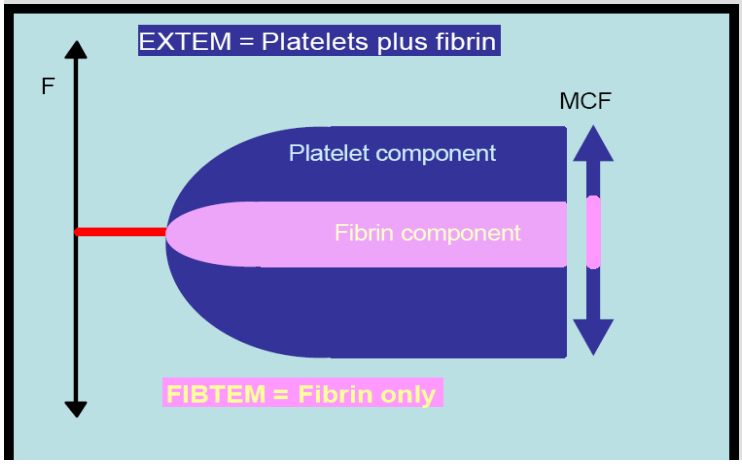
Dr Alastair Nimmo
Dept of Anaesthesia, Critical Care & Pain Medicine
Royal Infirmary of Edinburgh, Scotland

Implications for guidelines on blood component administration in surgery / trauma

- Many bleeding patients in the operating theatre are managed using TE results without standard laboratory tests.
- In this situation guidelines based on the results of SLTs e.g. platelet count, fibrinogen level are not useful
- Guidelines / protocols specific to TEG or ROTEM are required in this situation

Implications for guidelines on blood component administration in surgery / trauma

- Comparison of TE results with the clinical situation in the operating theatre suggest that it is not the platelet count or fibrinogen level alone that predict bleeding but the combination of the two.



Guidelines on the administration of blood components to bleeding patients which use the result of an SLT e.g. platelet count in isolation may be inappropriate

Clotting factor concentrates Haemophilia

Giovanni Minno

Inhibitors: the key problem of treatment in hemophilia

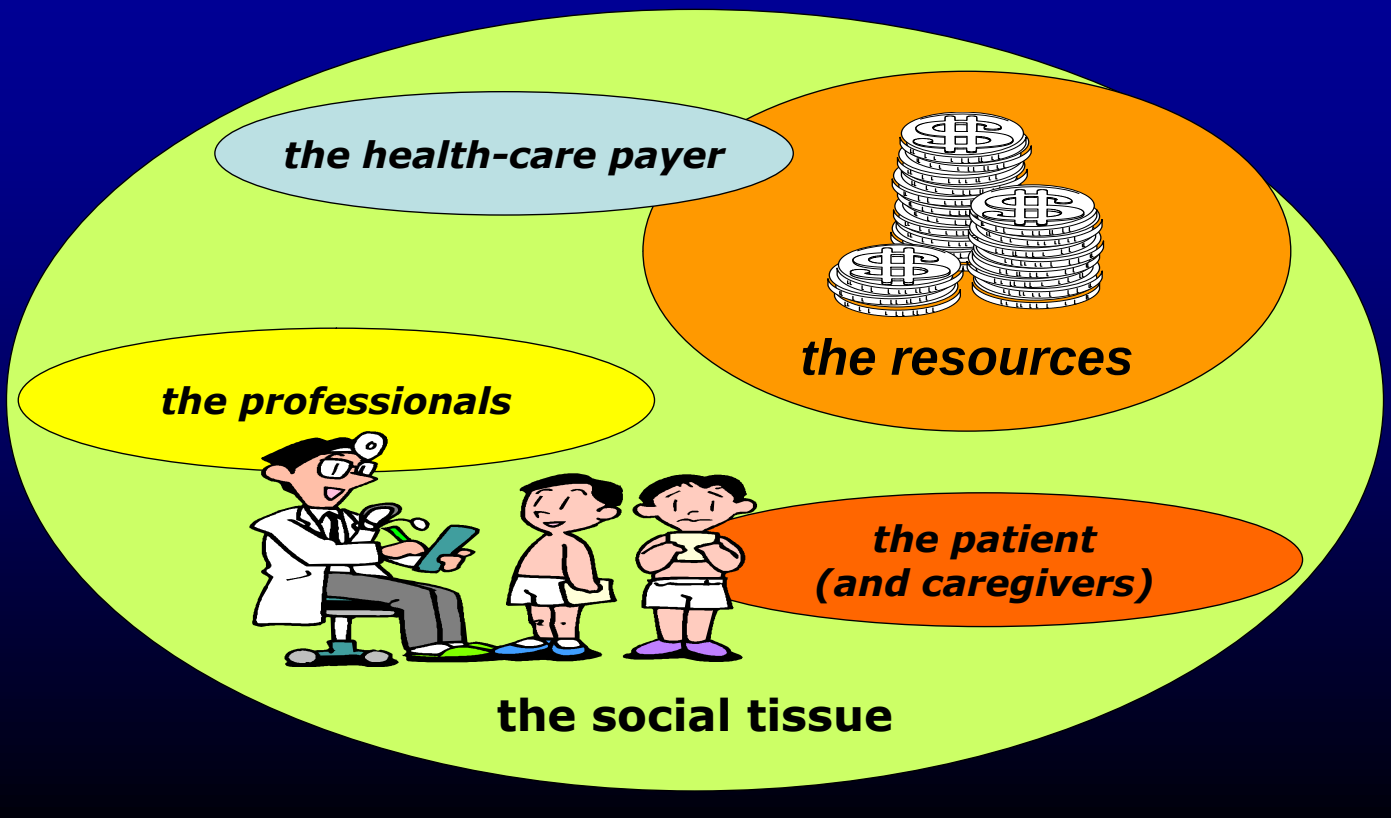
- *Given treatment products that are virtually free of transfusion-transmitted disease and the more widespread use of prophylaxis to prevent arthropathy, the development of an inhibitor in patients with severe hemophilia A remains the most significant debilitating therapeutic complication in the developed world.*

  D. Di Michele, Textbook of Hemophilia, 2005

- *"In the third millennium inhibitor development is the most challenging complication of hemophilia treatment and the highest economic burden for a chronic disease."*

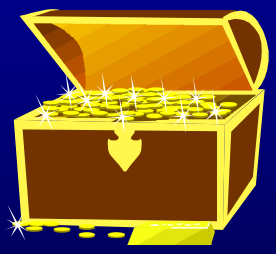
  P.M. Mannucci & coll, Haemophilia 2007, 13 (Suppl 5):65

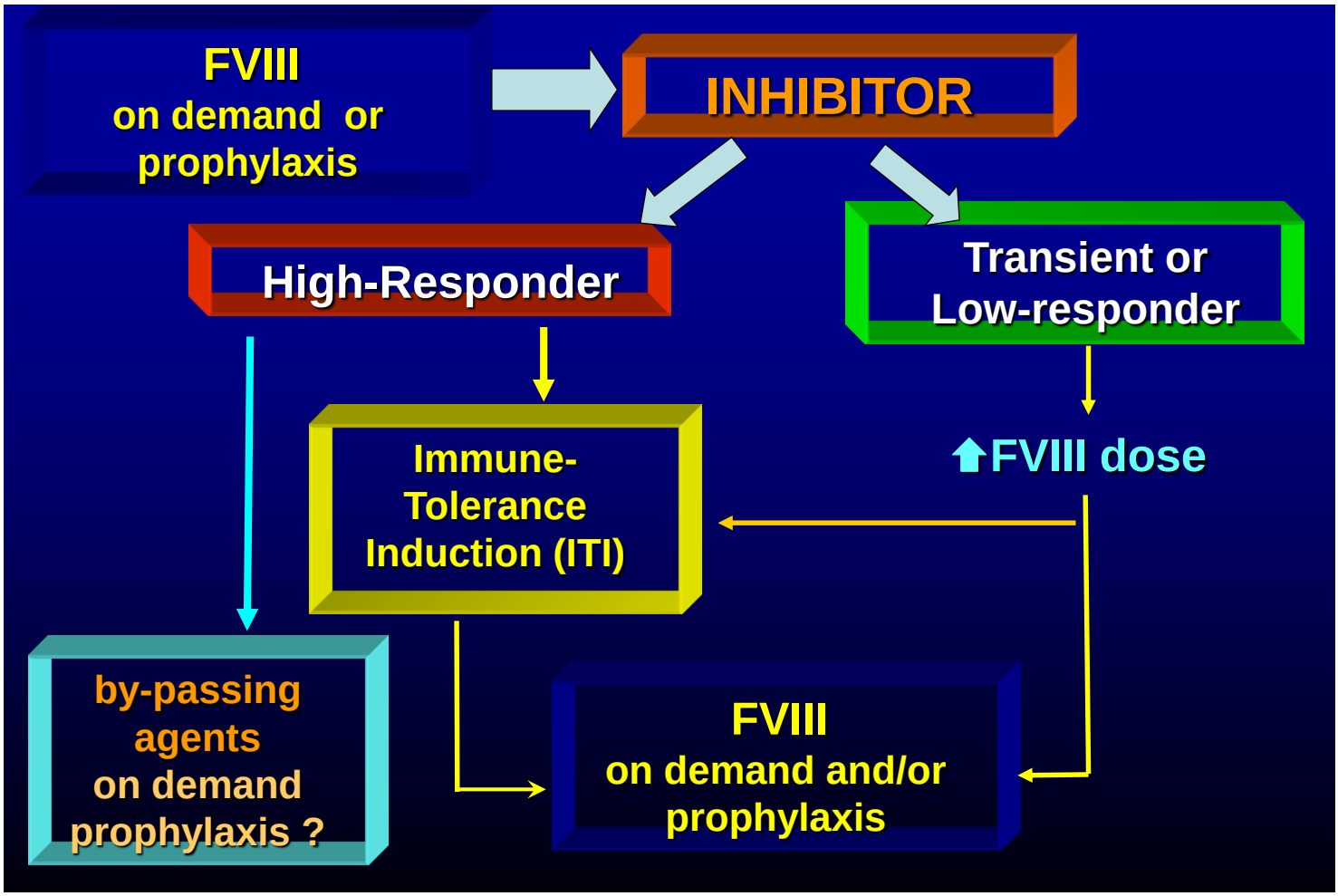
A complex approach...

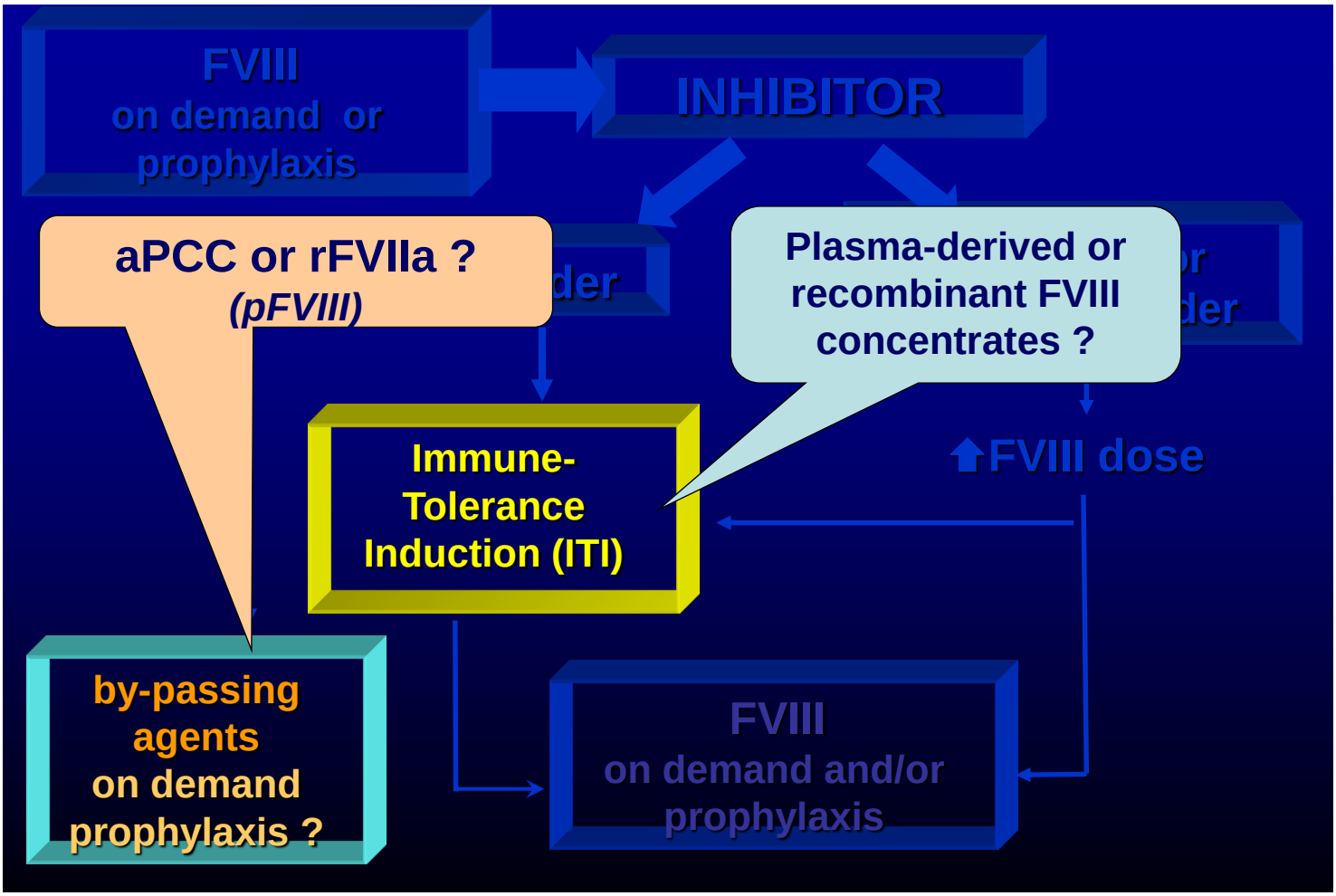


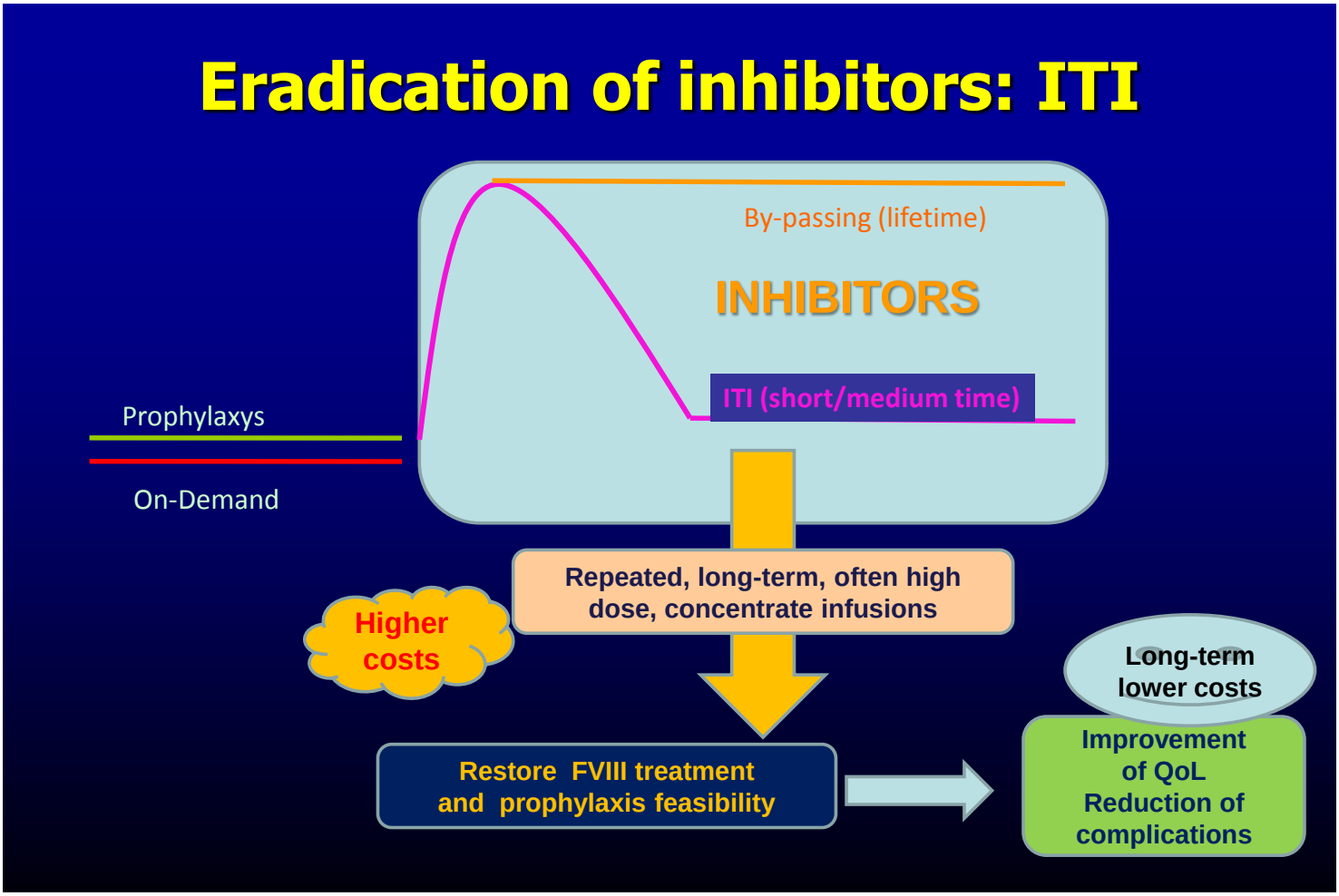
Haemophilia with inhibitors Pharmaco-economy

- **Limited data**
  - Few patients (rare complication of a rare disease)
  - Lack of rigorous studies
  - Analysis time- and region (country)- specific
- **Assumptions of outcomes**
  - Lack of prospective evidence
  - Introduction of orthopedic surgery
- ***Quality of life assessments (QUALY)***
- ***Heterogeneity of approaches for treatment***
  - Bypassing agents: on demand (type, regimen, doses), introduction of prophylaxis
  - ITI: different protocols
- ***Need for a lifetime perspective***
  - *Short-term evaluations in most studies*






FVIII
on demand or
prophylaxis
INHIBITOR
aPCC or rFVIIa ?
(pFVIII)
Plasma-derived or
recombinant FVIII
concentrates ?
Immune-
Tolerance
Induction (ITI)
FVIII dose
by-passing
agents
on demand
prophylaxis ?
FVIII
on demand and/or
prophylaxis


Eradication of inhibitors: ITI
By-passing (lifetime)
INHIBITORS
ITI (short/medium time)
Prophylaxys
On-Demand
Repeated, long-term, often high
dose, concentrate infusions
Higher
costs
Long-term
lower costs
Restore FVIII treatment
and prophylaxis feasibility
Improvement
of QoL
Reduction of
complications

How much does ITI cost ?

- Factors affecting concentrate use
  - Prescribed dose
  - Duration of treatment (time to success)
  - Patient body weight (adult, child)

Pre-titer
<10 BU
FVIII dose
>100 IU/Kg
Interval from
diagnosis
<5 yrs

Prognosis	*Time to 50% success (mo)*	*FVIII (IU)*	*Cost per patient (US$)*	
			pdFVIII	*rFVIII*
favourable	9.5	1,425,000	712,500	1,425,000
unfavourable	19.0	8,850,000	4,275,000	8,850,000

extrapolation from the IITR, Aledort et al, Haematologica 2000

How much does ITI cost… ?

- Decision model based on expert consensus and published data. Costs (mean/yr) in Germany (€).

Patients	*On Demand*		*ITI*	
	No inhibitors	Inhibitors	LR	HR
Children	27,857	76,511	421,740	1,150,200
Adults	128,993	353,794	575,100	5,751,000

~3-fold higher lifetime

~15-fold higher 1-3 yrs

- The high success rate and low number of inhibitor recurrence argue for a reduction of costs in the majority of ITI-treated patients.

Auerswald et al, Haemophilia 2004

Eradication of inhibitors: ITI

- Many open issues…
  - When to start
  - Which dose and regimen
  - Which FVIII type of product
  - Associated/alternative immunomodulatory approaches

Di Michele et al, Haemophilia 2007

The Frankfurt ITI experience

	1979-1993	*1993-2000*		
	FVIII/vWF	FVIII/vWF	rFVIII	Switch to FVIII/vWF
Patients, n HR/LR	21 16/5	2 1/1	14 14/0	10 10/0
Success (%)	91 %	100 %	28 %	80 %
HR, n (%)	14/16 (88)	1/1 (100)	4/14 (28)	8/10 (80)
LR, n (%)	5/5 (100)	1/1 (100)	-	-
Median mo. (range)				
HR	4 (0,5-42)	3	3 (2-7)	17 (5-36)
LR	1,5 (0,5-3)	1,5	-	-

Kreuz et al, Haematologica, 2001

Type of concentrate and ITI outcome

Study	FVIII Dose	Type of concentrate	Success
NAITR° *Di Michele, 2002*	Various	Int/high purity 25% mo/r FVIII 75%	68% 71%
Brackmann, 1996	High	most Haemate P	88%
Lusher, 1997	High	Kogenate	63%
Gruppo, 1997	High	Recombinate	50%
Rotschild, 1998	High	Recombinate	25%
Battle, 1999	High	Kogenate	77%
Rocino, 1999	Intermediate	Mo/r FVIII	83%
Courter, 2001	High	ReFacto	81%
Barnes, 2006	High/interm	most rFVIII	79%
Rocino, 2006	High/interm	rFVIII	73%
Gringeri, 2007	Various	Fanhdi	53% *
Kutrth, 2008	High	most Alphanate	32% *

*° North American Immune Tolerance Registry; in the other ITI registries the large majority of patients used plasmaderived products. * most patients with negative predictors of success*

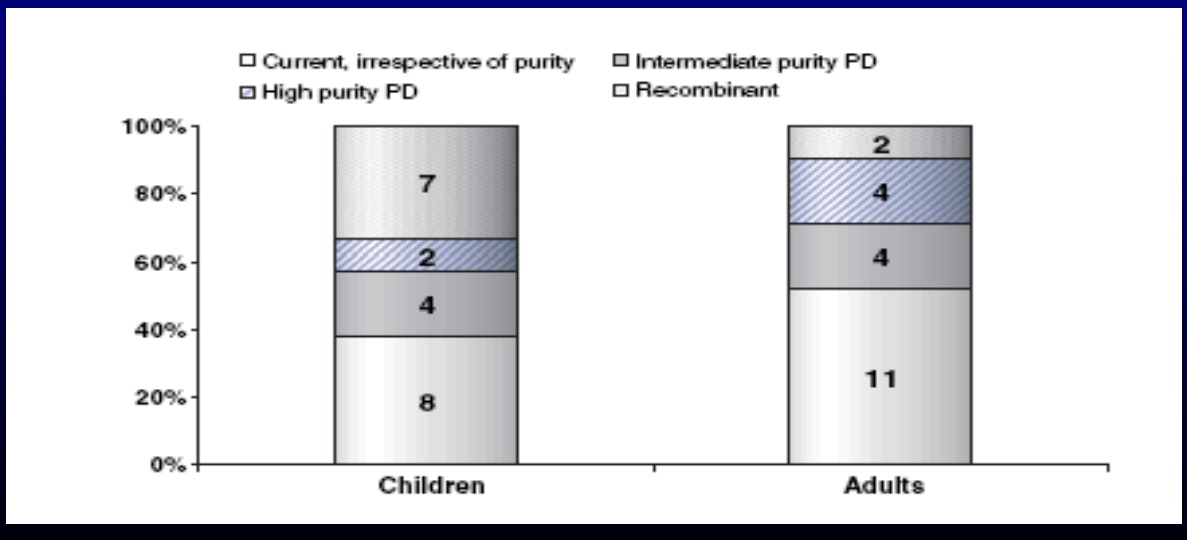
Preferred type of concentrate for ITI

Haemophilia (2006), **12**, 363–371 DOI: 10.1111/j.1365-2516.2006.01296.x

Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors

J. ASTERMARK,* M. MORADO,† A. ROCINO,‡ H. M. VAN DEN BERG§, M. VON DEPKA¶, A. GRINGERI,** L. MANTOVANI,†† R. P. GARRIDO,‡‡ M. SCHIAVONI,§§ A. VILLAR,† and J. WINDYGA¶¶ ON BEHALF OF THE EHTSB[1]

- same concentrate as at inhibitor diagnosis
- Recombinant products in children



The Italian experience

PROgnostic Factors in Immune Tolerance induction of haemophiliacs A with inhibitors: an Italian retrospective-prospective registry

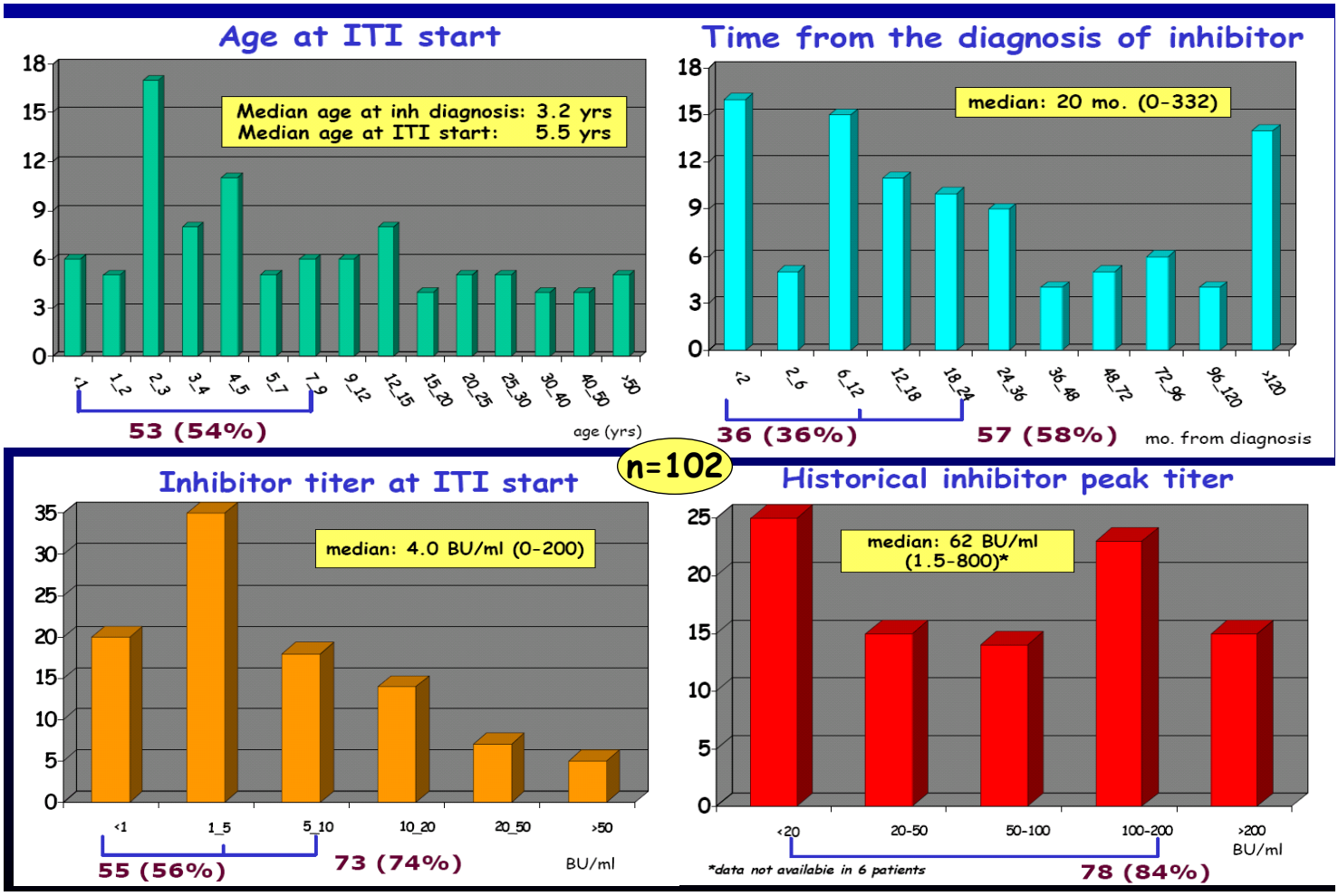
the PROFIT study

The PROFIT Study

At March 2009:

- 24 participating AICE Centers
- 102 registered and 90 completed first ITI courses
- 60 retrospective, 42 prospectively followed
- 37% ~100 IU/Kg/d, 27% ~200 IU/Kg/d
- Central review of ITI outcome
- 70% of patients with one or more negative predictors of success*

*Age at ITI start > 8 yrs
Time from diagnosis of inhibitor > 24 mo.
Historical peak titer > 200 BU/ml
Inhibitor titer at ITI start >10 BU/ml



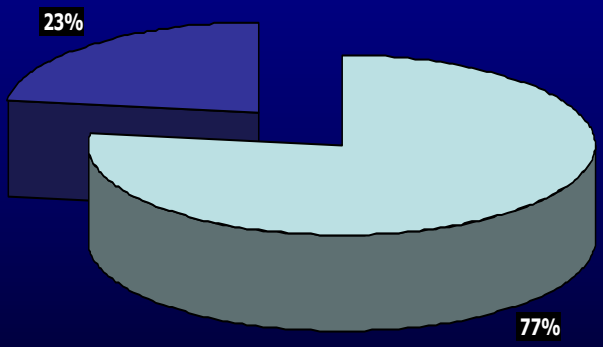
PROFIT study: type of concentrate

Different concentrate on ITI

3 rFVIII→FVIII/VWF

2 rFVIII→ other rFVIII

14 pdFVIII→ other pdFVIII

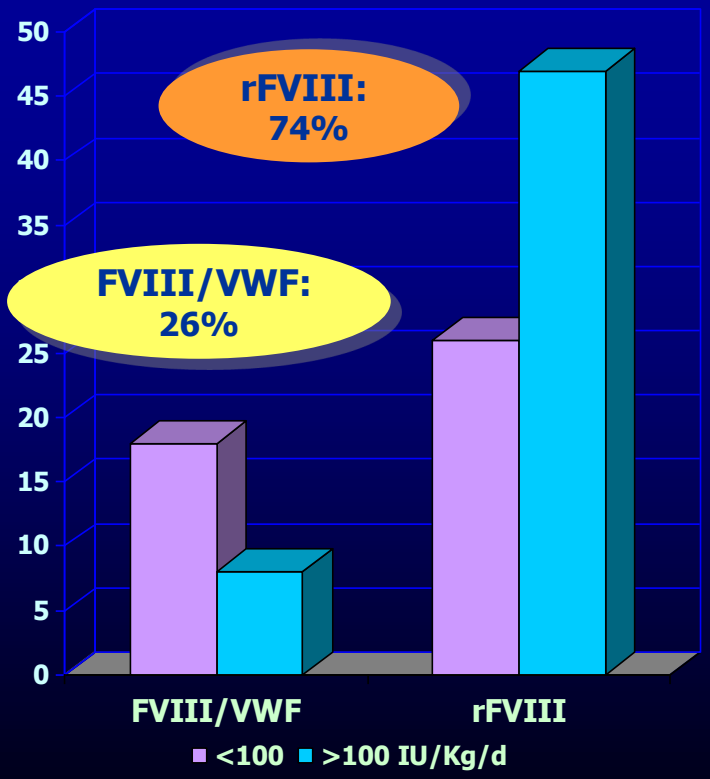


same concentrate

at inhibitor diagnosis *

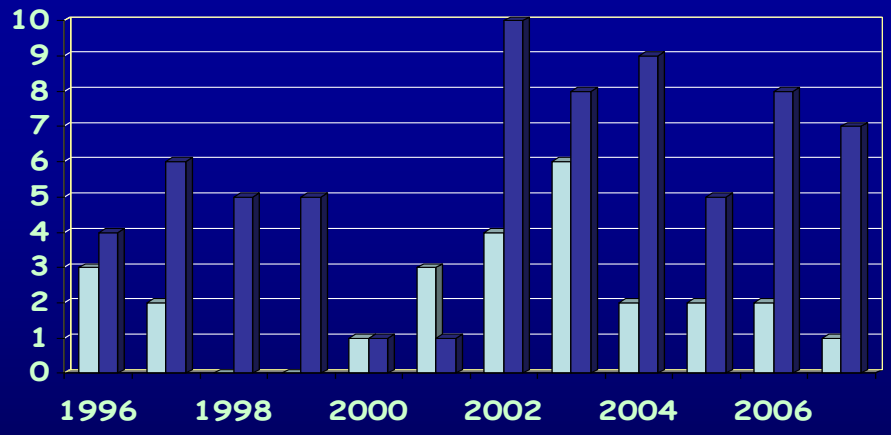
**data not available in 11 patients*

70% of pts trated with medium/high regimens



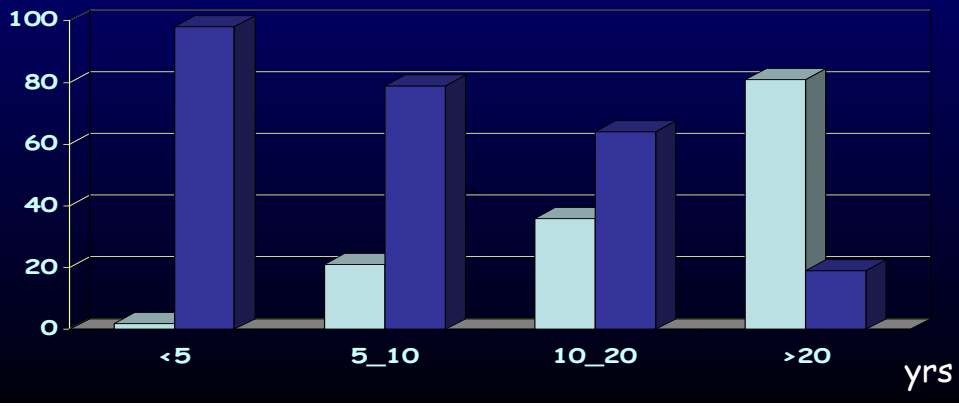
p<0.05, <100 vs >100, rFVIII vs FVIII/VWF

PROFIT study: use of FVIII/VWF



First ITI:
type of concentrate

% of patients according to **age at ITI start**



Predictors of success

Type of Concentrate	SUCCESS	PARTIAL RESP	FAILURE
FVIII/VWF (n=25)	9 (36.0%)	8 (32.0%)	8 (32.0%)
rFVIII (n=65)	37 (56.9%)	8 (12.3%)	20 (30.8%)

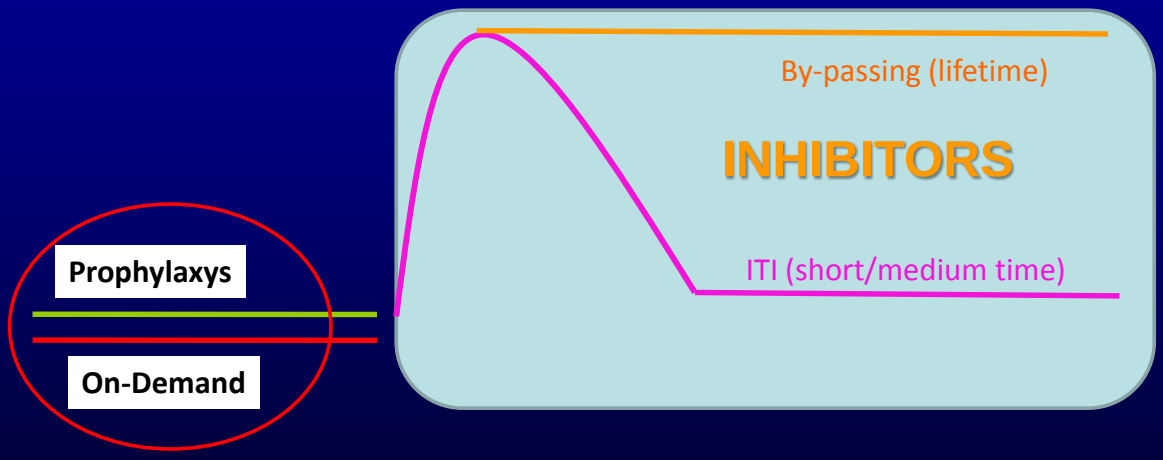
- At multivariate analysis, significant predictors:
  - Inhibitor titer at ITI start
  - FVIII dose
  - Inhibitor peak titer on ITI

Optimization of treatment

Pharmacoeconomics in hemophilia with inhibitors
Perspectives

- Need for prospective controlled studies in this setting
  - Costs of treatments (outliers!) and cost-effective approaches (HRQoL)
  - Long-term outcomes and evaluations
  - Identifiction of specific treatment approaches for specific patients
    - type of bypassing agent
    - dose, prophylaxis?
  - Identification of predictors of ITI success
    - Definitions of outcomes
    - Selection of candidates
    - Optimization of ITI regimens
    - Strategies for patients with negative predictors of success (? pdFVIII)

Perspectives…



Prevention of inhibitor development….?

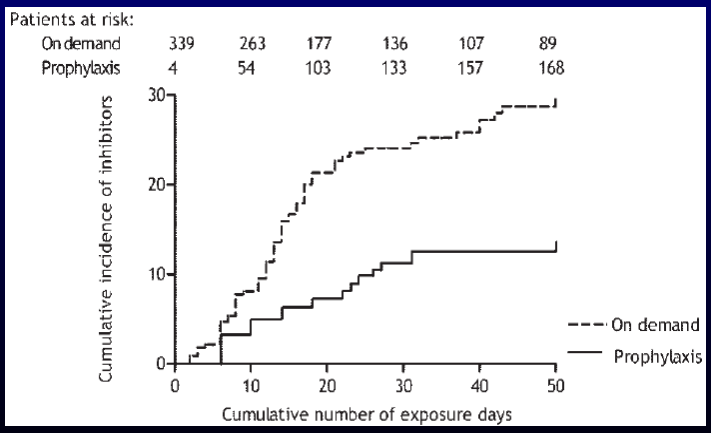
Prophylaxis vs. on-demand treatment

- Case-control Italian study: 80% reduction of inhibitor risk in patients on prophylaxis *(OR, 95 CI 0.2, 0.06-0.5)*

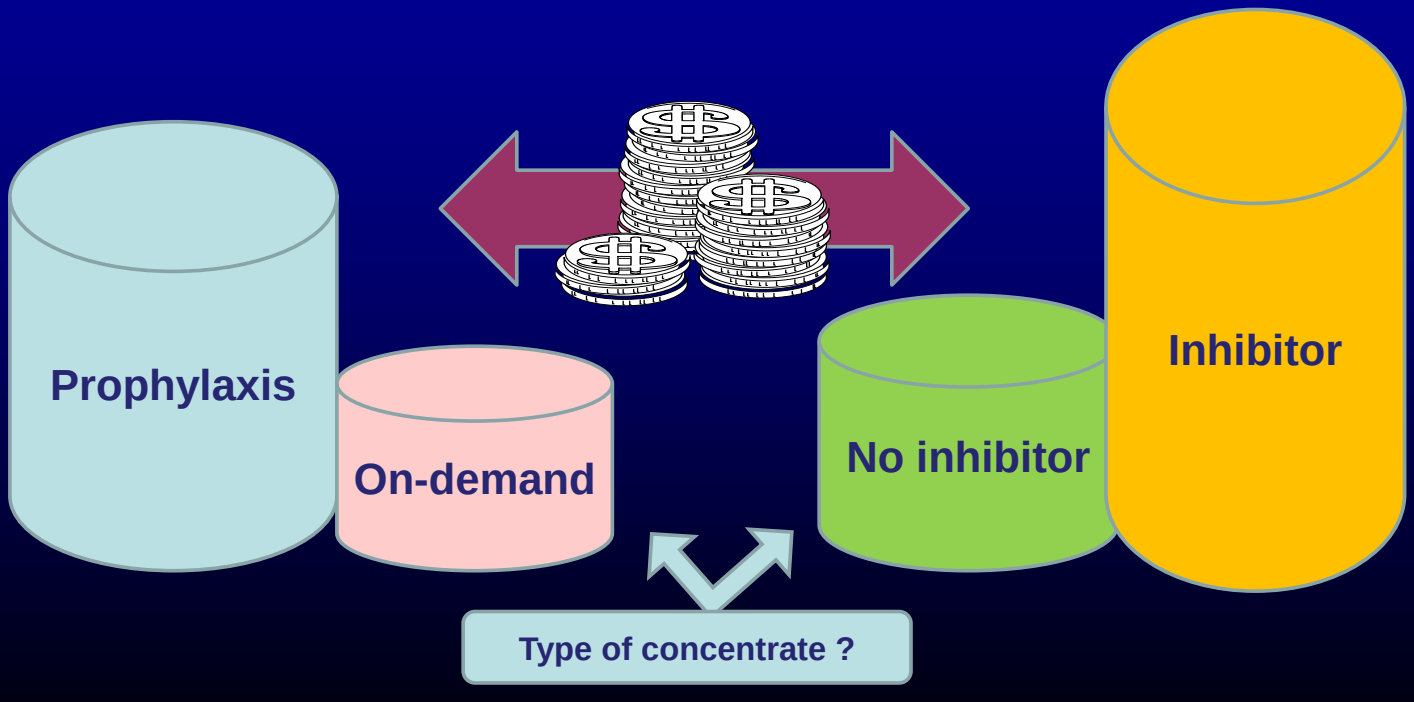
  Santagostino et al, Br J Haematol, 2005

- CANAL cohort Study: ~60% reduction of inhibitor risk in patients on regular prophylaxis *(OR, 95 CI 0.4, 0.2-0.8)*

  Gouw et al, Blood, 2007



Pharmacoeconomics of hemophilia



A key issue: cost of concentrates

- Mean cost of pdFVIII in Italy: 0.65 €/IU (range 0.56-0.77)
- Mean cost of rFVIII in Italy: 0.77 €/IU (range 0.76-0.83)
- The cost for safety…

Prophylaxis in hemophilia

A concerted Action for an European prospective randomized clinical trial

- Early regular prophylaxis (pd-FVIII vs r- FVIII) in newborn haemophiliacs.
- *Primary end-point* : inhibitor development (ad-interim analyses every six mo for 5 yrs)
- *Secondary end-point:* pharmacoeconomic comparison (cost of care and quality of life, pd-FVIII vs r- FVIII)

Haemophilia (2006), **12**, 363–371 DOI: 10.1111/j.1365-2516.2006.01296.x

Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors

J. ASTERMARK,* M. MORADO,† A. ROCINO,‡ H. M. VAN DEN BERG§, M. VON DEPKA¶, A. GRINGERI,** L. MANTOVANI,†† R. P. GARRIDO,‡‡ M. SCHIAVONI,§§ A. VILLAR,† and J. WINDYGA¶¶ ON BEHALF OF THE EHTSB[1]

4. Although there is insufficient evidence concerning the factor product to use for ITI, it is reasonable to suggest the same type of product as used at the time of inhibitor detection (Grade C, level IV).

11. VWF-containing FVIII concentrates might be considered an option in patients who fail the initial attempt of ITI with highly purified FVIII concentrates (Grade B, level III).

Haemophilia (2007), 13 (Suppl. 1), 1–22

International workshop on immune tolerance induction: consensus recommendations[1]

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

Consensus recommendations for FVIII product (Fig. 1)

1 ITI is successful using FVIII products with and without VWF (level IIb).
2 No data support the superiority of any FVIII product (level IIb).

3 Most patients are tolerized with the same FVIII product in use at the time of inhibitor detection. This approach works, and there is no evidence to support switching to another FVIII product for *de novo* ITI (level IIb).

Discussion for the final Recommendations:

DISCUSSION FOR THE FINAL RECOMMENDATIONS:

Group 1 Rapporteur: E. Seifried

Group 1 dealt with the optimal use of blood products, particularly red blood cells, platelets, fresh frozen plasma and albumin. The new versions of the recommendations are listed below. Several new recommendations have been added, although most of the preceding versions have either been left unchanged or slightly modified (marked with *).

General recommendations

Six fully new recommendations have been added (1 to 6 below).

Recommendation 1 emphasised the necessity that blood establishments should make every effort to forestall the problems presented by the increases in the demands for blood products, coupled to the aging of the population. It was felt that measures should be taken to increase the percentage of donors.

Recommendation 2 expressed the necessity of preparing plans for emerging pathogens, such as HIV. Alert systems and disaster plans were essential. This was clearly a response to problems in recent years.

Recommendation 3 expressed the need for evidence-based clinical guidelines throughout Europe. This is evidently compatible with the growing importance of evidence-based medicine.

Recommendation 4 proposed a European benchmark project, coupled to the identification of centres of excellence. One objective was to improve patient blood management.

Recommendation 5 expressed the need for improving training in transfusion medicine and proposed the development of a common curriculum. This was aimed at improving the expertise of professional workers in the field.

Recommendation 6 proposed the development of long-term biorepositories. This was intended to preserve reference samples.

Red blood cells

One new recommendation (16) has been added and 7 other recommendations have been slightly rephrased (new numbers 7, 9, 10, 11, 12, 14 and 15).

Recommendation 10 now emphasises the risk of ABO mismatch.

Recommendation 16 proposes that blood establishments should analyse patterns of red blood cell use to minimise wastage.

Platelets

Six new recommendations have been added (new numbers 19, 20, 23, 27, 28 and 29) and 6 other recommendations have been slightly rephrased (new numbers 17, 18, 22, 24, 25 and 26).

Recommendation 19 mentions the possibility of using platelet-additive solutions when clinical equivalence has been demonstrated.

Recommendation 20 mentions the possibility of using novel platelet-derived products when there is adequate clinical data to support their use.

Recommendation 23 mentions the possibility of prophylactic treatment with platelet concentrates for patients with thrombocytopenia. The type of thrombocytopenia is not specified.

Recommendation 27 advocates that blood establishments in Europe should have the capability of diagnosing and managing the blood supply in different forms of thrombocytopenia.

Recommendation 28 advocates the use of methods to reduce the risk of bacterial contamination of platelet concentrates.

Recommendation 29 emphasises that the impact of ABO-incompatible platelet transfusion should be clarified.

Fresh frozen plasma

One new recommendation has been added (new number 36) and 4 other recommendations have been slightly rephrased (new numbers 30, 31, 32 and 33).

Recommendation 36 now advocates the precaution of using only male donors or female donors without a history of pregnancy, as this reduces the risk of immune TRALI.

Albumin

No changes have been made.

Group 2 Rapporteur: P. Giangrande

Group 2 dealt with the optimal use of clotting factor concentrates. The new versions of the recommendations are listed below. Six new recommendations have been added (new numbers 43, 46, 49, 50, 51 and 52). A further 7 recommendations have been slightly modified (marked with *) - new numbers 39, 40, 41, 42, 130, 131 and 133. Recommendation 47 is unchanged.

Recommendation 43 proposes that a formal mechanism should be established in each country to develop best practice in haemophilia care.

Recommendation 46 supports the encouragement of home treatment with coagulation factor for patients with severe haemophilia.

Recommendation 49 proposes that family trees should be drawn up for patients with haemophilia and other inherited bleeding disorders. Genetic counselling should be offered.

Recommendation 50 states that awareness to rare bleeding disorders should be enhanced.

Recommendation 51 supports the use of specific coagulation factors for patients with rare bleeding disorders. Prophylaxis should be considered in patients with severe phenotype. The development of orphan drugs should be encouraged.

Recommendation 52 states that the development of equitable care in all member states should be fostered by the European Union.

Group 3 Rapporteur: W. Korte

Group 3 dealt with quality management and clinical management. The new versions of the recommendations are listed below. Eight new recommendations have been added (new numbers 54, 55, 57, 58, 59, 62, 64 and 66). Recommendation 56 has been slightly modified. The other recommendations are unchanged.

Recommendation 54 suggests the implementation of so-called “clinical champion” status for persons with special expertise and experience in using blood components. Clinical champions should have a series of responsibilities, including educational activities, coordination between persons producing and persons using blood products, developing markers of efficacy and outcome, securing adherence to guidelines and detection of overuse or underuse of blood components.

Recommendation 55 states that implementation of transfusion quality is the responsibility of hospital management, possible in collaboration with a national committee.

Recommendation 57 proposes that quality management of blood components should be integrated within total quality management and general risk assessment in the respective institution.

Recommendation 58 proposes that national legislation or regulations should be modified to allow implementation of recommendation 55.

Recommendation 59 advocates the development of national and international registers on adverse effects with the use of blood components.

Recommendation 62 advocates the definition of subgroups of patients requiring different approaches for transfusion therapy.

Recommendation 64 advocates regular training workshops.

Recommendation 66 advocates permanent personal identification which should not be variable between hospital visits.

Group 4 Rapporteur: C. Politis

No changes were made in the recommendations.

The group decided, however, that the following list of items needed further exploration in the future.

- Transfusion therapy should be regularly reviewed, and revised according to evidence
- There is an urgent need to define relevant clinical outcomes from transfusion, such as QOL and functional status
- Outcomes need to be defined and benchmarked for disease/condition specific groups, but also relevant demographic groups within populations (e.g. elderly, IHD)
- Outcomes need to be measured at relevant time points, including short and long-term
- Transfusion specific tools to measure clinical outcomes need to be developed and validated
- Consequences of withholding or giving transfusion need to be measured in relevant patient groups
- A better understanding of the optimal correction of anaemia and the optimum duration of correction is needed, for major patient groups, eg major surgery; chronic anaemia.
- Observational studies are needed to focus prospective studies on the outcome of transfusion therapy
- Large adequately powered randomised clinical trials in transfusion medicine are needed to optimise blood use
- Evaluate zero-risk versus risk-based analysis for overall decision making process for assessing safety and effectiveness of blood transfusion and cellular therapies
- Data from haemovigilance programmes should be used for learning and improvement
- When evaluating plasma derived products for treating coagulation disorders, the issue of alternative strategies and their clinical relevance should be taken into consideration. This is true for clinical outcomes as well as for cost-effectiveness issues
- The effectiveness and safety of plasma derived and recombinant products for treating coagulation disorders needs to be assessed.This is relevant in view of the different costs of treatments with plasma derived products as compared to recombinant products

- Research funding should be committed to generate adequately powered in clinical trials.
- Translation of high quality study findings in transfusion medicine, particularly related to RBC, are likely to be cost-saving
- Clinicians should receive training that enables design of and participation in clinical trials
- Registries should be established that include high quality relevant outcome data. These should be used to promote clinical trial that maximise patient and societal outcome
- Research is urgently needed to define optimum practice in management of massive bleeding including the optimum product(s)
- Need to evaluate clinical and cost effectiveness of new methods of monitoring haemostasis
- Clear SPCs of the different types of plasma intended for transfusion should be defined based on comparative studies
- The goals of plasma and platelets transfusion in non-bleeding patients need to be better defined in terms of clinical outcome
- Established and new transfusion therapies should be subject to Health Technology Assessment (HTA) taking into account :
    - Specific product characteristics
    - Specific patient groups
- As precautionary measures may have a major impact on health care resources. They require reassessement using HTA
- Developing common models for cost-effectiveness and cost benefit analysis in transfusion with a view to benchmarking would help in assessing and comparing action plan in transfusion medicine

Recommendations

Group 1 **Rapporteur: E. Seifried**

3. RECOMMENDATIONS

3.0. GENERAL

1) (New) Blood establishments across Europe must undertake all efforts to increase public awareness about future shortages in blood supply with respect to demographic changes. Measure shall be undertaken to increase the percentage of donations per capita on a regional basis.

2) (New) Measures have to be undertaken across Europe to be able to respond quickly to emerging pathogens and epidemic outbreaks of infections. Blood establishments across Europe shall be included into existing rapid alert systems for infectious diseases. The relevance of the infectious agents for the blood transfusion chain should be evaluated by the responsible authorities and necessary measures have to be balanced with the safety of the blood supply and communicated to the blood establishment. Each European country and each blood establishment should have a disaster plan in place.

3) (New) Evidence-based clinical guidelines shall be established across Europe in order to support best clinical practice in transfusion medicine.

4) (New) A European benchmark project should be undertaken and based on the results centres of excellence should be identified.

5) (New) Attention should be given to the development of effective education programmes in transfusion medicine at undergraduate and postgraduate level. A common curriculum should be agreed on and implemented.

6) (New) Develop long term donor and recipient biorepositories complying with biobanking best practices.

3.1. RED BLOOD CELLS

3.1.1. General

7) * (97) Reduction of inappropriate Red Cell use should help to minimise the incidence and severity of blood shortages. Hospital inventory management should be optimised and should include the use of blood ordering schedules and patient blood management.

8) (98) A blood exchange programme could be envisaged as a single office serving as a central co-ordinating base matching shortages and available stock in different blood centres. Such networks exist with varying success in several European centres. A pilot project would be necessary to assess whether the system would be useful or effective.

3.1.2. Residual risk

9) * (99) Introduction of new strategies to improve transfusion safety should be prioritised on the basis of achievable safety gains. Optimising blood transfusion practices in the hospital could be the most important goal in terms of health gain and cost benefit.

10) * (100) The administrative practices related to transfusion, including recipient identification and compatibility testing, vary widely across Europe. ABO mismatch remains a very serious problem. Effective systems that reduce this administrative risk must be identified and adopted particularly at the hospital level.

11) * (101) Based on clinical and organisational experiences pre-storage universal leucodepletion is highly recommended.

3.1.3. Product quality and clinical outcome

12) * (102) Optimum storage time and conditions as defined by patient outcome must be determined in prospective clinical trials.

3.1.4. Appropriate use

13) (103) Every hospital undertaking blood transfusion must have a quality management system in place, that includes a designated and specially trained professional with responsibility for the quality of transfusion practice in the hospital and that includes a systematic programme of ongoing education and a documented and systematic approach to clinical audit. This system of clinical audit should use accepted specified audit measures uniformly adopted across Europe and a standardised, published audit report format, with published annual reports.

14) * (104) Appropriate patient management programmes for transfusion should be established in every hospital.

(105) [Attention should be given to the development of effective education programmes in transfusion at undergraduate and postgraduate level.]
deleted

15) * (106) There is an urgent need for well-designed large-scale studies in blood transfusion in well-defined patient groups, addressing clinical safety and efficacy. Prospective randomized trials must be organised and funded from out-side the blood establishments.

16) (New) Blood establishments should analyse patterns of Red Cell use to provide an appropriate inventory for optimal patients care and to minimise Red Cell wastage. The effects of Red Cell transfusions shall be monitored on an individual basis so as to match the number of units transfused with the patient’s need. In some circumstances one-unit Red Cell transfusion might represent optimal care.3.2. PLATELETS

3.2.1. Products and their availability

17) * (107) Platelet products should be prepared and stored in a fashion that retains adequate haemostatic function while maintaining the safety of the component.

18) * (108) Concerning availability, there is an urgent need to evaluate the impact of possible delays throughout the platelet transfusion chain resulting from new technologies or other safety measures. Blood services should be organised in such a way so as to:

- minimise temporary and other possible shortages, e.g. rare phenotype platelets; and

- minimise the wastage of products without compromising the quality and supply of platelet concentrates.

19) *109) [The implementation of NAT tests should enable the release of platelet concentrates preferably in less than 24 hours after donation]*
(deleted)

20) (New) The use of platelet-additive solutions in order to save plasma and to reduce side-effects of platelet transfusion is recommended where clinical equivalence of the novel platelet product is shown.

21) (New) Novel platelet-derived products for local treatment shall be established only after proper clinical evaluation and shall meet the same safety and quality requirements as blood products.

3.2.2. Indications and platelet transfusion threshold levels

22) (110) The clinical decision to transfuse platelets should be based on careful evaluation of the individual patient's condition, including bleeding history, bleeding tendency, in addition to actual platelet count or any laboratory result reflecting platelet function.

23) * (111) To support clinical decision making, it is strongly recommended that an algorithm for defining transfusion needs be developed. Such algorithms should be developed and implemented through the cooperative efforts of clinical and transfusion medicine specialists, and be subject to regular review. There is a need for rapid platelet function tests in selected patients at risk. Before implementation the clinical benefit has to be shown.

24) (New) There is an ongoing debate regarding the need for prophylactic transfusion of platelet concentrates in the treatment of thrombocytopenic patients. However the current standard of care is prophylactic treatment.

3.2.3. Dosage and efficacy

25) * (112) The outcome of platelet transfusion in terms of corrected count increment (CCI), for example, should be evaluated as a basis for improved transfusion practice. This involves assessing platelet recovery, actual increase in platelet count, and time (days) between two transfusions and most importantly clinical bleeding.

26) * (113) Research on developing better techniques to monitor the efficacy of platelet transfusion shall be supported.

3.2.4. Alloimmunisation and Refractoriness

27) * (114) Leucocyte depleted cellular blood components shall be used in all patients to prevent alloimmunisation. HLA- and/or HPA-compatible or cross-match negative platelets should be given to refractory alloimmunized recipients.

28) (New) Blood establishments across Europe should have the capability of diagnosing and managing the blood supply in autoimmune and neonatal thrombocytopenia.

3.2.5. Quality aspects and haemovigilance

29) *(115) [Development of algorithms in the appropriate use of platelet concentrates, in addition to the establishment of haemovigilance systems, is advocated as part of a quality system. The efficacy of platelet transfusion as well as the associated side effects should be assessed. Parameters on transfusion out-come should be registered and evaluated within an appropriate healthcare quality system.]*
(deleted)

30) (New) Measures shall be taken to reduce the risk of bacterial contamination in platelet concentrates. Different methods, such as testing and pathogen inactivation should be further investigated.

31) (New) The impact of ABO-incompatible platelet transfusion has to be clarified.

FRESH FROZEN PLASMA

32) * (116) For improved safety, plasma for clinical use products that have been quarantined or pathogen attenuated should be used.

33) * (117) The clinical and biological results of Fresh Frozen Plasma for clinical use infusion should be monitored since there are different FFP preparations with different product characteristics available and the individual response of the patients with coagulation disorders may be variable.

34) * (118) Since the intended benefit of FFP is the correction of bleeding in patients with coagulation disorders, tests (which might include point of care) that assess the haemostatic functions and provide results rapidly are essential for its optimal use. This implies the permanent availability of a laboratory to perform coagulation tests.

35) (119) The dosage and duration of therapy should be determined by clinical evaluation * and serial determination of coagulation tests.

36) (120) The numerous existing guidelines should be harmonised. Their dissemination and implementation should be strongly reinforced by quality assurance systems. As a possible way to improved application, summarised guidelines should be included on prescription forms and their impact should be measured

37) (121) The education of health professionals should be improved.

38) (New) As a precautionary measures to reduce the risk of immune TRALI, in case of single donor plasma units it is recommended to use only male donors and females without a history of pregnancy. Alternatively adequate testing should be performed.

3.4. ALBUMIN

39) (122) The existing evidence from published clinical studies addressing albumin use for volume substitution is insufficient. A convincing elaboration of benefits of albumin with respect to measurable clinical endpoints in comparison to other colloids will need substantially augmented evidence by further well-designed clinical studies.

40) *[123 - Since a potential deleterious effect of albumin infusion has been highlighted in the Cochrane Injuries Group Albumin Reviewers meta-analysis, further studies on mortality are required.]*
(deleted)

41) (124) The impact of preparations with different albumin concentrations and their respective sodium content is unresolved and should be studied further with respect to clinical efficacy and economic consequences.

* *Modified*

Group 2 **Rapporteur: P. Giangrande**

Recommendations on clotting factor concentrates:

* (125) Registers of patients with haemophilia and related disorders should be established and maintained in each country.

* (126) Gathering pharmacovigilance information on such complications as inhibitor development, allergic reactions, viral transmission and other miscellaneous adverse events is mandatory. A European initiative (EUHASS) has recently been launched and it is hoped that this will be financed beyond the initial three year term.

* (127) A network of Comprehensive Care Centres should be established in each country and should provide a seven days a week 24 hour clinical and laboratory service and be accessible to all patients. In order to be so designated, such a centre should normally provide treatment for at least 40 patients with severe haemophilia in order to maintain the expertise required

* (128) Adequate amounts of coagulation factor concentrates for the treatment of patients with hemophilia and related disorders should be available in each country. There is a continuing need for both plasma-derived and recombinant products. At national level, the minimum acceptable level of factor concentrate use should be 2 units per capita. Coagulation factor concentrates are now included in the WHO list of essential medications and cryoprecipitate should no longer be used for the treatment of haemophilia

(New) In order to foster the cooperation of patient organizations and physicians, it is recommended that a formal mechanism be established in each country to develop best practice in haemophilia care.

* (130) The various guidelines from medical bodies in different countries should be harmonized and expanded to include advice on dosages for the treatment of common bleeding problems. These should include details of the level of evidence and grade of recommendations.

* (131) As a general rule, prophylactic treatment for children with severe haemophilia is recommended. Ongoing prophylaxis in adults may also be considered.

(New) Home treatment with coagulation factor concentrate should be encouraged in patients with severe haemophilia.

(132) Immune tolerance should be offered to all patients with haemophilia who develop clinically-significant inhibitory antibodies.

* (133) Data on outcome of treatment should be collected, including clinical data such as frequency of bleedings and assessment of joint function as well as quality of life and economic information.

(New) Family trees for patients with haemophilia and other inherited bleeding disorders should be drawn up and genetic counselling offered.

(New) Awareness should be drawn to rarer bleeding disorders which affect both men and women. Data on these patients should also be included in the national registers.

(New) Patients with rare bleeding disorders should be treated with specific coagulation factor concentrates wherever possible. The development of “orphan drugs” for the treatment of such patients should be encouraged. If fresh frozen plasma is used, it should be subjected to viral inactivation/removal treatment. Prophylaxis in patients with a severe phenotype should be considered.

(New) The European Union should foster the development of equitable care in all member states.

* *Modified*

Group 3 **Rapporteur: W. Korte**

Discussionpoints :

Transfusion : Qualitymanagement --- Clinical Management

134. There is an urgent need to foster the commitment of decision makers, both at national and local levels, to establish a Quality Management System within hospitals for the clinical use of blood products.

(New A) The implementation of a "Clinical Champion" (CC) status is suggested *(see also 136)*; CCs are persons with a recognizable track record for and first-hand clinical experience with the use of blood components.
CC activities should include educational activities *(see 138)*; "translation" and coordination between persons involved in the (centralized) process of production and the (decentralized) process of clinical use; to develop markers of efficacy and outcome; to develop or define potential surrogate markers for efficacy and outcome; to define minimal requirements for all aspects of blood component use (collaboration with national committee); to prospectively secure adherence to guidelines *(see 140)*; to look for and comment on under- or overuse of blood components *(see 137)*.

(New B) The realization of the transfusion quality management scheme is in the responsibility of the hospital management. It should be implemented in collaboration with the respective national committee where necessary. *(see 135)*

135. There is the need to ensure that a quality manager for clinical use of blood products is appointed and empowered to take appropriate actions to ensure and improve quality, in co-operation with the hospital transfusion committee; and the quality manager, along with the transfusion committee, should be responsible for defining and disseminating guidelines and SOPs for optimal use of blood products, and verifying their application by the healthcare professionals. *[to be modified for overlapping responisbilities with "new, A" and "new, B"]*

(New C) The quality management (QM) of blood component use needs to be integrated within the "total quality management" and "general risk assessment" of the respective institution e.g. hospital. Such a quality management system (QMS) needs to allow incorporation of all aspects of the production chain. It must be simple and must be applicable everywhere. It needs to recognize outcome as a parameter that is to be monitored. It incorporate hemovigilance tools. *(see 135)*

(New D) National legislation / regulations need to be modified (where necessary) to allow development of tasks mentioned in "new B".

(New E) The development and/or support of a national and international register on adverse events with the use of blood components is to be targeted. This should be supported by "Clinical Champions". *(see new, A)*

136. There is the need to ensure that strategies are developed to maximise the cooperation of all healthcare professionals in the achievement of optimal use of blood products *(see new, A)*.

137. There is an urgent need to carry out controlled studies to define the appropriate use for blood products and the parameters needed to evaluate their effcacy and outcome; to document the indications for the use of blood products on the request form; and to define a limited number of common indicators in order to allow comparison between different hospitals and increase awareness of inappropriate use. *[to be modified for overlapping areas with "new, A" and "new, F"]*

(New, F) Subgroups of patients that will require different kinds of approaches for transfusion therapy need to be defined, e.g. patients that need therapy of acute bleeding; prophylaxis in the periinterventional setting; prophylaxis / therapy in oncology.
It is necessary to recognize the need to differentiate therapeutic approaches in different patient populations.

138. There is an urgent need to foster a continuing education programme for healthcare professionals involved in the clinical use of blood products organised by the transfusion committee; and the inclusion of transfusion medicine in undergraduate and postgraduate training. *(see new, G)*

(New, G) Regular training workshops (both for new and experienced users) should be offered on a national and/or regional level. Workshops with experienced users should be utilized to develop and improve the training procedures and to develop new or improve existing standards (e.g. within working groups). These processes should occur in collaboration with the national committee.

139. In defining SOPs, particular attention should be given to preventing transfusion errors, re-engineering the process, and introducing, if possible, information instruments, such as portable barcode readers, to assess the identity of the patient, the blood samples and the assigned unit.

(New, H) Person identification ("traceability") should be permanent (e.g. not variable for different hospitalizations); every potential possibility to reduce and prevent transmission errors must be taken hold of; these issues need to be considered at any point during the process, i.e. beginning with the screening of the donor to the follow-up of the recipient.

140. The establishment of an integrated hospital information and documentation system is strongly recommended, since this could greatly facilitate the collection and analysis of data related to the use of blood products.

Group 4 **Rapporteur: C. Politis**

EFFICACY IN TERMS OF OUTCOME (INCLUDING ECONOMICAL ASPECTS)

Conclusions and recommendations

Recommendations of economic aspects (141 – 150) from Kreuth Initiative in 1999 are still valid.

Information needs

141 - The epidemiology of blood components and blood products use should be assessed in the European to determine the likely clinical need and assist in planning future provision

142 -Blood and blood products use for the treatment of patients with index conditions should be recorded for each country on an annual basis, to provide baselines and indicators for comparison

143 - Consideration should be made for a linkage between product usage and the clinical conditions for which they are being used. This might be best achieved through the use of automated databases, the use of electronic patient records and electronic prescribing

144 - Reviews of blood and blood products use should be conducted using economics as well as clinical measures to determine the patterns of usage, to ascertain appropriateness of use, and to assess the effect of education programmes. Indicators should be developed to reflect optimum usage

145 -Consideration should be given to sponsoring these kinds of studies across the EU and else where

Future demands

146 - It is recognised that there are changes underway in the relative use of the plasma derived albumin, immunoglobulins, Fs VIII and IX. This will have important consequences on the costs and availability of these products in the future.
A study of the future demand and need for blood and blood products should be undertaken with appropriate assessment of the economic factors to determine the viability of blood collection and fractionation centres

147 - Considerations should be given to the rational distribution of these centres throughout the EU, their commercial viability and national dependency in the context of self-sufficiency

Educations requirements

148 - Undergraduate and post-registration educational and training of all clinicians who use blood and blood products should be promoted. Ways of increasing the impact of clinical recommendations and guidelines should be investigated

General recommendation

149 - Economic evaluation should underpin the drive to improve the efficiency of resourcing and optimal use of blood and blood products, while maintaining the principle of voluntary non-remunerated donors

150 - The principle and the need for self-sufficiency should be re-assessed in the context of safety, availability, ethics and economics, in view of continuing development of the EU and other countries

For new recommendations a comprehensive list of items needs further exploration in the future (look at page 322).