



BLOOD SAFETY IN THE EUROPEAN COMMUNITY: AN INITIATIVE FOR OPTIMAL USE

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Conclusions and Recommendations Discussion Papers Syllabus

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VORWORT

Blut ist einzigartig. Obgleich es zur Erhaltung des menschlichen Lebens unbedingt notwendig ist, kann es von Menschen gespendet, dann verarbeitet und anderen Personen therapeutisch verabreicht werden. Leben können gerettet und die Lebenserwartung durch das Verabreichen von Blut und Blutprodukten, einschließlich Gerinnungsfaktoren, angehoben werden. Blut ist aber auch Einschränkungen unterworfen. Mit Blut können Krankheiten übertragen werden. Blut steht nicht uneingeschränkt für therapeutische Zwecke zur Verfügung, da seine Verfügbarkeit von der Spendenbereitschaft einzelner abhängt. Es ist daher von herausragender Bedeutung, daß das in der Europäischen Gemeinschaft erhältliche Blut und Blutprodukte mit äußerster Umsicht und unter Ausschöpfung ihres gesamten Potentials genutzt werden.

Hinweise auf übermäßigen, zu geringen oder unangebrachten Gebrauch dieses außergewöhnlichen Stoffes veranlaßten die Ludwig-Maximilians-Universität unter der Schirmherrschaft des Bundesgesundheitsministeriums und mit Unterstützung der Europäischen Kommission, ein Expertentreffen einzuberufen, um Fragen zum optimalen Gebrauch von Blut anzusprechen. Da wir nicht alle Fragen in Bezug auf Blut und Blutprodukte anschneiden konnten, richteten wir unser Augenmerk auf Erythrozytenkonzentrate, Thrombozytenkonzentrate, Albumin, Gefrorenes Frischplasma (GFP), Faktor VIII / IX und insbesondere Qualitätsmanagement und ökonomische Aspekte. Diese Schlußfolgerungen und Empfehlungen sind das Ergebnis konstruktiver Arbeit in Zusammenhang mit diesem Treffen und sollten die Grundlage für die weitere Diskussion bilden, so daß die Initiative von Wildbad Kreuth weitergehen kann.

Die Initiative von Wildbad Kreuth, wie sie nun allgemein bezeichnet wird, hätte ohne die Hilfe und Unterstützung vieler Personen nicht durchgeführt werden können. Ich schulde Friedger von Auer besonderen Dank, der die Verbindungen zur Bundesregierung während ihrer Präsidentschaft des Europäischen Rates herstellte und Frances M. Delaney, auf deren uneingeschränkte Unterstützung in organisatorischer Hinsicht sowie der Vorbereitung und dem Editieren von Papieren für dieses Treffen wir stets zählen konnten. Ich spreche Professor Hanno Riess, Professor Erhard Seifried, Professor Rainer Seitz, Dr. Paul Giangrande, und Frau Karin Berger meinen großen Dank für ihre Bereitschaft aus, die Diskussionspapiere zu erstellen. Ebenso möchte ich den sechs Personen, die freundlicherweise die schwierige Aufgabe des Diskussionsleiters übernommen haben, sowie deren unermüdlichen Berichterstatern (diese Personen sind in der Teilnehmerliste besonders vermerkt) im Namen aller Teilnehmer danken. Und herzlichen Dank den Teilnehmern selbst. Herzlichen Dank für Ihre Bereitschaft, Ihren Sachverstand, Ihre Anliegen und Ihre Gesellschaft mit uns zu teilen. Sie machten das Treffen zu dem, was es war.

Ich möchte nicht versäumen, die Mitwirkung meines Teams und von Interplan dankend hervorzuheben. Schließlich die Unterstützung des Bundesgesundheitsministeriums und der Europäischen Kommission, insbesondere von Mr. Ron Haigh. Ich hoffe, daß diese Initiative, die sie alle unterstützt haben, den Grundstein für künftige Bemühungen zur Sicherung einer optimalen Nutzung von Blut innerhalb in der Europäischen Gemeinschaft bilden wird.

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PREFACE

Blood is unique. Although essential for maintaining human life, it can be donated by a person, then processed and therapeutically administered to other individuals. Lives can be saved and life-expectancy can be normalised by administering blood components and plasma derivatives including blood coagulation factor concentrates. But blood also has its limitations. It can transmit diseases and its availability for medical purposes is not unlimited as it is dependent on the willingness of individuals who donate it. Therefore, it is of crucial importance that the blood and blood products that are available in the European Community are used with the greatest of care and to their full potential.

Indications of overuse, underuse and inappropriate use of this exceptional substance led the Ludwig-Maximilian University, under the auspices of the Federal Ministry of Health of the Federal Republic of Germany and with support from the European Commission, to convene a meeting of experts to address issues related to the optimal use of blood. As we could not raise all issues relevant to blood components and derivatives we, therefore, focussed on Red Cells, Platelets, Albumin, Fresh frozen plasma (FFP), Factor VIII / IX and in particular Quality Management and Economic Aspects. This report is the result of the constructive work associated with that meeting and should be the basis for further discussions so that the initiative taken at Wildbad Kreuth will be continued.

The 'Wildbad Kreuth Initiative', as it is now commonly referred to, could not have been realised without the help and support of many individuals. I am particularly indebted to Friedger von Auer who ensured the linkages with the German Federal Government during its Presidency of the European Council and to Frances M. Delaney whose unstinting support in administrative matters as well as with the preparation and editing of documents for this meeting never wavered. To Professor Hanno Riess, Professor Erhard Seifried, Professor Rainer Seitz, Dr. Paul Giangrande, and Frau Karin Berger, I express my gratitude for their willingness to draft the discussion documents. To the six individuals who kindly accepted to assume the difficult task of discussion leaders and also to their dedicated rapporteurs (all identified in the list of participants), I want to express my sincere thanks on behalf of all participants. And to the participants themselves: My thanks for your willingness to share your expertise, your concerns, and your fellowship. They made the meeting what it was.

I do not want to miss acknowledging the cooperation of my own staff and Interplan. And finally, the support given by the Federal Ministry of Health and the European Commission, in particular from Mr. Ron Haigh, is gratefully acknowledged. I hope that this 'Initiative', which they have supported, will lay the foundation for future efforts to ensure the optimal use of blood in the European Community.

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Inhaltsverzeichnis / Table of Contents

VORWORT	i
PREFACE.....	ii
INHALTSVERZEICHNIS	iv
TABLE OF CONTENTS	iv
TEILNEHMER	X
PARTICIPANTS	X
SCHLUSSFOLGERUNGEN UND EMPFEHLUNGEN.....	1
CONCLUSIONS AND RECOMMENDATIONS.....	1/1
1. EINLEITUNG	2
INTRODUCTION.....	3
2. SCHLUSSFOLGERUNGEN	2
CONCLUSIONS.....	3
2.1. ERYTHROZYTENKONZENTRATE.....	4
RED BLOOD CELLS.....	5
2.1.1. Probleme.....	4
Problems	5
2.1.2. Analyse.....	6
Analysis.....	7
2.1.3. Erhaltung des Blutvolumens	6
The role of blood conservation	7
2.2. THROMBOZYTENKONZENTRATE	8
PLATELETS.....	9
2.2.1. Probleme.....	8
Problems	9
2.2.2. Produkte und ihre Verfügbarkeit	8
Products and their availability.....	9
2.2.3. Indikationen und Transfusionstrigger	10
Indications and platelet transfusion threshold levels.....	11
2.2.4. Dosierung und klinische Wirksamkeit.....	10
Dosage and efficacy.....	11
2.2.5. Refraktärzustände	10
Refractoriness	11
2.2.6. Aspekte der Qualität und der Transfusionssicherheit	12
Quality aspects and haemovigilance.....	13
2.3. GEFRORENES FRISCHPLASMA.....	12
FRESH FROZEN PLASMA.....	13
2.3.1. Angestrebte Anwendung.....	12
Intended use	13
2.3.2. Klinische Anwendung von GFP	14
Clinical use of FFP.....	15
2.3.3. Einfluß verschiedener GFP Qualitäten.....	14
Impact of different FFP qualities	15
2.3.4. Dosierung und Dauer der Therapie.....	16
Dosage and duration of therapy	17
2.3.5. Rolle von Leitlinien	16
Role of guidelines.....	17
2.4. ALBUMIN	16
ALBUMIN	17
2.4.1. Angestrebter klinischer Nutzen	16
Intended use	17

2.4.2.	Klinische und laborchemische Kriterien.....	16
	<i>Clinical and laboratory criteria necessary for clinical use</i>	17
2.4.3.	Schwerpunkt der klinischen Anwendungen	18
	<i>Main clinical uses</i>	19
2.4.4.	Rolle von Leitlinien.....	18
	<i>Role of guidelines.....</i>	19
2.4.5.	Verfügbarkeit und ökonomische Aspekte	18
	<i>Impact of supply and economic aspects</i>	19
2.5.	GERINNUNGSFAKTOREN.....	20
	CLOTTING FACTOR CONCENTRATES	21
2.5.1.	Epidemiologische Aspekte.....	20
	<i>Epidemiological aspects.....</i>	21
2.5.2.	Organisation der Hämophilen-Betreuung.....	20
	<i>Organisaton of haemophilia care</i>	21
2.5.3.	Auswahl der Blutprodukte.....	22
	<i>Choice of blood products</i>	23
2.5.4.	Therapie der Hämophilie.....	24
	<i>Therapy for haemophilia.....</i>	25
2.5.5.	Prophylaktische Therapie	24
	<i>Prophylactic therapy.....</i>	25
2.6.	QUALITÄTSMANAGEMENT.....	24
	QUALITY MANAGEMENT.....	25
2.6.1.	Probleme	26
	<i>Problems</i>	27
2.6.2.	Qualitätsmanagement-System	28
	<i>Quality management system.....</i>	29
2.6.3.	Aufgaben und Verantwortlichkeiten.....	28
	<i>Tasks and responsibilities</i>	29
2.7.	ÖKONOMISCHE ASPEKTE.....	32
	ECONOMIC ASPECTS.....	33
2.7.1.	Perspektiven	34
	<i>Perspectives</i>	35
2.7.2.	Informationsbedarf.....	34
	<i>Information needs</i>	35
2.7.3.	Ökonomische Evaluation	34
	<i>Economic evaluations</i>	35
3.	EMPFEHLUNGEN.....	36
	RECOMMENDATIONS.....	37
3.1.	ERYTHROZYTENKONZENTRATE.....	36
	RED BLOOD CELLS	37
3.1.1.	Versorgung.....	36
	<i>Supply.....</i>	37
3.1.2.	Verbleibendes Risiko.....	36
	<i>Residual Risk.....</i>	37
3.1.3.	Klinische Wirksamkeit.....	36
	<i>Efficacy</i>	37
3.1.4.	Unangemessener Gebrauch	38
	<i>Inappropriate Use</i>	39
3.2.	THROMBOZYTENKONZENTRATE.....	38
	PLATELETS	39
3.2.1.	Produkte und ihre Verfügbarkeit.....	38
	<i>Products and their availability.....</i>	39
3.2.2.	Indikationen und Transfusionsgrenzen	38
	<i>Indications and platelet transfusion levels.....</i>	39
3.2.3.	Dosierung und klinische Wirksamkeit.....	40
	<i>Dosage and efficacy</i>	41

3.2.4.	<i>Refraktärzustände</i>	40
	<i>Refractoriness</i>	41
3.2.5.	<i>Qualitätsaspekte und Hämovigilanz</i>	40
	<i>Quality aspects and haemovigilance</i>	41
3.3.	GEFRORENES FRISCHPLASMA	40
	FRESH FROZEN PLASMA	41
3.4.	ALBUMIN	42
	ALBUMIN	43
3.5.	GERINNUNGSFAKTOREN	42
	CLOTTING FACTOR CONCENTRATES	43
3.6.	QUALITÄTSMANAGEMENT	44
	QUALITY MANAGEMENT	45
3.7.	ÖKONOMISCHE ASPEKTE	46
	ECONOMIC ASPECTS	47
3.7.1.	<i>Information</i>	46
	<i>Information needs</i>	47
3.7.2.	<i>Zukünftige Anforderungen</i>	46
	<i>Future demands</i>	47
3.7.3.	<i>Anforderungen an die Schulung</i>	48
	<i>Education requirements</i>	49
3.7.4.	<i>Allgemeine Empfehlung</i>	48
	<i>General recommendation</i>	49
DISCUSSION PAPERS		51
1.	BACKGROUND DOCUMENT	53
1.1.	Introduction	53
1.2.	Background	53
1.3.	Towards optimal use	54
2.	RED BLOOD CELLS	56
2.1.	Introduction	56
2.2.	Background	56
2.3.	Medical indications for transfusion	57
2.4.	Conservation of erythrocytes	58
2.4.1.	<i>Recombinant erythropoietin</i>	58
2.4.2.	<i>Pharmacological interventions</i>	58
2.4.3.	<i>Intraoperative normovolaemic haemodilution</i>	59
2.4.4.	<i>Autologous blood transfusion</i>	59
2.4.5.	<i>Autologous blood salvage</i>	60
2.5.	Screening requirements	60
2.5.1.	<i>PCR</i>	60
2.5.2.	<i>Filtration/ leucocyte depletion</i>	60
2.6.	Closing remark	61
3.	PLATELET CONCENTRATES	62
3.1.	Introduction	62
3.2.	Background	62
3.3.	Medical indications for transfusion	63
3.4.	Reducing need for platelets	64
3.5.	Screening requirements	64
3.5.1.	<i>Filtration/leucocyte depletion</i>	64
3.6.	Recipients refractory to platelet transfusion	65
3.7.	Closing remark	65
4.	ALBUMIN	66
4.1.	Introduction	66
4.2.	Background	66
4.3.	Current clinical use	66
4.4.	Outlook	67

5.	FRESH FROZEN PLASMA.....	69
5.1.	Introduction.....	69
5.2.	Background.....	69
5.3.	Current clinical use.....	69
5.4.	Concluding remark.....	71
6.	COAGULATION FACTOR CONCENTRATES / FACTOR VIII & IX.....	72
6.1.	Introduction.....	72
6.2.	Background.....	72
6.3.	Therapeutic aspects.....	73
6.3.1.	<i>The role of prophylaxis.....</i>	<i>73</i>
6.3.2.	<i>Recombinant products.....</i>	<i>74</i>
6.3.3.	<i>Patients with inhibitory antibodies.....</i>	<i>74</i>
6.4.	Organisational aspects.....	75
6.5.	Economic aspects.....	75
7.	QUALITY MANAGEMENT.....	76
7.1.	Introduction.....	76
7.2.	Background.....	76
7.3.	Provision of health care.....	77
7.4.	Implementing quality management.....	77
7.5.	In-process control.....	79
7.6.	Concluding remark.....	79
8.	ECONOMIC ASPECTS.....	80
8.1.	Introduction.....	80
8.2.	Background.....	80
8.3.	Assessing outcomes of blood product use.....	80
8.4.	Economic evaluation.....	81
8.5.	Cost-savings.....	81
8.6.	Effectiveness of blood use.....	82
8.7.	Concluding remarks.....	82
	SYLLABUS.....	83
1.	RED BLOOD CELLS.....	85
1.1.	Studies and Articles.....	85
1.2.	Guidelines and Recommendations.....	85
1.3.	Glossary: Conservation, Documentation, Crossmatch and Side-Effects.....	91
1.3.1.	<i>Conservation.....</i>	<i>91</i>
1.3.2.	<i>Documentation.....</i>	<i>92</i>
1.3.3.	<i>Side effects.....</i>	<i>92</i>
1.3.4.	<i>Crossmatch.....</i>	<i>93</i>
1.4.	Literature.....	94
1.5.	Glossary: Literature.....	95
2.	PLATELETS.....	96
2.1.	Indications, transfusion triggers, doses.....	96
2.2.	Dosage.....	98
2.3.	Refractoriness.....	98
2.4.	Glossary: thrombocyte concentrates - production and preparations ⁽¹⁸⁾	102
2.4.1.	<i>Production.....</i>	<i>102</i>
2.4.2.	<i>Preparations.....</i>	<i>102</i>
2.5.	Literature.....	103
3.	ALBUMIN.....	104
3.1.	Indications and studies.....	104
3.2.	Surgery: peri-operative period.....	104
3.3.	Thermal injury.....	104
3.4.	Hypoalbuminaemia in patients receiving parenteral nutrition.....	105
3.5.	Albumin administration in children.....	105
3.6.	Randomised Clinical trials.....	109
3.7.	Guidelines and recommendations.....	109

3.8.	Glossary: albumin - production and effective components ⁽²⁰⁾	115
3.8.1.	<i>Production</i>	115
3.8.2.	<i>Effective components</i>	115
3.9.	Literature	116
4.	FRESH-FROZEN PLASMA	119
4.1.	Clinical trials	119
4.2.	Guidelines and recommendations	120
4.3.	Glossary: FFP - production, quarantine storage, quality criteria and effective components ⁽⁸⁾	125
4.3.1.	<i>Production</i>	125
4.3.2.	<i>Quality criteria</i>	125
4.3.3.	<i>Quarantine storage</i>	125
4.3.4.	<i>Effective components</i>	125
4.4.	Literature	126
5.	COAGULATION FACTOR CONCENTRATES (FACTOR VIII & IX)	127
5.1.	General remarks and recommendations ^(CA)	127
5.2.	Choice of concentrates	128
5.3.	Comprehensive care ^(CA / US-G)	131
5.4.	Continuous infusion	131
5.5.	Inhibitor treatment ^(CA / NL / NZ / ZA / CH / UK)	132
5.5.1.	<i>Inhibitor treatment – acute bleeding</i>	134
5.5.2.	<i>Inhibitor treatment – immunoadsorption</i> ^(CA / DE / IT / NL / NZ / SE / CH / UK)	134
5.5.3.	<i>Inhibitor treatment – immunosuppression</i> ^(CA / NZ)	136
5.5.4.	<i>Inhibitor treatment - Immune tolerance treatment (ITT)</i>	136
5.6.	Product / treatment material use in general ^(KE / NZ / UK)	137
5.7.	Prophylaxis ^(AU / CA / DE / IS / IT / NL / NZ / SE / CH / UK)	138
5.8.	Treatment at home ^(CA / IS / NL / SE / US-G)	141
5.9.	Literature and References	141
5.10	National Treatment Guidelines	142
6.	QUALITY MANAGEMENT IN HAEMOTHERAPY	145
6.1.	Quality management	145
6.2.	Quality in haemotherapy: clinical guidelines	145
6.2.1.	<i>Quality criteria of clinical guidelines</i>	146
6.2.2.	<i>Level of evidence</i>	146
6.2.3.	<i>Development of clinical guidelines</i>	147
6.2.4.	<i>Central versus decentral development of clinical guidelines</i>	147
6.3.	Quality of structure, processes and outcome in haemotherapy	148
6.4.	Glossary: Quality	149
6.5.	Literature and references	150
7.	ECONOMIC ASPECTS IN MEDICINE	151
7.1.	Economic evaluations in medicine	151
7.2.	When do we need a socioeconomic evaluation?	152
7.3.	Concept of costs and consequences	152
7.3.1.	<i>Costs</i>	152
7.3.2.	<i>Consequences</i>	154
7.3.3.	<i>Discounting</i>	155
7.4.	Marginal and Incremental Costs	155
7.5.	Externalities	156
7.6.	Conclusion	156
7.7.	Glossary: Health Economics	157
7.8.	Literature	161
7.9.	Further Literature	162
TABELLEN		165
LIST OF TABLES		165

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der
Europäischen Gemeinschaft



**BLUTSICHERHEIT
IN DER EUROPÄISCHEN GEMEINSCHAFT:
EINE INITIATIVE FÜR OPTIMALE ANWENDUNG**

*Unter der Schirmherrschaft
des Bundesgesundheitsministeriums
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Wildbad Kreuth, Deutschland
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Schlußfolgerungen und Empfehlungen



BLOOD SAFETY IN THE EUROPEAN COMMUNITY: AN INITIATIVE FOR OPTIMAL USE

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Conclusions and Recommendations

1. EINLEITUNG

1. Die Experten der Wildbad Kreuth Initiative stimmen darin überein, daß:

- Blut und die aus ihm gewonnenen Blutprodukte wesentliche Hauptbestandteile klinischer Therapie und präventiver Medizin darstellen;
- die therapeutische Anwendung von Blut und Blutprodukten das letztliche Ziel aller transfusionsmedizinischer Einzelprozesse darstellt;
- auch in Zukunft erhebliche Anstrengungen unternommen werden müssen, um Qualität, Sicherheit und Effektivität von Blut und Blutprodukten während des Sammelprozesses, der Verarbeitung und der Verteilung zu gewährleisten;
- die Sicherung höchster Sicherheitsstandards in der Anwendung von Blut und Blutprodukten dazu beiträgt, das Vertrauen der Bürger der Europäischen Gemeinschaft in die Blutspende-Institutionen zu stärken;
- unnötige und unangemessene Anwendung von Blut und Blutprodukten vermieden werden muß;

und unterstützen die fortlaufenden Anstrengungen der Europäischen Gemeinschaft zur Entwicklung und Implementierung einer einheitlichen Strategie bezüglich Blut und Blutprodukten, wie bereits durch das Europäische Parlament, den Europäischen Rat und die Europäische Kommission bestätigt.

2. Als Beitrag zur Verwirklichung dieses Ziels und entsprechend den Beschlüssen des Europäischen Rats vom Juni 1995¹ und vom November 1996², und weiterhin unter Berücksichtigung der Anforderungen des Artikels 152 des Amsterdamer Vertrages unter anderem bezüglich eines hohen Standards der Qualität und der Sicherheit von Blut und Blutprodukten, wurden von den Teilnehmern der Wild Bad Kreuth Initiative zentrale Fragestellungen bezüglich der therapeutischen Anwendung von Erythrozytenkonzentraten, Thrombozytenkonzentraten, GFP, Albumin, der Gerinnungsfaktoren VIII und IX, als auch ökonomische Aspekte und Aspekte des Qualitätsmanagements erörtert. Die im Anschluß an Problemfindung und Diskussion von Lösungsmöglichkeiten erarbeiteten Schlußfolgerungen und Empfehlungen werden im Folgenden präsentiert:

2. SCHLUSSFOLGERUNGEN

3. Die therapeutische Anwendung von Blut und Blutprodukten ist einer der letzten Schritte in einer Folge komplexer Abläufe, die damit beginnt, daß ein Spender Blut oder Plasma zum Nutzen Dritter zur Verfügung stellt und die mit der Nachbehandlung des Patienten, der das entsprechende Blutprodukt erhalten hat, endet. Beträchtliche Aufmerksamkeit wurde in der Vergangenheit darauf verwendet, das gesammelte Material und die anschließenden Verarbeitungs- und Verteilungsprozesse so sicher wie möglich zu machen. Obwohl auch der therapeutischen Anwendung durch die Erstellung von Leitlinien und Konsensus-Konferenzen etc. Aufmerksamkeit geschenkt wurde, sind die diesbezüglichen Ergebnisse nicht zufriedenstellend. Der übermäßige, zu geringe oder der unangebrachte Gebrauch von Blut und Blutprodukten besteht weiterhin. Dies kann zu einem erhöhten Risiko für Patienten und zur Verschwendung von Ressourcen beitragen.

¹ O.J. No C164, 30.6.95. p.16

² O.J. No C374, 11.12.96. p.1

1. INTRODUCTION

1. The experts participating in the 'Wildbad Kreuth Initiative', recognising that:

- blood and the blood products derived from it are a mainstay in clinical treatment and preventive medicine;
- the therapeutic use of these products is the ultimate goal of the blood transfusion chain;
- significant efforts continue to be made in ensuring the quality, safety and efficacy of blood and blood products during collection, processing, and distribution;
- ensuring the highest level of safety in the use of blood and blood products can contribute to improving confidence among Community citizens in the blood services; and
- the unnecessary and inappropriate use of blood and blood products needs to be avoided;

support the on-going efforts towards the development and future implementation of a blood strategy in the European Community already endorsed by the European Parliament, the Council of the European Union, and the European Commission.

2. To contribute towards the attainment of this goal, and pursuant to the Council Resolutions of June 1995¹, and November 1996², and taking into account the requirements of Article 152 of the Treaty of Amsterdam regarding *inter alia* a high standard of quality and safety of blood and blood derivatives, participants discussed key issues related to the therapeutic use of red blood cells, platelets, fresh frozen plasma, albumin, coagulation factors VIII and IX, as well as associated economic and quality management aspects. Following identification and discussion of key problems and possible options for action, participants arrived at the following conclusions and recommendations.

2. CONCLUSIONS

3. The therapeutic use of blood and blood products is one of the final steps in a series of complex processes that begins with the willingness of a donor to provide blood or plasma for the benefit of others and ends with the follow-up of the patient who has received such products. Considerable attention has been given to ensuring that the material collected and the processes adhered to in the preparation and distribution of these products are as safe as possible. While attention has also been given to the therapeutic use of these products through the preparation of guidelines, consensus conferences etc., there is increasing evidence that the results have been less than satisfactory and as a consequence over-use, under-use and inappropriate use of blood and blood products persists. This can contribute to increased risks for patients and the waste of resources.

¹ O.J. No C164, 30.6.95. p.16

² O.J. No C374, 11.12.96. p.1

2.1. ERYTHROZYTENKONZENTRATE

4. Erythrozyten sind die Träger des Hämoglobins und notwendig für die Aufnahme, den Transport und die Weitergabe von Sauerstoff in Lunge und Gewebe.

2.1.1. Probleme

5. Um Fragestellungen bezüglich der therapeutischen Verabreichung von Erythrozytenkonzentraten erörtern zu können, müssen zunächst verschiedene Probleme in Betracht gezogen werden. Diese beinhalten:
 - Versorgung. In unregelmäßigen Abständen kommt es zur ernsthaften Unterversorgung mit Erythrozytenkonzentraten (zur Transfusion) in den Krankenhäusern der Europäischen Gemeinschaft.
 - Restrisiko. Ein mit der Transfusion von Erythrozytenkonzentraten verbundenes Restrisiko verbleibt, wie durch nationale Studien gezeigt wurde [z.B. Studien der Agence Française du Sang in Frankreich, SHOT – Studie (Serious Hazards of Transfusion) in England];
 - Effektivität. Eine optimale Lagerungszeit, definiert durch den klinischen Nutzen, wurde bis jetzt nicht bestimmt.
 - Evidenz. Ausreichende Evidenz als Grundlage für fundierte Schlußfolgerungen ist für viele wichtige Aspekte im Bereich der Transfusionspraxis nicht vorhanden, z.B. bezüglich der Sicherheit von Eigenblutspende im Vergleich mit allogener Transfusion, bezüglich sogenannter “Transfusionstrigger”, oder bezüglich der Qualität von Erythrozytenkonzentraten.
 - Standards für Blutprodukte. Ein einheitlicher Standard für Blutprodukte innerhalb der Länder der Europäischen Gemeinschaft ist nicht vorhanden. Ein solcher Standard könnte den Vergleich von Daten zwischen am Umgang mit Blut und Blutprodukten beteiligten Einrichtungen erleichtern.
 - Unangemessene Anwendung. Große Unterschiede im Gebrauch von Blut innerhalb von Krankenhäusern und zwischen verschiedenen Krankenhäusern weisen auf eine beträchtliche Überkonsumierung hin. Diese Unterschiede implementieren Unterschiede in der chirurgischen Vorgehensweise, im Blutverlust und in Einsparstrategien.

Da bis zu 70 % der Erythrozytenkonzentrate für chirurgische Patienten bestimmt sind und die Überkonsumierung, wie anhand von Studien gezeigt wurde, ungefähr 30 % beträgt, ist es besonders wichtig der perioperativen Anwendung von Erythrozytenkonzentraten besondere Aufmerksamkeit zu widmen.
6. Der Einfluß von Leitlinien und Empfehlungen auf die Verschwendung und den übermäßigen Gebrauch von Blut ist gering. Da klinische Entscheidungen auf individuellen und häufig sehr subjektiven Einschätzungen der jeweiligen Situation beruhen, ist es möglich, daß bestimmte Empfehlungen den Verbrauch von Blut sogar erhöhen.

2.1. RED BLOOD CELLS

4. Red blood cells are the carriers of haemoglobin and are necessary for the uptake, transport and transfer of oxygen in the lung and tissues.

2.1.1. Problems

5. In addressing issues related to the therapeutic use of red blood cells, several problems need to be taken into consideration. These include:
 - Supply. From time to time severe shortages of red cells for transfusion arise in hospitals within the European Community (EC);
 - Residual risk. A persistent residual risk associated with red cell transfusions exists as indicated by national surveys [e.g. those of the Agence Française du Sang and SHOT (Serious Hazards of Transfusion) of the United Kingdom];
 - Efficacy. Optimum storage time as defined by clinical utility has never been determined.
 - Evidence base. Sound evidence on which to base firm conclusions on many important aspects of transfusion practice is lacking, e.g. the comparative safety of autologous and allogeneic transfusion programmes, transfusion triggers, and the quality of red blood cells.
 - Standard blood components. A single standard in place for blood components is wanting in the EC. Such a standard would facilitate the comparison of data between blood establishments throughout the Community.
 - Inappropriate use. Wide variations in blood use within and between hospitals is an indication of significant overuse. These variations include differences in surgical technique, as well as blood loss and conservation strategies.

As up to 70% of red cell use is for surgical patients, continued overuse in the order of 30%, as indicated by studies, highlights the need to focus attention on the perioperative use of red cell transfusions.
6. The impact of guidelines and recommendations on reducing the waste and overuse of blood products is poor. As clinical decisions are based on individual and often highly subjective assessments of the situation, some recommendations may even enhance the use of blood products.

7. Es liegen zunehmend Daten vor, die zeigen, daß die Transfusion von Erythrozytenkonzentraten nicht notwendigerweise die Morbidität und Mortalität von Patienten, die aufgrund von Blutverlusten bei elektiven Eingriffen, im Rahmen der Intensivmedizin, oder aufgrund anderer Indikationen transfundiert wurden, senkt und daß sie sogar mit einem schlechteren Outcome assoziiert sein kann.
8. Derzeit steht noch keine effektive, nicht-invasive Methode zur Messung der Sauerstoffabgabe in Geweben zur Verfügung, um den Entscheidungsprozess bei Transfusionen zu unterstützen. Bestehende Angaben zur Sauerstoffabgabe an vitale Organe bei Notfallpatienten und im Rahmen größerer Operationen haben wahrscheinlich zu einer höheren Verabreichung von Erythrozytenkonzentraten geführt.

2.1.2. Analyse

9. Die unangebrachte Transfusion von Erythrozytenkonzentraten in der Chirurgie erhöht das Risiko für die Patienten, erhöht die Kosten für das Gesundheitswesen und trägt außerdem zur Knappheit von Blut bei. Auf der anderen Seite liegt ohne diese Transfusionen für anämische Patienten eine erhöhte postoperative Morbidität und Mortalität vor. Das Risiko ist für Patienten mit einer kardiovaskulären Grunderkrankung erhöht und steigt weiter mit dem perioperativen Blutverlust.
10. Das Risiko für die postoperative Morbidität und Mortalität kann vermindert werden, indem einer Anämie durch folgende Maßnahmen vorgebeugt wird: Reduzierung des durch chirurgische und diagnostische Maßnahmen bedingten Blutverlustes, perioperative Vermeidung einer Anämie, und – soweit möglich - Behandlung einer vorliegenden kardiovaskulären Erkrankung. Der Stellenwert perioperativer Transfusionen bei der Reduzierung dieses Risikos ist unklar. Allgemein zeigen die veröffentlichten Daten, daß bei Erwachsenen die Transfusion von Erythrozytenkonzentraten unterhalb einer Hämoglobinkonzentration von 6 g/dl erforderlich wird und oberhalb von 10 g/dl kaum notwendig ist. Vergleichende Studien mit Erwachsenen mit Hämoglobinkonzentrationen zwischen 6 – 10 g/dl haben nicht gezeigt, daß die Transfusion von Erythrozytenkonzentraten das Outcome chirurgischer und intensivmedizinischer Patienten verbessert.
11. Die Indikation zur perioperativen Transfusion von Erythrozytenkonzentraten sollte von Patient zu Patient gestellt werden, in Abhängigkeit von relevanten klinischen Parametern und nicht anhand einer vorgefaßten Transfusionsformel. Zu solchen Parametern können hämodynamische Instabilität, wie z.B. Hypotonie, Tachykardie oder andere Rhythmusstörungen, oder Veränderungen der ST-Strecke im EKG bei normovolämischen Patienten gehören.
12. Ähnliche Prinzipien können für erwachsene internistische Patienten angewendet werden. Transfusionen bei chronischer Anämie werden im Allgemeinen zur symptomatischen Therapie verabreicht.

2.1.3. Erhaltung des Blutvolumens

13. Optimales Management des Patienten und optimales Management der Anwendung von Blut im perioperativen Bereich sind notwendig, um den Bedarf an Transfusionen zu reduzieren. Dies schließt die Beachtung von Blut-Einsparprogrammen ein, mit dem Ziel, die Notwendigkeit allogener und autologer Transfusionen zu vermindern, ohne das Risiko für den Patienten zu erhöhen.

7. There is an increasing amount of supportive data to show that red cell transfusions do not necessarily reduce morbidity and mortality in patients transfused due to blood losses during elective surgery, in intensive care, or for other indications, and may even be associated with negative outcomes.
8. There is currently no effective non-invasive method of measuring tissue oxygen delivery to aid in the transfusion decision-making process. Existing protocols for oxygen delivery to vital organs in patients under critical care or undergoing major surgery may have led to increased administration of red blood cells.

2.1.2. Analysis

9. Inappropriate red cell transfusion in surgery increases risk to patients, augments health care costs, as well as contributes to blood shortages. On the other hand, without such transfusions anaemic patients are at increased risk of postoperative morbidity and mortality. This risk increases in those with concomitant cardiovascular disease, and increases further with perisurgical blood loss.
10. The risk of postoperative morbidity and mortality can be diminished by preventing anaemia through: the reduction of surgical and diagnostic blood losses, the preoperative reversal of anaemia, and by treating cardiovascular disease where possible. The role of perioperative blood transfusions in reducing this risk is unclear. In general, the published data indicate that in adults red cell transfusions will usually be required when the haemoglobin level is <6 g/dl, and will rarely be required when it is >10 g/dl. Comparative studies in adults with haemoglobin levels within the range of 6 – 10 g/dl have not shown red cell transfusions to improve outcome in surgical and intensive-care-unit (ICU) patients.
11. Indications for perioperative transfusions of red cells, however, should be determined on a patient by patient basis according to relevant clinical signs and not according to a predetermined transfusion formula. Such signs may include haemodynamic instability, e.g. hypotension, tachycardia or other dysrhythmias, or changes in the ST segment of the electrocardiogram in normovolaemic patients.
12. Similar principles can be applied to adult medical patients. Transfusions in chronic anaemia are generally given for relief of symptoms.

2.1.3. The role of blood conservation

13. Optimum patient management and blood use in the perioperative setting are needed in order to reduce all transfusion requirements. This includes attention to blood conservation programmes with the goal of reducing the need for allogeneic and autologous transfusion, without increasing the risk for the patient.

14. Diese Maßnahmen beinhalten:

- Qualifizierte Erfassung jedes Patienten vor OP mit Hinblick auf Transfusionsbedürfnisse, einschließlich – sofern erforderlich – der präoperativen Behandlung einer Anämie.
- Das Bemühen von chirurgischer Seite, Blutverluste zu vermeiden;
- Die Verfügbarkeit entsprechender autologer Transfusionsverfahren;
- Die Anwendung bewährter medikamentöser Verfahren;
- Die optimale Einstellung der Gerinnung, einschließlich der Erhaltung der Körpertemperatur des Patienten während der perioperativen Phase; und
- Die fortwährende Evaluation der Sicherheit und klinischen Wirksamkeit von Blut und Blutprodukten auf lokaler und internationaler Ebene.

15. Zu präoperativen Behandlung einer Anämie sollte die Auffüllung der Eisenspeicher und nicht die prophylaktische Verabreichung von Erythrozytenkonzentraten gehören.

2.2. THROMBOZYTENKONZENTRATE

16. Thrombozyten spielen eine Hauptrolle in der primären Hämostase und sind an der Bildung des hämostatischen Pfropfs beteiligt.

2.2.1. Probleme

17. In Zusammenhang mit der optimalen Anwendung von Thrombozyten müssen die folgenden Probleme beachtet werden:

- Unterschiede in der Verfügbarkeit und in der klinischen Anwendung von Thrombozytenkonzentraten innerhalb der Europäischen Gemeinschaft;
- Das Fehlen von Methoden, um das aktuelle, von Thrombozyten abhängige, Blutungsrisiko eines Patienten zu erkennen und abzuschätzen;
- Die Notwendigkeit, verbesserte Methoden zum Monitoring der klinischen Wirksamkeit von Thrombozytentransfusionen zu entwickeln und zu implementieren; und
- Das Fehlen von verlässlichen Hämovigilanz-Daten zu Thrombozyten;

18. Unter Berücksichtigung dieser Probleme sind verschiedene Schlußfolgerungen möglich.

2.2.2. Produkte und ihre Verfügbarkeit

19. Die Unterschiede in den verschiedenen Aufbereitungen und in der Verfügbarkeit, als auch die jeweilige Indikation für gepoolte und durch Apherese gewonnene Thrombozytenkonzentrate müssen berücksichtigt werden. Es gibt regionale und saisonale Schwankungen, die zu einer Knappheit von Thrombozyten führen können, obwohl nicht bekannt ist, ob diese Knappheit klinische Relevanz besitzt oder nicht.

20. Thrombozyten mit seltenen Phänotypen (HLA- und HLA-Typisierung) können unter Umständen schwer verfügbar sein.

14. These programmes include:

- Skilled evaluation of each patient before surgery with a view to managing their transfusion requirements, including preoperative treatment of anaemia where required;
- Emphasis by surgeons on avoiding blood losses;
- Availability of appropriate autologous transfusion programmes;
- Use of proven pharmacological strategies;
- Optimal coagulation management, including maintaining the patient's body temperature in the perioperative period; and
- Ongoing evaluation of safety and efficacy of blood and blood products at local and international levels.

15. Pre-operative treatment of anaemia should entail the restoration of iron stores and not the use of prophylactic transfusion of red cells.

2.2. PLATELETS

16. Platelets play a major role in primary haemostasis and are involved in the formation of the haemostatic plug.

2.2.1. Problems

17. In relation to the optimal use of platelets, the following problems need to be considered:

- the variation in availability and clinical use of platelets throughout the European Community;
- the lack of methods to identify and to estimate the actual platelet-related bleeding risk in the patient;
- the need to develop improved methods to monitor the efficacy of platelet transfusions and to implement them; and
- the lack of reliable haemovigilance data on platelet transfusion.

18. Bearing these in mind, several conclusions can be reached.

2.2.2. Products and their availability

19. Differences in the preparations and availability of, and indications for, pooled and apheresis platelet concentrates need to be recognised. Regional and seasonal variations, which can result in a relative shortage of platelets, exist although whether such shortages have any clinical consequences is not known.

20. Platelets of rare phenotypes may be difficult to have readily available (HLA- and HPA-typed).

21. Die Einführung neuer Screening-Tests, wie DNA-Nachweisverfahren, können die Verfügbarkeit von Thrombozytenkonzentraten reduzieren und eine Verzögerung in ihrer Bereitstellung verursachen. Es ist offensichtlich, daß die unmittelbare Konsequenz, die sich aus der Einführung solcher Tests ergibt, eine Verlängerung der durchschnittlichen Lagerdauer ist.

2.2.3. Indikationen und Transfusionstrigger

22. Thrombozytenkonzentrate sind indiziert zur Behandlung von Blutungsereignissen, die mit einer niedrigen Thrombozytenzahl oder einer herabgesetzten Thrombozytenfunktion einhergehen. Prophylaktische Transfusionen werden als wirksam bei einer durch Knochenmarkshypo- oder -dysplasie bedingten Thrombozytopenie betrachtet.
23. Die Patientenpopulation, die die prophylaktische Gabe von Thrombozyten benötigt, ist heterogen, so daß allgemeine Transfusionstrigger nicht zur Anwendung kommen können. Die Kriterien, aufgrund derer die Entscheidung zur Transfusion von Thrombozyten getroffen wird, variieren sogar innerhalb spezifischer Diagnosegruppen und können nicht auf der Thrombozytenzahl basieren.
24. Eine Thrombozytopenie kann auf einen erhöhten Abbau von Thrombozyten zurückzuführen sein. Hier sind Thrombozytentransfusionen nur selten indiziert, z.B. wenn es darum geht, ernsthafte Blutungen zu unterbrechen.

2.2.4. Dosierung und klinische Wirksamkeit

25. Bezüglich der Dosierung von Thrombozyten sind Unterschiede in der Praxis bekannt. Die einzelne Dosis kann um das zwei- bis dreifache variieren. Die Transfusion einer angemessenen Dosis geht mit einem meßbaren Anstieg der Thrombozytenzahl und der Unterbrechung der Blutung einher. Wissenschaftliche Daten zur Beurteilung der klinischen Wirksamkeit, wie z.B. die verminderte Notwendigkeit zur Erythrozytentransfusion oder eine verminderte Anzahl an Tagen mit Blutungsrisiko, sind nur spärlich vorhanden.

2.2.5. Refraktärzustände

26. Refraktärzustände sind durch das Ausbleiben der erwarteten Antwort nach Thrombozytentransfusion gekennzeichnet: Der Refraktärzustand bei einem Patienten kann immunologischen oder nicht-immunologischen Ursprungs sein.
27. Immunologische Refraktärzustände sind hauptsächlich auf eine HLA-abhängige Alloimmunisierung zurückzuführen. Obwohl es prinzipiell möglich ist, dem Patienten HLA-kompatible Thrombozytenkonzentrate zukommen zu lassen, sind diese nicht immer verfügbar. Nicht-immunologische Refraktärzustände können z.B. durch Fieber, eine disseminierte intravasale Gerinnung (DIC), eine Septikämie, eine Splenomegalie oder durch eine Antibiotikatherapie verursacht sein.
28. Es besteht keine Evidenz, daß sich leukozytendepletierte, durch Apherese gewonnene Thrombozytenkonzentrate von gepoolten Thrombozytenkonzentraten hinsichtlich des klinischen Outcomes, einschließlich des Risikos zur Induktion von Autoantikörpern unterscheiden.

21. The introduction of new screening tests such as those based on nucleic acid amplification technology (NAT) may reduce the availability of platelet concentrates and cause delays in their release. It is evident that the immediate consequence of introducing such tests will be the prolongation of the average storage time.

2.2.3. Indications and platelet transfusion threshold levels

22. Platelet transfusions are indicated for the treatment of bleeding associated with low platelet count or deficient function. Prophylactic platelet transfusions are considered to be effective in thrombocytopenia due to bone marrow hypo- and dysplasia.
23. The patient population that may need prophylactic platelet support is heterogeneous and general trigger levels cannot be applied. The criteria upon which the decision to transfuse platelets is made, even for specific diagnosis groups, vary and cannot be based on platelet count.
24. Thrombocytopenia may be due to increased platelet destruction, where platelet transfusions may rarely be indicated, e.g. to stop serious bleeding.

2.2.4. Dosage and efficacy

25. When it comes to the dosage of platelets administered, variations in practice have been reported. A single dose itself may vary 2 - 3 fold. It is recognised that the transfusion of an appropriate dose is followed by a measurable increase in platelet level and parallels the cessation of bleeding. The amount of scientific data upon which efficacy can be measured, however, is scarce: e.g. reduced need for red cell transfusions, reduced number of days at risk of bleeding.

2.2.5. Refractoriness

26. Refractoriness is characterised by a failure to achieve the expected response after consecutive platelet transfusions: the refractory state in the patient may be of immunological or non-immunological origin.
27. Immunological refractoriness is due primarily to HLA-alloimmunisation. Although it may be possible to support the patient with HLA compatible platelets, these may not always be available. Non-immunological refractoriness may be due to e.g. bleeding, fever, disseminated intravascular coagulation (DIC), septicemia, splenomegaly, and antibiotic treatment.
28. There is no evidence that leucodepleted apheresis platelet concentrates differ from leucodepleted pooled concentrates in terms of clinical outcome including the risk of inducing alloantibodies.

2.2.6. Aspekte der Qualität und der Transfusionssicherheit

29. Sowohl das Fehlen von verbindlichen Indikationen, als auch die zusätzliche Verabreichung von Acetyl-Salicylsäure (ASS) oder von nichtsteroidalen Antiphlogistika (NSAR) können zur unangebrachten Anwendung von Thrombozytenkonzentraten beitragen.
30. Weiterhin kann die Vernachlässigung von Medikamenten, die die Hämostase unterstützen (z.B. Aprotinin, Desmopressin oder Tranexamsäure) und von Medikamenten zur Korrektur von Anämien und Gerinnungsdefekten zu einem überhöhten Verbrauch von Thrombozytenkonzentraten beitragen.
31. Die Transfusion von Thrombozyten kann zu unerwünschten Effekten, wie zur Alloimmunisierung, zu Refraktärzuständen, zu einer Graft-versus-Host-Krankheit (GvHD) oder zu durch kontaminierte Thrombozytenkonzentrate bedingte Symptomen führen.
32. Transfusionskomitees zur Aufsicht der Transfusionsabläufe im Krankenhaus und zu ihrer fortlaufenden Verbesserung, sowie Hämovigilanz-Systeme / Systeme zur Sicherheit des Transfusionswesens sind noch nicht innerhalb der gesamten Europäischen Gemeinschaft eingeführt.

2.3. GEFRORENES FRISCHPLASMA

33. Gefrorenes Frischplasma (GFP) ist der antikoagulierte, flüssige Anteil des Blutes, der durch Abtrennung der Blutzellen gewonnen wird (durch Zentrifugieren von Vollblut oder durch Apherese) und bis zur Transfusion eines Patienten gefroren gelagert wird. GFP enthält sämtliche Plasmaproteine, z.B. Gerinnungsfaktoren und –inhibitoren in physiologischer Konzentration. Zur Erhöhung der Sicherheit und zur Abdeckung des diagnostischen Fensters kann GFP über einen bestimmten Zeitraum in Quarantäne gehalten werden, bis der Spender erneut auf virale Marker hin getestet wurde.
34. In den Ländern der Europäischen Gemeinschaft besteht weiterhin der übermäßige und unangebrachte Gebrauch von GFP. Es gibt keinen dokumentierten klinischen Nutzen für die Anwendung zum Volumenausgleich, zur parenteralen Ernährung oder zum Proteinersatz.

2.3.1. Angestrebte Anwendung

35. Der beabsichtigte klinische Nutzen der Infusion von GFP besteht in der Korrektur von komplexen Gerinnungsstörungen, bei denen viele Gerinnungsfaktoren und –inhibitoren beteiligt sind. GFP kann ebenfalls den isolierten Mangel eines Plasmaproteins ausgleichen, sofern das spezifische Produkt nicht verfügbar ist.
36. Der klinische Nutzen der Verabreichung von GFP wurde durch langjährige klinische Erfahrung etabliert und kann anhand der folgenden Zielkriterien eindeutig belegt werden:
 - Klinisches Ergebnis:
 - Blutstillung;
 - Verbesserung des klinischen Bildes nach GFP-Transfusion im Rahmen spezieller klinischer Indikationen, wie z.B. thrombotisch-thrombozytopenische Purpura (TTP) oder Plasma-Austausch.

2.2.6. Quality aspects and haemovigilance

29. Lack of strict indications as well as co-medication with acetosalisylic acid (ASA) or non-salislyic anti-inflammatory drugs (NSAID) may contribute to inappropriate use of platelet concentrates.
30. In addition, failure to consider the use of drugs supporting haemostasis (e.g. aprotinin, desmopressin or tranexamic acid) and to correct anaemia and coagulation defects may contribute to platelet overuse.
31. The transfusion of platelets may cause untoward effects such as alloimmunisation, refractoriness, graft versus host disease (GvHD) or symptoms caused by contaminated platelet products.
32. Transfusion committees to review transfusion practices within the hospital and to contribute to their continuous improvement, as well as haemovigilance systems, are not yet in place throughout the European Community.

2.3. FRESH FROZEN PLASMA

33. Fresh frozen plasma (FFP) is the anticoagulated liquid part of blood that is obtained by separation from the blood cells (centrifugation of whole blood donations or apheresis) and stored frozen until transfusion to patients. FFP contains all plasma proteins, e.g. coagulation factors and inhibitors, in physiological concentrations. For improved safety and in order to cover the diagnostic window, FFP may be quarantined for a specified period until the donor has been retested for viral markers.
34. Overuse and misuse of FFP persists in the European Community. There is no documented benefit for its use in volume replenishment, nutrition, or protein replacement.

2.3.1. Intended use

35. The intended benefit of FFP infusion is in the correction of complex coagulation disorders, where many coagulation factors and inhibitors are involved. FFP may also correct an isolated deficiency of a plasma protein when a specific product is not available.
36. The benefit of FFP administration has been established as a consequence of long-standing clinical experience and can be shown clearly by assessing major endpoints such as:
 - Clinical outcome:
 - Cessation of bleeding;
 - Clinical improvement in specific indications such as thrombotic thrombocytopenic purpura (TTP) after FFP transfusion, or use of FFP for plasma exchange.

- Laboruntersuchungen:
 - Anstieg der Plasmaspiegel von Fibrinogen und anderer Gerinnungsfaktoren;
 - Korrektur der globalen Gerinnungsuntersuchungen [z.B. aktivierte partielle Thromboplastinzeit (aPTT), Thromboplastinzeit (TPZ)], oder spezifischerer Untersuchungen.

2.3.2. Klinische Anwendung von GFP

37. Prinzipiell sollte die Anwendung von GFP immer auf die Behandlung komplexer Gerinnungsstörungen ausgerichtet sein, oder zum Ersatz von für die Gerinnung wichtigen Proteinen, wenn spezifische Produkte nicht verfügbar sind. Zum optimalen Einsatz von GFP sollten mindestens die globalen Gerinnungsuntersuchungen permanent verfügbar sein, da der Anstieg der Gerinnungsfaktoren und das klinische Ansprechen beim einzelnen Patienten beträchtlich variieren können.

38. Es gibt verschiedene, allgemein akzeptierte Indikationen für den Einsatz von GFP:

- Kompensation des Abfalls von Gerinnungsfaktoren bei massiven Blutungen. GFP ist nicht zum Volumenersatz indiziert. Die Möglichkeit komplexer Gerinnungsstörungen sollte in Betracht gezogen und entsprechend abgeklärt werden. Üblicherweise ist die Anwendung von GFP nicht indiziert, wenn der Blutverlust nicht 70 % des gesamten Blutvolumens überschreitet;
- Die disseminierte intravasale Gerinnung (DIC) in Abhängigkeit von der klinischen Situation und von der mit Laboruntersuchungen erfaßten Dynamik des Verbrauchs von Gerinnungsfaktoren und –inhibitoren. Die Anwendung von GFP sollte immer als Teil der jeweiligen therapeutischen Strategie verstanden werden, die von der entsprechenden Grunderkrankung abhängt;
- Thrombotisch thrombozytopenische Purpura (TTP);
- Mangel an Gerinnungsproteinen wie Faktor V oder Faktor XI, Protein C oder Protein S, abhängig von der Verfügbarkeit spezifischer Konzentrate;

39. Bei korrekter Indikationsstellung zur Anwendung von GFP gibt es hierzu keine alternativen Präparate.

40. Gerinnungsstörungen aufgrund gestörter Synthese bei chronischer Leberschädigung stellen keine Indikation für die Anwendung von GFP dar, solange der Patient klinisch stabil ist.

2.3.3. Einfluß verschiedener GFP Qualitäten

41. In den Mitgliedstaaten der Europäischen Gemeinschaft ist GFP in verschiedenen Qualitäten verfügbar. Es kann aus Vollblut-Spenden oder durch Plasmapherese gewonnen werden. Es gibt Quarantäne-gelagerte und Virus-attenuierte GFP-Aufbereitungen aus Einzelspenden oder aus gepooltem Plasma. Aufgrund des unterschiedlichen individuellen Proteingehalts bei Plasmaspendern und den oben erwähnten Unterschieden in der Aufbereitung kann der Gehalt an gerinnungsaktiven Proteinen im GFP beträchtlich variieren. Daher besteht die Notwendigkeit zum Monitoring der klinischen Wirksamkeit von GFP beim jeweiligen Patienten.

- Laboratory tests:
 - Rise of plasma levels of fibrinogen and other coagulation factors;
 - Correction of global coagulation tests [e.g. activated partial thromboplastin time (aPTT) or prothrombin time (PT)], or more specific assays.

2.3.2. Clinical use of FFP

37. As a principle, the use of FFP should always be directed at the treatment of complex coagulation disorders, or replacement of proteins that are relevant for haemostasis, where specific products are not available. For optimal use of FFP, at least global tests for coagulation should be permanently available, since the recovery of coagulation factors and the response in the individual patient may vary considerably.
38. There are several generally accepted indications for using FFP:
- To compensate for the decrease in coagulation factors in massive bleeding. FFP is not indicated for volume replacement. The possibility of relevant coagulation disorders, however, should be considered and adequately assessed. Usually FFP administration is not indicated when blood loss does not exceed 70% of total blood volume;
 - Disseminated intravascular coagulation (DIC) depending on the clinical situation and the dynamics of consumption of factors and inhibitors as assessed by laboratory testing. The use of FFP should always be considered as a part of the therapeutic strategy, which depends on the underlying diseases;
 - Thrombotic thrombocytopenic purpura (TTP);
 - Deficiencies of haemostasis proteins such as factor V or IX, Protein C or Protein S depending on the availability of specific concentrates.
39. If the clinical indication for using FFP is correctly established, there is no alternative to this product.
40. Coagulation disturbances due to impaired synthesis in chronic liver failure are not an indication for FFP as long as the patient is clinically stable.

2.3.3. Impact of different FFP qualities

41. There are different qualities of FFP available in the Member States of the European Community. It may be recovered from whole blood donations or obtained by plasmapheresis. There are quarantined and virus attenuated FFP preparations, which may be single donor units or preparations from pooled plasma. Due to protein variations in the individual blood or plasma donors and the above-mentioned differences in preparations, the content of haemostatic active proteins of FFP may vary considerably. Hence, there is a need for monitoring the efficacy of FFP in the individual patient.

2.3.4. Dosierung und Dauer der Therapie

42. Bei der Behandlung von Gerinnungsstörungen ist es außerordentlich wichtig, daß die initiale Dosis hoch genug ist. Eine initiale Dosis von weniger als 10 ml / kg Körpergewicht ist klinisch nicht wirksam und daher eine Verschwendung von Ressourcen. Bei vielen Patienten ist eine beträchtlich höhere Dosierung notwendig. Die Behandlung mit GFP sollte einem Monitoring unterliegen und an den klinischen Verlauf und die laborchemischen Gerinnungsuntersuchungen angepaßt werden.

2.3.5. Rolle von Leitlinien

43. Obwohl zahlreiche Leitlinien auf nationaler, europäischer und internationaler Ebene existieren, scheint ein allgemeines Defizit in der Umsetzung der darin enthaltenen Anweisungen zu bestehen. Dies ist anscheinend sowohl auf die mangelhafte Verbreitung, als auch auf die mangelhafte Implementierung zurückzuführen.

2.4. ALBUMIN

44. Albumin ist ein natürliches Kolloid und Transportprotein. Humane Albumin-Zubereitungen wurden von Cohn während des Zweiten Weltkrieges als ein Volumenersatz bei Blutverlusten zur Rettung verletzter Soldaten entwickelt. Seitdem wird es seit über 50 Jahren zum Volumenersatz verwendet.
45. Klinische Situationen, die einen Volumenersatz notwendig machen, sind häufig. Heutzutage sind Alternativen in Form von kristalloiden oder kristallinen Substanzen und synthetischen Kolloiden verfügbar. Diese Alternativen sind preiswerter, die maximal zuführbare Menge ist aber durch Nebenwirkungen, wie z.B. Wechselwirkungen mit dem Gerinnungssystem, eingeschränkt.

2.4.1. Angestrebter klinischer Nutzen

46. Der angestrebte klinische Nutzen der Anwendung von humanen Albumin-Lösungen beruht auf theoretischen und pathophysiologischen Überlegungen. Dies trifft sowohl auf die Anwendung von 4 – 5 % -tigen ("isoonkotischen") als auch von 20 – 25 % -tigen ("hyperonkotischen") Lösungen zu. Die Definition klinischer Endpunkte ist jedoch schwierig.

2.4.2. Klinische und laborchemische Kriterien

47. Es besteht wenig Konsens bezüglich der klinischen Kriterien zur Anwendung von Albumin. Allgemeine Vorschläge zur Dosierung und zur Dauer der Therapie sind derzeit nicht möglich. Ein erniedrigter Albumin Serum-Spiegel ist für die Indikationsstellung nicht ausreichend. Es besteht keine Übereinkunft bezüglich alternativer Zielparameter. Um den Effekt von Albumin festzustellen, sollte ein Monitoring der Kreislaufparameter erfolgen. Die individuelle Situation des Patienten, einschließlich kataboler Vorgänge, Integrität der Mikrozirkulation (z.B. capillary leak syndrom), Status der Makrozirkulation und Flüssigkeitsbilanz muß berücksichtigt werden.

2.3.4. Dosage and duration of therapy

42. In the treatment of coagulopathies, it is of the utmost importance that the initial dose administered to a patient is high enough. An initial dosage less than 10 ml/kg body weight is not clinically effective and is therefore a waste of resources. In many patients, a considerably higher dosage is needed. The treatment with FFP should be monitored and the duration of treatment adjusted to clinical course and coagulation tests.

2.3.5. Role of guidelines

43. Although numerous guidelines on national, European, and international levels exist, there appears to be a general lack of application of the directions provided. This appears to be due to deficiencies in both their dissemination and implementation.

2.4. ALBUMIN

44. Albumin is a natural colloid and transport protein. Human albumin preparations were developed by Cohn during World War II as a replacement for blood losses in the resuscitation of injured soldiers. It has been used for volume replacement therapy for about 50 years.
45. Clinical situations requiring volume replacement are frequently encountered. In current practice, there are alternatives in the form of crystalloid and synthetic colloid preparations. Such alternatives are less expensive but the maximum permissible dose is restricted e.g. due to side effects such as interference with the coagulation system.

2.4.1. Intended benefits

46. The intended benefits of human albumin use may be derived from theoretical and pathophysiological considerations. This is also true for the differential use of 4 - 5% ('isooncotic') or 20 - 25% ('hyperoncotic') solutions. However, clinical endpoints are difficult to define.

2.4.2. Clinical and laboratory criteria necessary for clinical use

47. There is little consensus about the clinical criteria for albumin use. There is currently no possibility of providing general guidance for dosage and duration of therapy. Measurement of a lowered albumin serum level is not sufficient to indicate its use. There is no agreement, however, about the choice of surrogate parameters. Monitoring of circulatory parameters should be used to assess the effect of albumin. The particular situation of the patient must be taken into account including catabolism, integrity of microcirculation (e.g. capillary leakage syndrome), and the status of macrocirculation and fluid homeostasis (cave hypervolaemia).

48. Es besteht Übereinkunft über die Anwendung von Albumin in den folgenden Situationen:

- Austauschtransfusion und Plasmaaustausch;
- Bei klinischer Notwendigkeit zum Einsatz von Kolloiden zur Volumensubstitution bei Neugeborenen und schwangeren Frauen; Albumin sollte hier aufgrund der potentiellen Nebenwirkungen von Alternativpräparaten, bzw. aufgrund des unvollständigen Wissenstandes über deren Nebenwirkungen bevorzugt werden;
- Einige spezifische Indikationen bei Neugeborenen zur Nutzung der Transporteigenschaften des Moleküls (z.B. Hyperbilirubinämie).

2.4.3. Schwerpunkt der klinischen Anwendungen

49. Der weitaus größte Anteil an Albumin wird derzeit in den unten aufgeführten klinischen Situationen - in denen Alternativen verfügbar sind - verbraucht.

- Volumenersatz. Da Albumin-Zubereitungen eine unterschiedliche Menge an Natrium enthalten, muß das Risiko einer Natrium-Überdosierung in Betracht gezogen werden.
- Verbrennungen. Abhängig vom Ausmaß der betroffenen Hautfläche und der Fähigkeit der Leber, einen Abfall des Albumin-Spiegels zu kompensieren, besteht eine gewisse klinische Grundlage, aufgrund derer Albumin nach Ablauf der ersten 24 Stunden angewendet werden kann.
- Hypoproteinämie. Ein niedriger Plasma-Spiegel von Albumin im Rahmen von Erkrankungen, die mit einer chronischen Hypoproteinämie assoziiert sind, ist keine Indikation zur Anwendung von Albumin.

50. Die Kosten von Albumin sind beträchtlich höher als die von Kristalloiden und synthetischen Kolloiden. Auf der anderen Seite kann die maximal tolerierbare Menge solcher Alternativpräparate durch deren Nebenwirkungen eingeschränkt sein. Vergleichende Studien haben keinen eindeutigen Vorteil von Albumin in solchen Situationen gezeigt. Tatsächlich wurde eine mögliche schädliche Wirkung durch Albumin-Infusionen in der Metaanalyse der "Cochrane Injuries Group" aufgezeigt. Weitere Studien sind erforderlich.

2.4.4. Rolle von Leitlinien

51. Angesichts des ausgesprochenen Mangels an Evidenz aus klinischen Studien besteht derzeit keine Möglichkeit, harmonisierte und allgemein gültige Leitlinien zu entwickeln.

2.4.5. Verfügbarkeit und ökonomische Aspekte

52. Albumin ist ein teures Präparat. Die Einschränkung des Albumin-Gebrauchs und der nachlassende Gebrauch von aus Plasma gewonnenem Faktor VIII aufgrund der Verfügbarkeit rekombinanter Produkte könnte großen Einfluß auf die Plasmaindustrie ausüben.

48. There is agreement about the use of albumin in the following situations:

- Exchange transfusion and plasma exchange;
- If there is a clinical requirement to use colloids for volume replacement in neonates and pregnant women; due to the potential side effects or incomplete knowledge of side effects of alternatives in these situations, albumin appears preferable;
- Some specific indications in neonates using the transport properties of the molecule (e.g. hyperbilirubinemia).

2.4.3. Main clinical uses

49. By far the greater share of albumin consumption currently takes place in clinical settings, such as those listed below, where alternatives are available.

- Volume Replacement. As albumin preparations contain variable amounts of sodium, the risk of sodium overload has to be considered.
- Burns. Depending on the extent of the involved skin surface and the ability of the liver to compensate for the decrease in albumin level, there is some clinical basis for using albumin after the first 24 hours.
- Hypoproteinemia. A low level of plasma albumin is not an indication for its use in diseases associated with chronic hypoproteinemia.

50. Albumin has a considerably higher cost compared with crystalloids and synthetic colloids. On the other hand, the maximum tolerated dose of such alternatives may be limited by their side effects. Comparative studies have not clearly documented a definite advantage of albumin use in such situations. In fact, a potential deleterious effect of albumin infusion has been highlighted in the Cochrane Injuries Group Albumin Reviewers meta-analysis and further studies are required.

2.4.4. Role of guidelines

51. In the face of the serious lack of evidence from clinical studies, there is currently no possibility of harmonised and generally accepted guidelines.

2.4.5. Impact of supply and economic aspects

52. Albumin is an expensive preparation. A reduction in albumin use in parallel with a decreasing use of plasma-derived factor VIII due to the availability of recombinant products could have a major impact on the fractionation industry.

2.5. GERINNUNGSFAKTOREN

2.5.1. Epidemiologische Aspekte

53. Hämophilie betrifft weltweit ca. 1 von 10.000 Menschen. Es wird angenommen, daß in den Industrieländern die Zahl der Patienten mit schwerer Haemophilie in den nächsten Jahrzehnten ansteigen wird, verbunden mit einem Anstieg in der Nachfrage für Gerinnungsfaktoren.
54. Genaue Daten zur aktuellen Anzahl der Hämophilie-Patienten innerhalb der Europäischen Gemeinschaft oder über den momentanen Verbrauch an Gerinnungsfaktor-Konzentraten sind nicht verfügbar. Die Zusammenstellung epidemiologischer Informationen – unter voller Berücksichtigung der Gesetzgebung der Europäischen Gemeinschaft bezüglich Datenschutz - über an Hämophilie und an ähnlichen angeborenen hämorrhagischen Störungen Erkrankte könnte dazu beitragen, den Bedarf an Gerinnungsfaktor-Konzentraten innerhalb der Europäischen Gemeinschaft vorherzusagen. Diese Informationen könnten folgendes beinhalten:
- Anzahl der Patienten mit Hämophilie;
 - Wohnort oder Wohnbezirk;
 - Alter der Patienten;
 - Schweregrad der Erkrankung (bezogen auf einen etablierten Mindestspiegel an Faktor);
 - Inhibitor-Status;
 - HIV und HCV Status; und
 - Gesamter Konzentratverbrauch auf nationaler Ebene (im Gegensatz zum individuellen Verbrauch oder zum Verbrauch an einem entsprechenden Zentrum).
55. Diese Informationen könnten auch in ein Programm zur Sicherheit von Blutprodukten oder von Pharmaka (Hämo-, bzw. Pharmakovigilanz) integriert werden, innerhalb dessen die Patienten ein Monitoring von Komplikationen, wie die Entwicklung von Inhibitoren, allergische Reaktionen oder Virus-Übertragung erfahren könnten.

2.5.2. Organisation der Hämophilen-Betreuung

56. Viele Patienten mit Hämophilie oder ähnlichen angeborenen hämorrhagischen Erkrankungen werden durch einen Allgemeinarzt oder durch einen nicht spezialisierten Kinderarzt behandelt, da ihnen der Zugang zu Spezialisten mit spezifischer hämatologischer Ausbildung fehlt. Daher sollte die Einrichtung spezieller Einrichtungen in Erwägung gezogen werden, die auf die medizinische Versorgung solcher Patienten ausgerichtet sind. Solche Einrichtungen, im folgenden "Einrichtungen mit umfassender Betreuung" ("Comprehensive Care Centres" / "CCCs") genannt, würden die gesamte Erfahrung der verschiedenen Personen, die in die Behandlung von Haemophilie-Patienten involviert sind, zusammenführen. Ein sog. "Basisteam" bestünde aus einem Pädiater und einem Erwachsenen-Hämatologen mit Erfahrung in der Behandlung angeborener Blutungserkrankungen, aus einer Krankenschwester, einem orthopädischen Chirurgen, einem Physiotherapeuten, einem genetischen Berater und einem Sozialarbeiter. Das Basisteam würde zusätzliche Unterstützung durch einen Zahnarzt und durch Spezialisten auf den Gebieten der Infektiologie und Hepatologie erfahren.

2.5. CLOTTING FACTOR CONCENTRATES

2.5.1. Epidemiological aspects

53. Haemophilia affects approximately 1 in 10,000 of the world's population. Over the next few decades, the number of patients with severe haemophilia is expected to rise in developed countries with a concomitant increase in the demand for clotting factor concentrates.
54. Precise data on the actual number of haemophilia patients in the European Community, or on the current consumption of coagulation factor concentrates, are not available. The compilation of epidemiological information on those individuals with haemophilia and related congenital haemorrhagic disorders in each Member State, taking fully into account Community legislation regarding data confidentiality, could help in forecasting the need for coagulation factor concentrates within the Community. Such information could include:
- Number of patients with haemophilia;
 - Town or area of residence;
 - Age of patients;
 - Severity of condition (related to an established baseline factor level);
 - Inhibitor status;
 - HIV and HCV status; and
 - Total usage of concentrate on a national basis (as opposed to individual or centre usage).
55. Such information could also be included in a haemovigilance or pharmacovigilance programme in which patients could be monitored for such complications as inhibitor development, allergic reactions and viral transmission.

2.5.2. Organisation of haemophilia care

56. Many patients with haemophilia and related congenital haemorrhagic disorders are treated by general practitioners or paediatricians because they lack access to specialists with specific haematological training. Consideration, therefore, needs to be given to the establishment of centres specifically designed to provide medical care for such patients. These centres, which have been identified as Comprehensive Care Centres (CCCs), would bring together the collective experience of individuals involved in the treatment of haemophilia patients including, as the primary team, a paediatric and adult haematologist with experience in treating congenital bleeding disorders, a nurse, an orthopaedic surgeon, a physiotherapist, a genetic counsellor and a social worker, with additional support from a dentist, and specialists in infectious diseases and hepatology.

57. Diese "Zentren mit umfassender Betreuung" ("Comprehensive Care Centres" / "CCCs") müßten in den einzelnen Mitgliedstaaten durch autorisierte Instanzen in Bezug auf die Zahl der Patienten, die in den einzelnen Einrichtungen betreut werden und im Hinblick auf die Verteilung der Patienten im jeweiligen Land gekennzeichnet sein. Die Kennzeichnung der Einrichtungen würde in Zusammenarbeit mit maßgebenden medizinischen Einrichtungen und Patientenorganisationen erfolgen; sie würden - im Gegensatz zu einem Labor - im Rahmen eines klinischen Gesamtkonzeptes etabliert werden und allen Patienten zugänglich sein.
58. Die klinische und labortechnische Versorgung unter der Leitung dieser Zentren durch das speziell ausgebildete Personal sollte idealerweise rund um die Uhr verfügbar sein. Obwohl wahrscheinlich eher Bedarf für getrennte Einrichtungen für Kinder und Erwachsene besteht, gibt es dennoch Möglichkeiten zu einer verbesserten Kommunikation zwischen diesen. Benachbarte Einrichtungen sollten angehalten werden, vergleichbare klinische und therapeutische Protokolle zu entwickeln.

2.5.3. Auswahl der Blutprodukte

59. Die Vorteile rekombinanter Gerinnungsfaktor-Konzentrate gegenüber den konventionellen, aus Plasma gewonnenen Präparaten werden auch weiterhin kontrovers diskutiert. Sicherheitsaspekte sind aus naheliegenden Gründen von überragender Bedeutung. Das Zusammenführen ("Poolen") des Plasmas tausender Spender führte in der Vergangenheit zur Infektion vieler Hämophilie-Patienten mit HIV und Hepatitis C. Verbesserungen in der Rückverfolgung von Spendern und bei den Bluttests und die Anwendung Virus-abtötender Verfahren haben die Sicherheit der aus Plasma gewonnenen Präparate erheblich verbessert, auch wenn eine absolute Sicherheit bezüglich der Übertragung pathogener Substanzen nicht garantiert werden kann.
60. Obwohl die meisten der zugelassenen rekombinanten Faktor VIII Präparate aus Plasma gewonnenes Humanalbumin als Stabilisator enthalten und / oder im Rahmen ihrer Herstellung Proteine, die aus humanem Plasma stammen, verwendet werden, besteht Übereinkunft darüber, daß die rekombinanten Produkte bezüglich der Übertragung humaner Pathogene eine erhöhte Sicherheit gegenüber den aus Plasma gewonnenen Präparaten besitzen. Dennoch muß die Inzidenz der Inhibitorentwicklung bei Patienten, die rekombinanten Faktor VIII erhalten, beachtet werden. Weiterhin sind die Kosten für diese Produkte beträchtlich höher als die für konventionelle Plasmaprodukte.
61. Das derzeitige Angebot an rekombinanten Produkten durch eine begrenzte Anzahl von Herstellern aus den USA ist noch nicht ausreichend, um die wachsende Nachfrage auf dem Weltmarkt zu befriedigen. Unterbrechungen in der Herstellung oder in der Lieferung könnten ernsthafte Konsequenzen nach sich ziehen. Weiterhin könnte es zu ernsthaften Auswirkungen für die Europäische Gemeinschaft kommen, wenn ein Monopol für die Produktion von Gerinnungsfaktoren entstehen würde. Daher sollten ernsthafte Anstrengungen für die Entwicklung entstehender rekombinanter Technologien in Europa unternommen werden.
62. Die wissenschaftlichen Daten erlauben derzeit keine definitive Stellungnahme zugunsten rekombinanter Präparate gegenüber den aus Plasma gewonnenen Präparaten. Es besteht Übereinstimmung darüber, daß innerhalb der Europäischen Gemeinschaft beide Präparate auch in der nächsten Zeit eine Rolle spielen werden. Es wurde weiterhin festgestellt, daß die rekombinanten Produkte die aus Plasma gewonnenen schrittweise verdrängen könnten.

57. CCCs would need to be designated in Member States by the regulatory authorities with regard to both the number of patients attending individual centres and the distribution of patients in the country. Centres would be designated in consultation with relevant medical and patient organisations; be established within the framework of a clinical facility, as opposed to a laboratory; and be accessible to all patients.
58. Clinical and laboratory support from specialist staff would ideally be available on a 24-hour basis under the guidance of the CCC. Although the need for separate paediatric and adult facilities to treat haemophilia patients may exist, there is scope for improvement in communications between them and neighbouring centres should be encouraged to develop similar clinical and treatment protocols.

2.5.3. Choice of blood products

59. The merits of recombinant coagulation factor concentrates over conventional plasma-derived products remain controversial. Safety, however, is obviously of paramount importance. The pooling of plasma from thousands of donors resulted in many patients with haemophilia being infected with HIV and hepatitis C in the past. Improvements in determining the suitability of donors, blood testing and application of virucidal treatments to concentrates have dramatically improved the safety of plasma-derived products but absolute safety with regard to transmission of pathogenic agents cannot be guaranteed.
60. With regard to the transmission of human pathogens, it was agreed that recombinant products offer an increased margin of safety over plasma-derived products, although most currently licensed recombinant factor VIII products contain human plasma-derived albumin as a stabiliser and / or use human plasma-derived proteins during the production process. There is still concern, however, over the incidence of inhibitors in patients receiving recombinant factor VIII. Furthermore, the cost of these products is considerably higher than conventional plasma products.
61. The current output of recombinant products from a limited number of plants in the United States is not yet sufficient to satisfy the growing demand of the global market. Interruptions in manufacture or supply could have serious consequences. In addition, there could be serious repercussions in the European Community should a monopoly emerge for the production of coagulation factor concentrates. Serious attention, therefore, needs to be given to supporting the development of emerging recombinant technologies in Europe.
62. Scientific data do not permit a definitive statement with respect to the use of recombinant over plasma-derived products at present. It was agreed, however, that there continues to be a role for both within the European Community for the time being. It was also acknowledged that recombinant products could be expected to gradually supplant plasma-derived ones.

2.5.4. Therapie der Hämophilie

63. Es besteht weitgehende Übereinstimmung bezüglich der zur Behandlung spontaner Blutungen nötigen Mengen an Faktor VIII. Ein beachtlicher Zuwachs an Nutzen könnte entstehen, wenn die zahlreichen Leitlinien medizinischer Einrichtungen innerhalb der Europäischen Gemeinschaft harmonisiert und um Ratschläge zur Dosierung bei allgemeinen Problemen erweitert werden würden.
64. Es existieren viele unterschiedliche Auffassungen darüber, wie die verhältnismäßig wenigen Patienten mit inhibitorischen Antikörpern behandelt werden sollten. Die Teilnahme dieser Patienten an fundierten klinischen Studien könnte hier Klarheit schaffen. Es besteht Übereinstimmung darüber, daß Immuntoleranz-Verfahren in der Mehrzahl der Fälle wirksam sind und allen Patienten mit schwerer angeborener Hämophilie, die neue Inhibitoren entwickeln, angeboten werden sollten. Unterschiedliche Ansichten bestehen hingegen bezüglich der genauen Dosierung zur Induktion einer Immuntoleranz. Eine internationale klinische Studie zum Vergleich von Verfahren mit niedriger und hoher Dosierung von Faktor VIII ist geplant. Die Teilnahme der behandelnden Einrichtungen wäre von großem Wert.

2.5.5. Prophylaktische Therapie

65. Es ist erwiesen, daß die prophylaktische Behandlung der Hämophilie das Auftreten von Gelenkschäden und Behinderungen vermindert. Obwohl dies zu erhöhten initialen Ausgaben für Plasma-Produkte führt, könnten weitere Kosten durch eine geringere Anzahl von Krankenhausbesuchen und Krankenhausaufenthalten vermindert werden. Auf lange Sicht kann eine prophylaktische Therapie die Beschäftigungsmöglichkeiten, die Einkommen und das Steueraufkommen sichern und insbesondere die Lebensqualität verbessern.
66. Obwohl eine große Anzahl von Patienten selbst mit schwerer Hämophilie - sofern sie nur unregelmäßige Blutungsepisoden erfahren - keine Prophylaxe benötigt, besteht Übereinstimmung darin, daß als allgemeine Regel die Prophylaxe für Kinder mit schwerer Hämophilie empfohlen werden sollte. Obwohl keine Daten aus kontrollierten klinischen Studien vorliegen, ist offensichtlich, daß die regelmäßige Applikation von Faktor VIII spontane Blutungsepisoden verhindern kann und das Risiko bleibender Gelenkschäden vermindert. Die meisten Kinder können ohne einen implantierten Katheter behandelt werden. Einige umstrittene Fragen, einschließlich der folgenden, müssen noch geklärt werden:
- Der Zeitpunkt, an dem die Prophylaxe begonnen werden soll;
 - Das Alter, in dem die Prophylaxe eingestellt werden sollte.

2.6. QUALITÄTSMANAGEMENT

67. Die Transfusion von Blut ist ein therapeutischer Prozeß, der aus zahlreichen Einzelschritten besteht. Diese müssen genau kontrolliert werden, um Sicherheit für die Patienten zu garantieren und um unerwünschte Nebenwirkungen zu verhindern. Die einzelnen Schritte können direkt patientenbezogen sein, wie z.B. das Erfassen des körperlichen Zustandes und die Indikationsstellung zum Einsatz eines Blutproduktes, sowohl im Notfall, als auch in der Routine. Weitere patientenbezogene Schritte sind die Identitätssicherung, die Aufklärung und die Einverständniserklärung zur Transfusion und die Entnahme einer Blutprobe zur weiteren Diagnostik (Blutgruppe, Screening und Kreuzprobe) vor der Transfusion.

2.5.4. Therapy for haemophilia

63. Whilst there is general agreement on the doses of factor VIII required for spontaneous bleeding problems, considerable benefit could accrue if the numerous guidelines from medical bodies throughout the Community were harmonised and expanded to include advice on dosages for treating such common problems.
64. Differences of opinion abound in relation to the treatment of those few patients with inhibitory antibodies and their participation in relevant clinical trials could help in resolving them. It is accepted that immune tolerance is effective in the majority of cases and should be offered to all patients with severe congenital haemophilia who develop new inhibitors. Controversy remains, however, over the precise dosage regimen for establishing immune tolerance. An international clinical trial comparing low and high dosage regimens of factor VIII is now being set up and the participation of treatment centres would be valuable.

2.5.5. Prophylactic therapy

65. Prophylactic treatment of haemophilia has been shown to reduce the development of joint damage and disability. While this involves increased initial expenditure on plasma products, other related costs may be diminished as a consequence of fewer hospital visits and in-patient treatment episodes. Over the long-term, prophylaxis can improve employment opportunities, income and tax generation, and in particular quality of life.
66. It was agreed that as a general rule prophylaxis should be recommended for children with severe haemophilia, although a significant number of patients with even severe haemophilia may not need such treatment if they only experience infrequent bleeding episodes. Even in the absence of data from controlled clinical trials, common sense dictates that the regular administration of factor VIII can prevent spontaneous bleeding episodes and is likely to reduce long-term joint damage. Most children can be treated without the need for an indwelling catheter. Several contentious issues, however, still need to be resolved including:
- time when prophylaxis should start;
 - age at which prophylaxis should be suspended; and
 - dosage and frequency of injections.

2.6. QUALITY MANAGEMENT

67. The transfusion of blood is a therapeutic process that involves numerous steps, all of which need to be strictly controlled to ensure the safety of patients and to prevent adverse events. These steps can be directly related to the patient, including assessment of physical condition and the need for a blood product, under both emergency and non-emergency situations; verification of identity; informed consent to the transfusion; and taking of a blood sample for pretransfusion testing (type, screen and crossmatch).

68. Produktbezogene Schritte in diesem Prozeß schließen die Anforderung des jeweiligen Blutproduktes, die Bereitstellung von Blutprodukten durch den Transfusionsdienst, die Identifikation der gekennzeichneten Konserve, die Ausgabe an und die Lagerung auf der Station und die Verwaltung eingesetzter und nicht eingesetzter Blutprodukte (z.B. Überprüfung der Qualität nicht eingesetzter Blutprodukte) ein.
69. Zuletzt können die einzelnen Schritte sowohl den Patienten, als auch das Blutprodukt betreffen, wie es z.B. bei der Identifizierung von Patient und Produkt vor der Transfusion, bei der Verabreichung des Produktes und bei der Dokumentation von frühen und langfristigen Outcome-Parametern (z.B. klinische Wirksamkeit, Sicherheit) der Fall ist.
70. Einige dieser Schritte können vernachlässigt werden, wenn Plasma-Derivate (z.B. Gerinnungsfaktoren) zur Anwendung kommen.
71. In Bezug auf die oben erwähnten Schritte wurde folgende Definition beschlossen:

Qualität in Bezug auf die klinische Anwendung von Blutprodukten impliziert die Anwendung der richtigen Menge des richtigen Blutproduktes auf die richtige Art zur richtigen Zeit am richtigen Patienten und die erforderliche Dokumentation, sowohl des Prozesses als auch des Outcomes.

72. Sowohl die SANGUIS Studie, als auch jüngere Studien haben gezeigt, daß die gängige klinische Praxis in der Anwendung von Blutprodukten diese Kriterien meist nicht erfüllt.

2.6.1. Probleme

73. Als Hauptprobleme wurden identifiziert:

- Signifikante Unterschiede im Gebrauch von Blutprodukten in vergleichbaren klinischen Situationen implizieren sowohl den übermäßigen Gebrauch, der zu einer Verschwendung von Ressourcen und zu einem unnötigen Risiko für die Patienten führt, als auch einen potentiell zu geringen Gebrauch.
- Die unsachgemäße Anwendung von Blutprodukten (z.B. ist die Inzidenz von Transfusionszwischenfällen derzeit höher als die der durch Transfusion übertragenen viralen Erkrankungen); und
- Ein Mangel an Dokumentation, der zum Fehlen oder zur Unzugänglichkeit von einerseits prozeßbezogenen Daten führt, die für die Rückverfolgung von Produkten und die Feststellung von Verantwortlichkeiten erforderlich sind, und andererseits von Outcome-Daten, die zur Evaluation von klinischer Wirksamkeit und Sicherheit ("Hämovigilanz" / "Pharmakovigilanz") benötigt werden.

74. Während das erste Problem in den Defiziten sowohl in der Definition, als auch in der Verbreitung von Leitlinien zur optimalen Anwendung von Blut und Blutprodukten besteht, beruhen die übrigen auf Defiziten in der Organisation des Systems. In anderen Bereichen hat sich die Implementierung eines Qualitätsmanagement-Systems als erfolgreiche Lösung für derartige Probleme erwiesen. In der klinischen Anwendung von Blut und Blutprodukten könnte dieser Ansatz maßgeblich dazu beitragen, die Qualität von Prozeß und Outcome zu verbessern.
75. Beträchtliche Anstrengungen und Ressourcen werden auf die Qualitätssicherung beim Sammeln und bei der Verarbeitung von Blut und Blutprodukten verwendet, so daß ein Mangel an Qualität bei ihrer Anwendung nicht akzeptabel ist. Nicht akzeptabel nicht nur für die Patienten, die Blut und Blutprodukte erhalten, sondern auch für die Spender, deren Spendebereitschaft bei offensichtlichem Mißbrauch des von ihnen gespendeten Blutes nachlassen könnte.

68. They can also be related to the product itself, including: request for the blood product, reserving blood products in the transfusion service; identification of the assigned unit; delivery to and storage within the clinical ward; and management of used and unused blood products (e.g. re-qualification of unused blood products).
69. Finally, these steps can be related both to the patient and to the blood product, including the identification of both before transfusion, administration of the product to the patient, and measurement and documentation of early and long-term outcomes (e.g. effectiveness, safety).
70. Some of these steps could be omitted when plasma derivatives (e.g. coagulation factors) are requested and used.
71. Considering the aforementioned steps, the following definition was reached:
- Quality in the clinical use of blood products implies administering the right quantity of the right blood product in the right way at the right time to the right patient, and appropriate documentation of both the process and the outcome.**
72. The SANGUIS study, as well as more recent ones, has shown that the current clinical use of blood products generally does not satisfy these criteria.

2.6.1. Problems

73. The main problems that have been identified are:
- Significant variability in the use of blood products in comparable clinical situations, which implies both overuse, entailing waste of resources as well as unnecessary risks for patients, and potential underuse;
 - Misuse of blood products (e.g. the incidence of transfusion errors is currently higher than that of transfusion-transmitted viral diseases); and
 - Lack of documentation, entailing the absence or unavailability of data related to the process, needed for traceability of products and accountability of operators, and to the outcomes, which are needed for the evaluation of effectiveness and safety (haemovigilance, pharmacovigilance).
74. While the first problem is related to deficiencies both in the definition of guidelines for optimal use and in their dissemination, the others are related to deficiencies in the organisation of the system. In other settings the implementation of quality management system has proven to be a successful solution to these problems. In the clinical use of blood products this approach could contribute greatly to improving the quality of both the process and the outcomes.
75. Moreover, considerable efforts and resources are directed to ensuring quality in the collection and preparation of blood and blood components to ensure their quality, so that lack of quality in their use is unacceptable, not only for the patients receiving blood products, but also for donors, who could reduce their support in case of evidence of misuse of their donated blood.

76. Aus diesen Gründen sollte ein Qualitätsmanagement-System auf jeden Fall auch im klinischen Teil der Blut-Transfusionskette eingerichtet werden.

2.6.2. Qualitätsmanagement-System

77. Zur Einführung eines Qualitätsmanagement-Systems in der klinischen Anwendung von Blut und Blutprodukten ist das Engagement von Personen in leitenden Positionen und von Entscheidungsträgern unumgänglich, da nur mit deren Unterstützung die notwendigen personellen und ökonomischen Ressourcen verfügbar gemacht werden können. Die Einführung eines Qualitätsmanagement-Systems ist eine Investition. Die Kosten für seine Verwirklichung können durch den erreichten klinischen Nutzen gerechtfertigt werden.
78. Es muß ein Qualitätsbeauftragter auf lokaler Ebene für die klinische Anwendung von Blut und Blutprodukten ernannt werden, der die Verantwortung für die Implementierung des Systems trägt und weiterhin berechtigt ist, angemessene Schritte zur Sicherung und Verbesserung von Qualität zu vollziehen. Der Qualitätsbeauftragte sollte durch das Transfusions-Komitee des jeweiligen Krankenhauses unterstützt werden, das sich aus Repräsentanten der klinischen Fachabteilungen, die in den Gebrauch von Blut und Blutprodukten involviert sind und aus Repräsentanten des Pflegepersonals, der Blut-Transfusionsdienste, der Apotheke, der Verwaltung und gegebenenfalls auch Repräsentanten der Patienten zusammensetzt.
79. Wenn das entsprechende Krankenhaus bereits über ein Qualitätsmanagement-System verfügt, sollte das Qualitätsmanagement-System für die klinische Anwendung von Blut und Blutkomponenten in dieses integriert werden.
80. Es müssen anerkannte Standards für den Gebrauch von Blut und Blutprodukten geschaffen werden, die Qualität unter dem Aspekt der richtigen Anwendung definieren. Auf vielen Gebieten, wie z.B. beim Einsatz von Erythrozytenkonzentraten in der Chirurgie und beim Einsatz von Albumin, ist bis jetzt keine wissenschaftlich begründete Evidenz für Indikationen und für Situationen vorhanden, in denen keine Indikation vorliegt. Dies führt zu vielen Schwierigkeiten in der Evaluation der Angemessenheit in der Anwendung und der klinischen Wirksamkeit. Kontrollierte Studien zur Lösung dieser Problemstellungen sind dringend erforderlich.
81. Die Implementierung eines Qualitätsmanagement-Systems benötigt eine enge Kooperation und das Engagement aller an diesem Prozeß Beteiligten, wie Kliniker, Pflegepersonal und weiterer Leistungserbringer im Gesundheitswesen.

2.6.3. Aufgaben und Verantwortlichkeiten

82. Die Hauptaufgaben und wichtigsten Verantwortlichkeiten des Qualitätsbeauftragten und des Transfusionskomitees sind folgende:
- Die Sicherung der Einhaltung von Maßnahmen;
 - Die Anpassung, die Implementierung und die Aktualisierung von Leitlinien;
 - Die Definition von standardisierten Handlungsabläufen (“Standard Operating Procedures” / “SOPs”), die verpflichtend für das gesamte Personal im Gesundheitswesen sind;
 - Die Verbreitung implementierter Leitlinien und standardisierter Handlungsabläufe;

76. For all these reasons every effort should be made to provide a quality management system also in the clinical part of the blood transfusion chain.

2.6.2. Quality management system

77. The establishment of a QM system for the clinical use of blood products first requires the commitment of administrators and decision-makers since only with their support can the necessary human and economic resources be made available. The establishment of a QM system is an investment, and the cost of its implementation can be justified by the benefits achieved.
78. A local quality manager for the clinical use of blood products, with responsibility for the implementation of the system and empowered to take the appropriate actions to ensure and improve quality, needs to be identified. The quality manager should be supported by the Hospital Transfusion Committee, comprising representatives of clinical specialities involved in the use of blood products, nurses, blood transfusion service, pharmacy, administration and eventually patients' representation.
79. If the hospital already has a QM system, the QM system for the clinical use of blood products should become an integral part of it.
80. Accepted standards for the use of blood products, which define the quality in terms of appropriateness, need to be made available. In many areas, such as the use of red cells in the surgical setting and the use of albumin, scientific evidence as regards the indications and non-indications are still lacking. This presents many difficulties in evaluating both appropriateness and efficacy and controlled studies to resolve these issues are urgently needed.
81. The implementation of a QM system needs the strong co-operation and commitment of all operators involved in the process, such as clinicians, nurses and other healthcare providers.

2.6.3. Tasks and responsibilities

82. The main tasks and responsibilities of the quality manager and the transfusion committee are:
- Ensuring compliance with regulations;
 - Adapting, adopting and updating guidelines;
 - Defining standard operating procedures (SOPs), mandatory for healthcare personnel;
 - Disseminating adopted guidelines and SOPs;

- Die Überprüfung [internes Audit] der Einhaltung der Leitlinien und der standardisierten Handlungsabläufe;
- Die Evaluation von Effektivität und Sicherheit (“Hämovigilanz”);
- Die Vermittlung von Feedback an Kliniker; und
- Die Durchführung einer problemorientierten Qualitätssicherung.

83. Einige dieser Aufgaben wurden noch detaillierter analysiert. Folgende Schlußfolgerungen konnten erarbeitet werden:

2.6.3.1. Definition von SOPs

84. Standardisierte Handlungsabläufe (“Standard Operating Procedures” / “SOPs”) sollten alle Einzelschritte eines Prozesses berücksichtigen. Die folgenden sind jedoch in der Qualitätssicherung der klinischen Anwendung von Blut und Blutkomponenten von besonderer Bedeutung:

- Die Entnahme von Blutproben zur Durchführung von Testverfahren vor der Transfusion, mit Schwerpunkt bei der Identifizierung von Ausführendem, Patienten und Proben. Die Identifizierung sollte möglichst durch eine dem Patienten zugeordnete persönliche Identifizierungsnummer (“personal identification number” / “PIN”), sowie durch den durch das Krankenhaus zugeordneten ID-Code des Patienten und / oder durch Bar-Codes erfolgen;
- Die Information des Patienten, sowohl vor, als auch nach der Transfusion;
- Die Verabreichung von Blutprodukten;
- Die häusliche Transfusion;
- Das Follow-up nach der Transfusion;
- Das Vorgehen im Fall von unerwünschten Nebenwirkungen;
- Das Vorgehen in Notfallsituationen;
- Die Entnahme autologer Blutspenden;
- Die Handhabung ungebrauchter Konserven;
- Die Lagerung von Blutprodukten außerhalb der Blutbank; und
- Die Dokumentation der oben beschriebenen Schritte und der Outcomes.

2.6.3.2. Verbreitung von entwickelten Leitlinien und SOPs

85. Es ist offensichtlich, daß verfaßte Leitlinien nicht allein durch ihre Verbreitung praktische Anwendung finden. Daher sollte im Anschluß an die Definition der Leitlinien und der standardisierten Handlungsabläufe das beteiligte Personal, wie Kliniker und Pflegekräfte, in transfusionsmedizinischen Kursen geschult werden. Die Organisation sowohl dieser Kurse, als auch die von Auffrischkursen sollte unter der Verantwortung des Transfusions-Komitees erfolgen.

86. Die universitäre Ausbildung sollte transfusionsmedizinische Kurse beinhalten, um Kliniker im optimalen Umgang mit Blut und Blutprodukten zu schulen.

87. Es können auch verfeinerte Methoden zur Verbreitung von Leitlinien in Betracht gezogen werden, wie z.B. die Entwicklung von Anforderungsscheinen mit Algorithmen für die richtige Anwendung von Blut und Blutprodukten.

- Verification [internal audit] of the compliance to guidelines and SOPs;
- Evaluating effectiveness and safety (haemovigilance);
- Providing feedback to clinicians; and
- Conducting problem-oriented quality assurance.

83. Some of these tasks have been analysed more in detail, with the following conclusion reached.

2.6.3.1. Definition of SOPs

84. While standard operating procedures should cover all steps in the process, the following are of particular relevance for ensuring quality in the clinical use of blood products:

- Blood sampling for pretransfusion testing, focusing on identification of the operator, the patient and the samples. Confirmation of identification should be carried out preferably by verifying personal identification numbers (PINs) physically related to the patient, such as the patient's hospital ID code, and/or by barcodes;
- Patient's information, both before and after transfusion;
- Administration of blood products;
- Home transfusion;
- Follow up of transfusion;
- Management in case of adverse events;
- Emergency procedures;
- Collection of autologous blood;
- Handling of unused units;
- Storage of blood products outside the blood bank; and
- Documentation of the above described steps and outcomes.

2.6.3.2. Dissemination of adopted guidelines and SOPs

85. It is common experience that paper guidelines do not turn into installed guidelines simply by their distribution. Education of involved healthcare professionals, such as clinicians and nurses, through courses in transfusion medicine, should follow the definition of guidelines and SOPs. The organisation of these courses, as well of refresher courses, should be under the responsibility of the transfusion committee.

86. University courses should include transfusion medicine in order to educate clinicians in the optimal use of blood products.

87. More sophisticated means of dissemination can also be taken into consideration, such as the adoption of request forms with algorithms for appropriate use of blood products.

88. Die fortschrittlichste und effektivste Methode zur Schulung ist computergestützt möglich: Der Stationsarzt gibt die Anforderung in einem Programm mit programmierten Algorithmen ein, das vom Kliniker entweder die Übereinstimmung mit den gängigen Leitlinien oder die Angabe von zusätzlichen klinischen Gründen verlangt, die ein Außerkraftsetzen der Leitlinien rechtfertigen. Dieser Ansatz besitzt außerdem den Vorteil der Online-Dokumentation, kann aber nur implementiert werden, wenn das Krankenhaus über ein entsprechendes Computer-System verfügt.

2.6.3.3. Überprüfung der Einhaltung von Leitlinien

89. Es gibt zwei Möglichkeiten zur Überprüfung der Einhaltung von Leitlinien: Die retrospektive und die fortlaufende Auditierung:

- Die retrospektive Auditierung beruht auf dem Zusammentragen und der statistischen Analyse von Daten zum Gebrauch von Blut und Blutprodukten und zum Outcome. Es sollten Indikatoren auf nationaler oder zumindest regionaler Ebene vereinbart werden, die einen Vergleich zwischen verschiedenen Krankenhäusern ermöglichen. Dies ist zwar der am einfachsten durchführbare Ansatz, dennoch sind die Feedback-Mechanismen in ihrer Auswirkung auf die Verbesserung der klinischen Praxis verzögert.
- Die fortlaufende Auditierung basiert auf einer sogenannten “zweiten Meinung” bei der Bestellung der erforderlichen Blutprodukte. Ihre Auswirkung auf die Verbesserung der klinischen Praxis erfolgt unmittelbar durch Verhinderung einer unangebrachten Anwendung. Die “zweite Meinung” kann entweder durch einen verantwortlichen Kliniker auf Station erfolgen, der sämtliche, nicht dringend erforderlichen Blutanforderungen auditiert oder durch den Transfusionsdienst, der die Anforderung erhält. Es gibt Beispiele für beide Möglichkeiten: Die erste Möglichkeit verhindert Konflikte zwischen den Klinikern auf Station und dem Transfusionsdienst und trägt zur Verbreitung der Leitlinien bei; die zweite kann anhand einer computergestützten Auditierung der Blutanforderungen erfolgen und besitzt den Vorteil, daß das Zusammentragen und die Analyse aller Daten bezüglich optimaler Anwendung erleichtert wird.

2.6.3.4. Evaluation der Effektivität

90. Sobald eine bestimmte Einhaltung von Leitlinien erreicht und dokumentiert ist, können die Outcome-Daten nicht nur für die Evaluation und die Verbesserung der Leitlinien verwendet werden, sondern es können auch Kosten-Analysen verschiedener Strategien durchgeführt werden. Die Parameter, anhand derer die Effektivität der verwendeten Blutprodukte evaluiert werden kann, müssen definiert werden. Weiterhin muß das Zusammentragen der Daten vereinfacht werden, ohne Kliniker durch das Vervielfältigen von Daten, die bereits in den medizinischen Aufzeichnungen vorhanden sind, zusätzlich zu belasten.

2.7. ÖKONOMISCHE ASPEKTE

91. Gesundheitsökonomie beschäftigt sich mit den Kosten und Konsequenzen in Zusammenhang mit der Bereitstellung klinischer Versorgung. Die Berücksichtigung ökonomischer Aspekte kann Entscheidungsträgern im Gesundheitswesen bei der richtigen Allokation von Ressourcen, bei der Beurteilung bestehender und neuer Technologien im Gesundheitswesen und bei der Setzung von Prioritäten bei rivalisierenden Technologien leisten.

88. The most advanced and effective means of education is provided by computer reminders: the physician in the ward enters the request in a computerised programme, with pre-established algorithms, that guides the clinician to comply with the accepted guidelines, or asks for additional clinical reasons to override them. This approach has the advantage of providing also an online documentation, but can be implemented only in case an integrated hospital information system has been put in place.

2.6.3.3. *Verification of compliance with guidelines*

89. There are two ways to verify the compliance with the accepted guidelines: retrospective audit and concurrent audit:

- Retrospective audit is based on the collection and statistical analysis of data related to the utilisation of blood products and to the outcome. Indicators should be agreed upon at national or at least regional level, in order to make possible a comparison between different hospitals. This is the most feasible approach, but its impact in improving clinical practice, based on a feedback to the clinicians, is delayed.
- Concurrent audit is based on a ‘second opinion’ at the time of issuing the request of blood products and its impact in improving clinical practice is immediate, preventing inappropriate use. The ‘second opinion’ can be given either in the clinical ward by a clinician in charge of auditing all non-urgent blood requests, or by the transfusion service receiving the request. There are examples of both solutions: the first solution avoids conflicts between the clinicians in the wards and the staff of the transfusion service and contributes to the dissemination of the guidelines; the second solution can be realised by means of a computerised audit of blood request in the transfusion service and has the advantage of facilitating the collection and analysis of data related to optimal use.

2.6.3.4. *Evaluation of effectiveness*

90. Once compliance with the guidelines has been achieved and documented, data on the outcomes can be used not only to verify their appropriateness and contribute to their improvement but also to carry out cost analysis of different strategies. Parameters to evaluate the efficacy of the blood products used, however, have to be defined and the collection of data needs to be facilitated without burdening clinicians with copying information that should already be in the medical records.

2.7. ECONOMIC ASPECTS

91. Health economics addresses the costs and consequences of providing clinical care. Consideration of economic aspects can offer assistance to health care decision-makers in the appropriate allocation of resources, in the review of existing and new health technologies, as well as on the prioritisation of competing technologies.

92. Die Europäische Gemeinschaft gibt jedes Jahr viele Millionen Euros für das Sammeln, die Verarbeitung und den Verbrauch von Blut und Blutprodukten aus. Die veröffentlichten Kosten enthalten häufig weder die ökonomischen Konsequenzen von zu geringer, zu hoher und unangebrachter Anwendung, noch beschäftigen sie sich mit weiterführenden ökonomischen Konsequenzen wie denjenigen, die sich aus unerwünschten Nebenwirkungen, aus Produktivitätsverlust oder aus menschlichem Leiden ergeben.
93. Obwohl die Ressourcen knapp sind, sind deutliche Unterschiede in der Transfusionspraxis und eine nicht optimale Anwendung dieser Produkte nachgewiesen, was Möglichkeiten zu einem effizienteren Einsatz impliziert. Die hohen Kosten dieser Produkte belasten die Wirtschaft einiger Länder vor allem dort, wo verbesserte Technologien neue Erwartungen auf den Gebieten der Sicherheit, Diagnosestellung und Anwendung schaffen. Begründungen für die Allokation von Ressourcen sollten nur nach sorgfältiger Betrachtung des klinischen und ökonomischen Benefits solcher Entwicklungen getroffen werden.

2.7.1. Perspektiven

94. Ökonomische Evaluationen können von verschiedenen Perspektiven aus durchgeführt werden: aus der Gesellschaftsperspektive, der Perspektive des Leistungsträgers oder der des Leistungserbringers. Die meisten Fachleute halten die Gesellschaftsperspektive für die wichtigste. Es ist wichtig, daß unabhängig von der betrachteten Perspektive die Möglichkeit gegeben ist, Ressourcen zwischen verschiedenen Budgets zu verteilen, um eine angemessene Leistungserbringung und die klinische Versorgung von Patienten ermöglichen zu können.

2.7.2. Informationsbedarf

95. Um die zukünftigen Bedürfnisse für Blut und Blutprodukte in der Europäischen Gemeinschaft planen zu können und um sicherzustellen, daß die optimale Anwendung unterstützt wird, ist ein hohes Maß an Evidenz notwendige Voraussetzung für das Verständnis wie und warum diese Produkte verwendet werden.

2.7.3. Ökonomische Evaluation

96. Eine Anzahl von mit Effektivitäts-Studien verbundenen ökonomischen Evaluationen sind erforderlich. Diese könnten beinhalten:
- Eine systematische Durchsicht der aktuellen Literatur über die Kosten-Effektivität von Blut und Blutprodukten;
 - Die optimale Größe von Blutsammel-, Blutverarbeitungs- und Blutverteilungseinrichtungen;
 - Eine Aufstellung der Kosten von Blut und Blutprodukten in jedem Mitgliedsland und die Methoden ihrer Berechnung;
 - Den Nutzen von rekombinanten versus aus Plasma gewonnenen Gerinnungsfaktoren;
 - Den Nutzen der primären Prophylaxe mit Gerinnungsfaktoren bei Kindern und Erwachsenen;
 - Die optimale Anwendung von DNA-Testverfahren bei Blut und Blutprodukten;
 - Die Leukozytendepletion von Erythrozytenkonzentraten versus “buffy-coat” - freie Erythrozytenkonzentrate;
 - Die gesamtökonomischen Auswirkungen der nicht optimalen Anwendung von Blut und Blutprodukten.

92. The European Community spends many million Euros each year on the collection, processing and use of blood and blood products. Published costs often do not include the economic consequences of underuse, overuse and misuse, nor do they address the associated wider economic consequences, including unwanted effects, loss of productivity, and human suffering.
93. While resources are scarce, there is evidence of marked variation in practice and the less than optimal use of these products indicating scope for improved efficiency. The high cost of these products places burdens on the economies of some countries especially where improving healthcare technologies can create new demands in the areas of safety, diagnosis and use. Justification for the allocation of resources should be made only after careful consideration of the clinical and economic benefits of such developments.

2.7.1. Perspectives

94. Economic evaluations can be viewed from a number of different perspectives: societal, payer, or provider. Most authorities consider the societal perspective to be the most important. It is important that whichever perspective is considered there is the ability to move resources between the various budgets in order to ensure appropriate service provision and clinical care for patients.

2.7.2. Information needs

95. In order to plan for the future needs for blood and blood products in the EC and to ensure that optimal use is supported, a strong evidence base is a necessary requirement to understand how and why these products are used.

2.7.3. Economic evaluations

96. A number of economic evaluations linked to effectiveness studies needs to be undertaken. These might include:
- A systematic review of current literature about the cost effectiveness of blood and blood products;
 - The optimal size of blood collection-processing-distribution services;
 - A review of each Member State's unit costs of blood and blood products and the method for calculation;
 - The use of recombinant vs. plasma-derived clotting factors;
 - The use of primary prophylaxis of clotting factors in children and adults;
 - The optimal use of NAT testing of blood and blood;
 - Leucodepletion of red cells vs. buffy coat-free red cells;
 - The overall economic implications of the failure to use blood and blood products optimally.

3. EMPFEHLUNGEN

3.1. ERYTHROZYTENKONZENTRATE

3.1.1. Versorgung

97. Die Verringerung der unangemessenen Anwendung von Blut könnte dazu beitragen, die Inzidenz und das Ausmaß von Blutknappheit zu minimieren. Die Einrichtung eines Blut-Austausch-Programms in der Europäischen Gemeinschaft sollte in Erwägung gezogen werden. Die Verwaltung von Krankenhauslagerbeständen sollte optimiert werden und den Gebrauch von Blut-Anforderungslisten einschließen.
98. Ein Blut-Austausch-Programm in der Europäischen Gemeinschaft könnte als eine Einzeleinrichtung geplant werden, die als koordinierende Zentrale Verknappungen und verfügbare Bestände verschiedener Blutzentren aufeinander abstimmen könnte. Solche Netzwerke existieren mit unterschiedlichem Erfolg an verschiedenen europäischen Zentren. Ein Pilotprojekt wäre notwendig um zu klären, ob ein entsprechendes System nützlich oder effektiv wäre.

3.1.2. Verbleibendes Risiko

99. Bei der Einführung neuer Strategien zur Verbesserung der Transfusionsicherheit sollten anhand der letztendlich erreichbaren Sicherheitszugewinne Prioritäten gesetzt werden. In Bezug auf den "Zugewinn an Gesundheit" und den Kostenvorteil könnte die Optimierung der Blut-Transfusionspraktiken wesentlich effektiver sein als die Einführung neuer Teststrategien.
100. Die organisatorischen Praktiken in Zusammenhang mit Transfusionen, einschließlich der Empfängeridentifizierung und der Kompatibilitätstestung zeigen innerhalb der Europäischen Gemeinschaft weite Unterschiede auf. Die Gründe für diese Unterschiede und ihr möglicher Vorteil müssen kritisch überprüft werden. Die durch ABO-mismatch verursachte Mortalität und Morbidität stellt in der gesamten Europäischen Gemeinschaft weiterhin ein sehr ernstes Problem dar und ist vermutlich weitaus größer als irgendein verbleibendes virales Risiko. Effektive Möglichkeiten, dieses Risiko gegen Null zu reduzieren, müssen gefunden werden und an die speziellen Gegebenheiten der einzelnen Krankenhäuser angepaßt werden.
101. Bestimmte eindeutige Indikationen zur Leukozytendepletion sind allgemein anerkannt und implementiert. Dort, wo die Leukozytendepletion notwendig ist, sollte sie auf kontrollierte Art und Weise in einer hierfür vorgesehenen Einrichtung durchgeführt werden. Dies sollte innerhalb eines optimalen Zeitraums nach der Blutspende erfolgen, um das Risiko von Bakterienwachstum auszuschließen.

3.1.3. Klinische Wirksamkeit

102. Die Patienten benötigen ein Produkt, das über eine maximale Fähigkeit zur Sauerstoffabgabe verfügt und ein minimales Risiko besitzt. Eine durch den klinischen Nutzen definierte, optimale Lagerungszeit und die optimalen Lagerungsbedingungen wurden noch nicht bestimmt. Dies ist dringend erforderlich.

3. RECOMMENDATIONS

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.
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.

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.
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.
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.

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.

3.1.4. Unangemessener Gebrauch

103. Jedes Krankenhaus, das Bluttransfusionen vornimmt, muß über ein Qualitätsmanagement-System verfügen, das eine hierfür ernannte und speziell geschulte Person mit Verantwortung für die Qualität der Transfusionsdurchführung an diesem Krankenhaus vorsieht und das sowohl ein fortlaufendes, systematisches Schulungsprogramm, als auch eine dokumentierte und systematische Form der klinischen Auditierung beinhaltet. Dieses System der klinischen Auditierung sollte spezifische, anerkannte Maßnahmen zur Auditierung benutzen, die innerhalb der Europäischen Union (wo sie erst noch spezifiziert werden müssen) einheitlich sein sollten und weiterhin eine standardisierte Form zur jährlichen Veröffentlichung des Auditierungsberichts.
104. Geeignete Blut-Einsparprogramme sollten in jedem Krankenhaus genutzt werden.
105. Auf die Entwicklung effektiver transfusionsmedizinischer Schulungsprogramme sollte sowohl während, als auch nach der Ausbildung geachtet werden.
106. Gut geplante Studien im großen Format zur Blut-Transfusion bei erwachsenen und pädiatrischen chirurgischen Patienten sind notwendig, um grundlegende Outcome-Daten zu liefern. Diese Studien könnten auf der Ebene der Europäischen Gemeinschaft organisiert und finanziert werden.

3.2. THROMBOZYTENKONZENTRATE

3.2.1. Produkte und ihre Verfügbarkeit

107. Thrombozytenkonzentrate sollten so aufbereitet und gelagert werden, daß der maximale therapeutische Nutzen erreicht und unerwünschte Effekte minimiert werden.
108. In Bezug auf die Verfügbarkeit besteht die dringende Notwendigkeit, sowohl die Auswirkungen möglicher Verzögerungen innerhalb der gesamten Thrombozyten-Transfusions-Kette, als auch die Kosten-Effektivität der Thrombozyten-Transfusion, die sich durch die Einführung von DNA-Testverfahren ergeben, zu untersuchen. Blutdienste sollten so organisiert sein, daß:
- zeitabhängige und anderweitige mögliche Verknappungen, wie z.B. die seltener Thrombozyten-Phänotypen, minimiert werden (hier könnte die Zusammenarbeit der Mitgliedstaaten zum Erfolg beitragen); und
 - die Verschwendung der Produkte minimiert wird, ohne daß die Qualität der Thrombozytenkonzentrate abnimmt.
109. Die Einführung von DNA-Testverfahren sollte die Freigabe von Thrombozytenkonzentraten in weniger als 24 Stunden nach der Spende ermöglichen.

3.2.2. Indikationen und Transfusionsgrenzen

110. Die klinische Entscheidung, Thrombozyten zu transfundieren, sollte auf der sorgfältigen Evaluation der individuellen Gegebenheiten des jeweiligen Patienten, einschließlich der Blutungsanamnese, der Blutungsneigung, der aktuellen Thrombozytenzahl oder anderer Laboruntersuchungen, die die Thrombozytenfunktion wiedergeben, basieren.

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.
104. Appropriate blood conservation programmes should be in use in every hospital.
105. Attention should be given to the development of effective education programmes in transfusion at undergraduate and postgraduate level.
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.

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

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.

111. Die Entwicklung eines Algorithmus zur Definition von Transfusionsbedürfnissen zur Unterstützung der klinischen Entscheidungsfindung wird dringend empfohlen. Solche Algorithmen sollten unter Zusammenarbeit klinischer und transfusionsmedizinischer Spezialisten entwickelt und regelmäßig überarbeitet werden.

3.2.3. Dosierung und klinische Wirksamkeit

112. Das Outcome einer Thrombozytentransfusion, beispielsweise in Form des korrigierten Thrombozyten-Inkrementes ("corrected count increment" / "CCI"), sollte als Grundlage für eine verbesserte Transfusionspraxis evaluiert werden. Dies erfordert die Untersuchung der Wiederfindungsrate der Thrombozyten ("platelet recovery" oder "CI"), des jeweiligen Anstiegs der Thrombozytenzahl und des Zeitraums (der Tage) zwischen zwei Transfusionen.

113. Es wird empfohlen, die Forschung zur Entwicklung geeigneterer Techniken für das Monitoring der klinischen Wirksamkeit der Thrombozytentransfusion zu unterstützen.

3.2.4. Refraktärzustände

114. Die Alloimmunisierung von Patienten, die aller Wahrscheinlichkeit nach wiederholt Thrombozytenkonzentrate benötigen werden, sollte verhindert werden. Dies sollte durch die Anwendung von Produkten mit geringerer Immunogenität, wie leukozytendepletierte Blutkomponenten erfolgen.

3.2.5. Qualitätsaspekte und Hämovigilanz

115. Algorithmen zur korrekten Anwendung von Thrombozytenkonzentraten sollten zusätzlich zur Einführung von Hämovigilanz-Systemen als Bestandteil eines Qualitätssicherungssystems entwickelt werden. Sowohl die klinische Wirksamkeit der Thrombozytentransfusion, als auch die assoziierten Nebenwirkungen, sollten registriert werden. Parameter zur Messung des Outcomes der Transfusionen sollten identifiziert und im Rahmen eines geeigneten Qualitäts-Systems evaluiert werden.

3.3. GEFRORENES FRISCHPLASMA

116. Zur Erhöhung der Sicherheit sollten virusattenuierte oder quarantänegelagerte GFP-Präparate zur Anwendung kommen.

117. Das klinische und das biologische Ergebnis der GFP-Infusion sollte einem Monitoring unterliegen, da verschiedene GFP-Qualitäten verfügbar sind und das individuelle Ansprechen von Patienten mit Gerinnungsstörungen unterschiedlich sein kann.

118. Da der beabsichtigte klinische Nutzen von GFP in der Korrektur von Gerinnungsstörungen besteht, sind Labortests zur raschen Erfassung hämostaseologischer Abläufe essentiell für seine optimale Anwendung. Dies setzt die ständige Verfügbarkeit eines Gerinnungslabors voraus.

119. Die Dauer der Therapie sollte durch klinische Beobachtung und durch Verlaufsbestimmung der Gerinnungsparameter bestimmt werden.

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.

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.

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

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.

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.

3.3. FRESH FROZEN PLASMA

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

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.

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.

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

120. Die zahlreichen vorhandenen Leitlinien sollten harmonisiert werden. Ihre Verbreitung und Implementierung sollte durch Qualitätssicherungs-Systeme energisch vorangetrieben werden. Als eine mögliche Maßnahme zur gezielteren Anwendung sollten in Anforderungs-, bzw. Verschreibungsformularen zusammengefaßte Leitlinien integriert werden. Der Effekt solcher Formulare sollte evaluiert werden.

121. Die Schulung des medizinischen Personals sollte verbessert werden.

3.4. ALBUMIN

122. Die Evidenz aus veröffentlichten klinischen Studien zur Anwendung von Albumin ist ungenügend. Zur überzeugenden Darstellung des klinischen Nutzens von Albumin in Bezug auf meßbare klinische Endpunkte im Vergleich zu anderen Kolloiden werden wesentlich umfangreichere Daten aus weiteren, gut geplanten klinischen Studien erforderlich sein.

124. Da ein möglicher schädlicher Effekt von Albumin durch die Meta-Analyse der "Cochrane Injuries Group Albumin Reviewers" aufgezeigt wurde, sind weitere Studien zur Mortalität notwendig.

124. Die klinischen Auswirkungen von Präparaten mit unterschiedlichen Albumin Konzentrationen und einem unterschiedlichen Gehalt an Natrium sind unklar und sollten hinsichtlich der klinischen Effektivität und der ökonomischen Konsequenzen weiter abgeklärt werden.

3.5. GERINNUNGSFAKTOREN

125. Um den zukünftigen Bedarf an teuren Blutprodukten innerhalb der Europäischen Gemeinschaft abschätzen zu können, sollten Patientenregister für Patienten mit Hämophilie oder ähnlichen Erkrankungen eingeführt werden und in jedem Land der Europäischen Gemeinschaft unterhalten werden.

126. In der Europäischen Gemeinschaft sollte in Kooperation aller Mitgliedstaaten ein Hämovigilanz- oder Pharmakovigilanz-Programm etabliert werden, um Daten über Patienten mit Inhibitor-Bildung, allergischen Reaktionen, Übertragung von Viren oder verschiedenen anderen Komplikationen zu sammeln.

127. In Übereinstimmung mit den üblichen Kriterien sollte in jedem Mitgliedslands ein Netzwerk von Zentren mit umfassender Betreuung ("Comprehensive Care Centres" / "CCCs") etabliert werden, das eine klinische und labortechnische Versorgung rund um die Uhr ermöglicht und allen Patienten zugänglich ist.

128. Ausreichende Mengen an Gerinnungsfaktor-Konzentraten für die Behandlung von Patienten mit Hämophilie und ähnlichen Erkrankungen sollten in jedem Mitgliedsland verfügbar sein. Obwohl festgestellt wurde, daß die rekombinanten Produkte die aus Plasma Gewonnenen schrittweise verdrängen könnten, sollten ausreichende Mengen sowohl an aus Plasma gewonnenen, als auch an rekombinanten Produkten weiterhin zur Verfügung stehen. Individuelle Präferenzen im Hinblick auf den jeweiligen Patienten sollten bei der Wahl der Produkte in Betracht gezogen werden.

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.

121. The education of medical personnel should be improved.

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.

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.

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.

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.

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.

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.

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.

129. Besondere Beachtung sollte die Europäische Gemeinschaft den möglichen negativen Auswirkungen für den Fall eines Monopols in der Produktion von Gerinnungsfaktor-Konzentraten zukommen lassen. Die Forschung im Bereich entstehender rekombinanter Technologien in der Europäischen Gemeinschaft muß gefördert und finanziert werden.
130. Die zahlreichen Leitlinien der medizinischen Institutionen in den verschiedenen Mitgliedstaaten der Europäischen Gemeinschaft sollten harmonisiert und um Ratschläge zu Dosierung in der Behandlung gewöhnlicher spontaner Blutungsprobleme erweitert werden.
131. Als allgemeine Regel wird die prophylaktische Behandlung von Kindern mit schwerer Hämophilie empfohlen.
132. Immuntoleranz-Verfahren sollten allen Hämophilie-Patienten, die neue inhibitorische Antikörper entwickeln, angeboten werden.
133. Das Outcome der Behandlung, einschließlich von Parametern zur Erfassung der Lebensqualität und von ökonomischen Aspekten, muß noch evaluiert werden. Weitere Studien, die finanzielle Unterstützung benötigen werden, sollten initiiert werden.

3.6. QUALITÄTSMANAGEMENT

134. Es ist dringend erforderlich, das Engagement der Entscheidungsträger auf nationaler und lokaler Ebene bei der Einführung eines Qualitätsmanagement-Systems an den Krankenhäusern zum klinischen Gebrauch von Blutprodukten zu fördern.
135. Es muß gewährleistet sein, daß:
- Ein Qualitätsbeauftragter für den klinischen Gebrauch von Blutprodukten ernannt wird und befugt ist, in Zusammenarbeit mit dem Transfusionskomitee des Krankenhauses Maßnahmen zur Qualitätssicherung und Qualitätsverbesserung durchzuführen;
 - Der Qualitätsbeauftragte sollte zusammen mit dem Transfusionskomitee für die Entwicklung und die Verbreitung von Leitlinien und von standardisierten Handlungsanweisungen (“standard operating procedures” / “SOPs”) verantwortlich sein und ihre Anwendung durch das medizinische Personal überprüfen.
136. Es muß gewährleistet sein, daß:
- Strategien zur optimalen Anwendung von Blutprodukten entwickelt werden, die die bestmögliche Kooperation zwischen allen Leistungserbringern im Gesundheitswesen ermöglichen.
137. Es ist dringend erforderlich:
- Kontrollierte Studien zur Definition der richtigen Anwendung von Blutprodukten und der für die Messung von klinischer Wirksamkeit und von Outcomes erforderlichen Parameter durchzuführen;
 - Die Indikationen für den Gebrauch von Blutprodukten auf den Anforderungsdokumenten festzuhalten;
 - Eine begrenzte Anzahl allgemeiner Indikatoren zu definieren, die den Vergleich zwischen verschiedenen Krankenhäusern erlauben und die Aufmerksamkeit gegenüber unangemessenem Gebrauch steigern.

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.

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.
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.
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.
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.

138. Es ist dringend erforderlich:

- Ein fortlaufendes, vom Transfusionskomitee organisiertes Schulungsprogramm für medizinisches Personal, das in den Gebrauch von Blutprodukten involviert ist, zu fördern; und
- Transfusionsmedizin in Aus- und Weiterbildung zu integrieren.

139. Bei der Entwicklung von standardisierten Handlungsabläufen sollte besonderes Augenmerk auf die Verhinderung von Transfusionszwischenfällen, auf die Neuordnung von Prozessen und - falls möglich - auf die Einführung neuartiger Hilfsmittel zur Informationsverarbeitung, wie z.B. tragbare Barcode-Lesegeräte, die zur Feststellung der Identität des Patienten, der Blutproben und der gekennzeichneten Konserven dienen, gerichtet werden.

140. Die Einführung eines Informations- und Dokumentationssystems im jeweiligen Krankenhaus ist dringend zu empfehlen. Dies könnte die Zusammenstellung und die Analyse von Daten zum Gebrauch von Blutprodukten stark vereinfachen.

3.7. ÖKONOMISCHE ASPEKTE

3.7.1. Information

141. Die Daten zum Verbrauch von Blut und Blutprodukten sollten innerhalb der Europäischen Gemeinschaft erfaßt werden, um den wahrscheinlichen klinischen Bedarf zu bestimmen und so die Planung der zukünftigen Versorgung zu unterstützen.

142. Der Verbrauch von Blut und Blutprodukten für die Behandlung von Patienten mit repräsentativem Befund ("index conditions"), sollte jährlich für jeden Mitgliedstaat festgehalten werden, um grundlegende Daten und Indikatoren für Vergleiche zu erhalten.

143. Es sollte versucht werden, den Verbrauch von Blutprodukten und die klinischen Umstände, unter denen sie verwendet werden, in Zusammenhang zu bringen. Dies könnte am besten durch automatisierte Datenbanken, den Gebrauch elektronischer Patientenbögen und elektronische Verschreibung erreicht werden.

144. Evaluationen zum Gebrauch von Blut und Blutprodukten sollten sowohl mit ökonomischen, als auch mit klinischen Methoden durchgeführt werden, um das Muster des Gebrauchs zu bestimmen, die Angemessenheit der Anwendung sicherzustellen und den Effekt von Schulungsprogrammen festzustellen. Zur Einschätzung der optimalen Anwendung sollten (geeignete) Indikatoren entwickelt werden.

145. Es sollte erwogen werden, derartige Studien innerhalb der gesamten Europäischen Gemeinschaft finanziell zu unterstützen.

3.7.2. Zukünftige Anforderungen

146. Der Gebrauch von aus Plasma gewonnenen Produkten wie Albumin, Immunglobulinen, Faktor VIII und Faktor IX ist im Wandel begriffen. Dies wird auf die zukünftigen Kosten und die zukünftige Verfügbarkeit dieser Produkte großen Einfluß haben. Es sollte eine Studie zur Untersuchung der zukünftigen Bedürfnisse an Blut und Blutprodukten mit angemessener Berücksichtigung ökonomischer Faktoren durchgeführt werden, um die wirtschaftliche Position von Blutspendediensten und fraktionierender Industrie zu ermitteln.

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.

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.

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.

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.

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.

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 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.

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

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.

147. Die Zentren der Plasmaindustrie sollten in der Europäischen Gemeinschaft auf sinnvolle Weise verteilt werden. Die wirtschaftliche Effizienz dieser Zentren und nationale Abhängigkeiten, die sich aus dem Konzept der eigenständigen Versorgung ("self sufficiency") ergeben, sollten berücksichtigt werden.

3.7.3. Anforderungen an die Schulung

148. Aus- und Weiterbildung, sowie Trainingsprogramme für alle Kliniker, die mit Blut oder Blutprodukten umgehen, sollten gefördert werden. Weiterhin sollten Möglichkeiten, den Einfluß von klinischen Empfehlungen und Leitlinien zu erhöhen, eruiert werden.

3.7.4. Allgemeine Empfehlung

149. Ökonomische Evaluation sollte die Anstrengungen zu einer verbesserten Effizienz im Umgang mit Ressourcen und in der optimalen Anwendung von Blut und Blutprodukten unterstützen und das Prinzip der freiwilligen unentgeltlichen Blutspende aufrecht erhalten.
150. Das Prinzip und die Notwendigkeit zur eigenständigen Versorgung ("self sufficiency") sollte im Hinblick auf die sich weiterentwickelnde Europäische Gemeinschaft im Kontext von Sicherheit, Verfügbarkeit, ethischen und ökonomischen Gesichtspunkten neu definiert werden.

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.

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.

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.

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.



BLOOD SAFETY IN THE EUROPEAN COMMUNITY: AN INITIATIVE FOR OPTIMAL USE

*Under the auspices of:
the Federal Ministry of Health
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Commission of the European Communities*
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Discussion Papers

1. Background Document

1.1. Introduction

1. In the course of the twentieth century, momentous advances in science and technology have resulted in remarkable developments in areas related to medicine and health care delivery. Notable among them is the routine utilisation of blood, its precursors, components, and derivatives in clinical treatment and preventive medicine. But what has become a cornerstone of modern medicine is also coming under increased scrutiny from the general public, governmental and regulatory authorities, politicians, and clinicians themselves. This scrutiny can be attributed not only to the tragic events associated with the transmission of HIV by blood and to recent concerns about the risk, although still theoretical, of transmission of new variant Creutzfeldt Jacob Disease (nvCJD), but also to: public expectations regarding blood safety; increasing technological advances and regulatory requirements; changing social practices; diminishing blood donor populations; and health-care cost-containment policies. The therapeutic use of blood itself as well as the products derived from it is one aspect of this increased examination.

1.2. Background

2. In 1989, the European Community extended its pharmaceutical legislation to include industrially-prepared medicinal products derived from blood and plasma.¹ Although the requirements did not include whole blood, plasma and blood cells of human origin, Directive 89/381/EEC did require Member States to encourage voluntary unpaid donations, develop the production and use of products derived from them, and promote Community self-sufficiency in human blood or plasma. A 1993 report,² prepared by the European Commission, on the extent to which the Community had attained self-sufficiency resulted in the Council not only reaffirming this goal but agreeing that it should be achieved through co-operation between the Member States.³
3. Further examination of issues related to the safety of the blood transfusion chain led to the Commission recommending in 1994⁴ that a Community blood strategy was needed which would help to improve public confidence and promote self-sufficiency. Proposed areas for action, which were supported by Council⁵, included donor selection, testing of donations, haemovigilance, public awareness, and inspection and accreditation. The Commission also recommended that the proposed activities should encompass:
 - ‘The development and use of quality-assessment criteria and good practices regarding the collection, processing **and transfusion of blood and blood products and patient follow-up procedures**’; and
 - The ‘encouragement of health professionals to make **optimal use** of blood and blood products’.

¹ Council Directive (89/381/EEC) of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma. O.J. L181 of 28.6.89. p.44

² Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee on Blood Self-Sufficiency in the European Community. [COM(93) 198 final. Brussels, 25 May 1993. 13p.]

³ Council Conclusions of 13 December 1993 on self-sufficiency in blood in the European Community (94/C15/03) O.J. n° C 15 of 18.01.94. p.6

⁴ Communication from the Commission on Blood Safety and Self-sufficiency in the European Community. COM(94) 652 final. 21.12.1994. 23p.

⁵ Council Resolution of 2 June 1995 on blood safety and self-sufficiency in the Community (95/C 164/01). O.J. No C164. 30.6.95. p.1

4. In its report, the Commission indicated *inter alia* that optimal use of blood and blood products, without depriving patients of what they need, can contribute to the attainment of Community self-sufficiency. It referred, however, to the profound and totally unexplained variations between hospitals in the use of blood products for the same elective surgical procedure that had been reported in the Sanguis study.⁶ The Commission also noted that consensus conferences and guidelines on the appropriateness of specific blood products appeared not to have made any significant impact on the way physicians used them. It concluded that there was a need for improved utilisation of blood resources through agreement on best blood transfusion practice.
5. In 1996, quality assurance and optimal use were among the subjects of discussion at a meeting of experts on blood safety and self-sufficiency held in Adare, Ireland.⁷ In their conclusions and recommendations, participants stated that:

The attainment of self-sufficiency is influenced by several factors: the willingness of the citizens of the Member States to donate blood and plasma; the interpretation in the Member States of non-remunerated donations as defined by the Council of Europe; **optimal use of these products by treating physicians taking fully into account the very special nature of their source**; and differing regulations and practices in the Community which may restrict the exchange of blood and blood products between Member States.

6. In July 1998, a group of experts meeting in Vienna to discuss the quality management of blood collection, processing and distribution in the European Community⁸ included issues related to distribution and transfusion in their deliberations. Among the numerous points presented in the final report, the two of particular significance in respect of the optimal use of blood and blood products are:

‘The distribution and transfusion of blood components are among the final links in the blood transfusion chain. They are concerned with both the maintenance of the quality of blood components themselves and the **quality of the service in delivering and using them.**’

‘Common European Community standards for good transfusion practice should be endorsed’.

1.3. Towards optimal use

7. Considerable effort has been directed to the management of blood resources during the collection, processing and distribution phases so as to minimise unnecessary wastage and maximise quality and safety. This has resulted in the elaboration of nationally or internationally accepted standards for determining donor suitability and the testing of donated blood or plasma, as well as the imposition of strict regulatory criteria for plasma-derived products. Such requirements or generally accepted standards appear to be non-existent or not to have been reached for the last and perhaps most crucial phase of the blood transfusion chain – transfusion itself.

⁶ Safe and good use of blood in surgery (SANGUIS) - Use of blood products and artificial colloids in 43 European hospitals. EUR 15398. G. Sirchia et al (eds). European Commission. 1994. 235p.

⁷ Department of Health, Ireland. Conclusions and Recommendations. Colloquium on Blood Safety and Self-sufficiency: An Agenda for the European Community. Adare, County Limerick, Ireland. 4-6 September 1996.

⁸ Federal Ministry of Labour, Health and Social Affairs, Austria. Discussion Document on Distribution and Transfusion Quality Management for Blood collection, Processing and Distribution in the European Community: A way forward. Baden/Vienna, Austria 13-15 July 1998.

8. The circulation of clinical guidelines; the institution of clinical audits; the establishment of hospital transfusion committees to oversee and monitor blood use; consensus development conferences; and utilisation reviews have, it appears, done little to increase the knowledge about the clinical effectiveness of varying approaches to the prescribing and use of blood and blood products across the Community. Nor do they appear to have had significant impact on changing the behaviour of physicians⁹ or improving the practice of transfusion itself. As a result, there continues to be unnecessary and often inappropriate use of blood and blood products. Lack of scientific evidence and a dearth of relevant information to justify certain transfusion practices, however, mitigate the establishment of policies regarding optimal use. Consideration, therefore, needs to be given to approaches that can be taken in order to promote such policies in the European Community.
9. The experts participating in the 'Wildbad Kreuth Initiative', scheduled for 20-22 May 1998, could draw upon the meeting's discussion documents related to various components and products derived from blood, such as erythrocytes, platelets, thrombocytes, coagulation factors VIII and IX, albumin, and fresh frozen plasma, and their therapeutic use in addressing necessary measures required to introduce and implement quality management of these resources in the European Community. The aim should be to identify possible, or best, options for action at Community level, including operational elements related to the distribution, transfusion, and infusion of blood products. These could contribute to on-going efforts by the authorities in refining their policies on blood safety and enabling the Community Institutions and the Member States to further their efforts towards the implementation of a blood strategy for the European Community and the attainment of self-sufficiency.

⁹

B. Jennett (Chairman), D.B.L. McClelland (ed.). Optimal use of donor blood: a report from a working party set up by the Clinical Resource and Audit Group. The Scottish Office; National Health Service in Scotland. May 1995.146p.

2. Red Blood Cells

2.1. Introduction

1. Multiple interacting factors strongly influence the decision as to whether a patient should or should not receive a transfusion with erythrocytes. Although tissue oxygenation is generally accepted as justification, variations in a patient's ability to compensate for acute blood loss and heterogeneity in the underlying medical problems often make the assessment of the metabolic need for transfusion difficult. On the one hand, efforts to safely limit allogenic blood transfusions and to optimise the use of erythrocytes have met with controversy and differences of opinion among physicians of various disciplines.^{1 2} On the other, decreasing numbers of donors, public concern about disease transmission, and inappropriate use of blood are placing increasing attention on the need to reduce unnecessary use of erythrocytes.

2.2. Background

2. Normally, blood is collected from a donor as a whole blood product which then can be further separated or filtered into several components, including erythrocytes.³ Requests for blood originating from the clinician are generally met with the provision of standard erythrocyte bags satisfying the following characteristics:⁴ a volume of at least 250 ml. of buffy-coat-free concentrate in additive solution; a haemoglobin level of approx. 65 grams; a haematocrit in the 50 — 70 percent range; a leucocyte content lower than 1.2×10^9 cells; and a plasma volume lower than 15 ml.
3. In order to minimise side effects directly associated with blood transfusion, several measures are taken with the erythrocyte preparations themselves including leucocyte-filtration, washing, and irradiation. In addition, the use of donations from patient's relatives is avoided in order to minimise the risk of transfusion-transmitted graft versus host disease (tt-GvHD).
4. In spite of numerous safety precautions, however, adverse events do occur. The transfusion of erythrocytes, as well as platelets, granulocytes and fresh plasma, can result in: graft-versus-host-disease (1 in 10^6 transfusions)⁵; transfusion-related acute lung injury occurring within a few hours of transfusion (approx. 1 in 5,000)⁶; fatal acute haemolytic reactions caused to a large extent by ABO incompatibility (1 in 250,000 — 1,000,000)⁷; clinical manifestations of a delayed reaction (1 in 1000)⁸; and overt haemolytic reactions due to minor red-cell antigens not detected by a routine antibody assay (1 in 260,000)⁹. These reaction rates are much higher in populations at increased risk, such as patients with sickle cell disease.¹⁰

¹ L.T. Goodnough, ME Brecher, MH Kanter and JP AuBuchon (1999): NEJM Vol 340, No 6, p.438f

² Surgenor DM, Wallace EL, Hao SDS, Chapman RH (1990): NEJM Vol 322, p.1646f

³ Council and Scientific Advisory Board of the German Medical Association (1996): 'Guidelines for therapy with blood components and plasma derivatives' Deutscher Ärzteverlag. (<http://www.bundesaerztekammer.de>)

⁴ Council and Scientific Advisory Board of the German Medical Association, #3

⁵ LindenJV, Pisciotto PT (1992): Transfusion Medicine Reviews 6: p.116f

⁶ Popovsky MA Moore SB (1985): Transfusion 25: p.537f

⁷ Sazama K. (1990): Transfusion 30: 583f

⁸ Ness, PM, Shirley RS, Thorman SK, Buck SA (1990): Transfusion 30: p.688f

⁹ Shulman IA (1990): Arch Pathol Lab Med: Vol 114, p.412f

¹⁰ Shulman IA (1990): Arch Pathol Lab Med: Vol 114, p.412f

5. In order to minimise the incidence of adverse events associated with blood transfusion and to decrease unnecessary and inappropriate use of erythrocytes, strategies need to be developed and implemented to ensure the optimal use of this limited resource.

2.3. Medical indications for transfusion

6. The clinical indications for the therapeutic use of erythrocytes remain subject to debate. It is generally agreed that adults should be given erythrocyte transfusions in order to increase the blood's oxygen carrying capacity in order to meet the oxygen demand of the cells. The intracellular pO₂ would be the best parameter to be monitored. The difficulty to directly measure intracellular oxygenation in the clinical setting, however, requires that surrogate markers, such as haemoglobin concentration, are used. It has been found, nevertheless, that in the majority of cases in intensive care, the reasons for erythrocyte administration were acute bleeding (35% of patients) and the augmentation of oxygen delivery (25% of patients) rather than haemoglobin concentration.¹¹ Consequently, the patient's clinical condition is also taken into account.
7. A haemoglobin concentration of < 50 g/l, either for healthy persons or patients, is considered to be critical for maintaining body function. This, it is recognised, can be influenced by accompanying diseases like fever, sepsis or cardio-pulmonary insufficiency, all of which further reduce the compensation capacity.¹² In patients with chronic anaemia, substitution of erythrocytes, done individually according to clinical symptoms, is normally recommended. For patients with leukaemia or myelodysplastic syndrome, the accepted haemoglobin concentration in clinical practice seems to range from 70 — 80 g/l.¹³ For preoperative transfusion practice, it is > 70 g/l.¹⁴
8. An analysis of the medical records of 8,787 patients who underwent surgical repair of fractured hips, found that transfusion in those with a haemoglobin of > 80 g/l did not affect mortality. Nor was there any significant effect, as reported in another study, on the 30- or 90-day mortality rate in patients undergoing similar operations with haemoglobin levels as low as 80 g/l.¹⁵
9. A prospective randomised study of critically ill patients with acute anaemia, in an intensive care unit, found no differences in mortality or organ dysfunction scores in randomly allocated groups with haemoglobin levels maintained either at 90 g/l versus 110 g/l.¹⁶
10. Results from another report on individuals who underwent orthopaedic surgery, showed that the patient's sex influences transfusion outcome.¹⁷ This could be attributed to the use of the same haematocrit level as a threshold for both women and men, thereby not taking into account lower levels in women.¹⁸

¹¹ Marik Perkin-Elmer, Sibbald WJ (1993): JAMA Vol 269, p.3024f

¹² Consensus conference. Perioperative red blood cell transfusion. JAMA 260: p.2700f
American College of Physicians (1992): Ann Intern Med Vol 116: p.403f

¹³ Expert Working Group. Canadian Medical Association. Can Med Assoc J (1997): Vol 156: Suppl. 11: S1-S24
Strauss R. et al. (1998): Education Programme Book of the American Society of Hematology, Miami Beach, Florida, December 4-8, 1998; p.455

¹⁴ Consensus conference. Perioperative red blood cell transfusion. JAMA 260: p.2700f

¹⁵ Carson JL, Duff A, et al. (1998): JAMA Vol 279, p.199f

¹⁶ Hebert PC, Well G, Marshall J et al. (1995): JAMA Vol 273: p.1439

¹⁷ Surgenor DM, Wallace EL, Churchill WH, et al. (1991): Transfusion 31: p.531f

¹⁸ Friedman BA, Burns TL, et al. (1980): Transfusion 20: p.179f

11. Can it be assumed that a haemoglobin level of 80 g/l is an appropriate threshold for transfusion in surgical patients with no risk factors for ischemia ? Should the threshold be 100 g/l for patients with risk factors ? In all situations, can prophylactic blood substitution or transfusion in order to replace volume be ruled out ?¹⁹

2.4. Conservation of erythrocytes

12. In order to maximise available blood resources, basic clinical strategies need to be developed that could help to reduce the number of inappropriate and unnecessary blood transfusions. Depending on the individual clinical situation, consideration could be given to:²⁰

- Correction of deficiencies in essential nutrients (Fe, folic acid, B12);
- Avoidance of pharmacologic coagulopathies (e.g. overdoses of phenprocoumon, etc.);
- Stimulation of bone-marrow function with recombinant erythropoietin;
- Pharmacological enhancement of haemostasis with antifibrinolytics (e.g. aprotinin, epsilon-amino-caproic acid (EACA));
- Intra-operative normovolemic haemodilution;
- Preoperative autologous blood donation;
- Intra-operative or post-operative blood salvage and re-transfusion; and
- Transfusion on a symptomatic basis.

2.4.1. Recombinant erythropoietin

13. Recombinant human erythropoietin (rHuEPO) has been utilised to stimulate erythropoiesis following surgery or alternatively to produce more red blood cell units for autologous donation. Its clinical effectiveness has been analysed most extensively in orthopaedic patients.²¹ Is it reasonable, bearing in mind cost-effectiveness, to use erythropoietin:

- preoperatively, to overcome anaemia;
- to expand red cells in those individuals who refuse blood transfusion on religious grounds;
- to enhance autologous blood donation or normovolemic haemodilution:
 - in severely immunised individuals;
 - in patients with severe IgA deficiency;
 - in patients with rare blood groups and irregular antibodies; and
 - in patients with chronic renal failure and dialysis.

2.4.2. Pharmacological interventions

14. Three anti-fibrinolytic drugs have been shown to decrease blood loss in cardiac surgery:

- the serine protease inhibitor aprotinin;
- synthetic lysine analogues epsilon-amino-caproic acid (EACA); and
- tranexamic acid.

15. Under what circumstances should these drugs be used in order to reduce requirements for erythrocytes and based on what criteria?

¹⁹ Valeri CR, Crowley JP, Loscalzo J (1998): Transfusion 38, p.602f

²⁰ Alving BA, Spivak JL, DeLoughery TL (1998): Education Programme Book of the American Society of Hematology, Miami Beach, Florida, December 4-8, 1998; p.320

²¹ Abraham PA, Halstenson CE, Macres MM, et al. (1992): Clin Pharmacol Ther 52: p.205f
Besä EC, Gorshein D, Gardner FH (1974) Arch Int Med 133: p.418f

2.4.3. Intraoperative normovolaemic haemodilution

16. The removal of a defined whole blood aliquot from a patient immediately before surgery and simultaneous replacement with a crystalloid fluid, and / or colloid to maintain normovolemia, has been proposed as an alternative method to reduce blood loss. It has a number of advantages including:
- no requirement for laboratory pre-testing;
 - autologous blood units are not removed from the operating room, reducing administrative errors; and
 - no delay in surgery, because an additional time investment is not required .
17. The safety and efficacy of normovolemic haemodilution has been shown to be most effective when potential surgical blood loss will exceed 20% of the blood volume of patients who have a preoperative haemoglobin > 100g/l and do not have a severe myocardial disease.²²

2.4.4. Autologous blood transfusion

18. Confirmation that the Human Immunodeficiency Virus (HIV) could be transmitted by blood resulted in an increase in pre-operative autologous blood donation. A study of autologous donations, however, showed that 1 in 16,783 was associated with an adverse reaction severe enough to hospitalise the patient²³ - a risk that is 12 times higher than that from allogeneic donors. Another study concluded that autologous blood donations appear to increase the risk of postoperative anaemia as well as the likelihood of additional transfusions.^{24 25}
19. Transfusion of autologous blood results in many of the same complications as that of allogeneic blood, including bacterial contamination, volume overload and haemolysis, particularly after ABO incompatibility due to administrative errors.²⁶ Other events, like ischemic heart attacks, have been reported to occur during autologous donation, although there may be no direct correlation.
20. Another important consideration with regard to autologous donations is the fact that patients, and not healthy donors, donate blood for preoperative surgery, at an additional risk, and that in 50 - 80% of cases their blood is not used. Since use of surplus autologous units for patients other than the donor is not recommended²⁷, can preoperative autologous donation be considered to be inherently wasteful?
21. Do these problems as well as the decreased likelihood of viral transmission from an allogeneic blood transfusion, demand a re-evaluation of the practice of autologous blood donation for each medical discipline?²⁸

²² Helm RE, Klemperer JD, Rosengart TK, et al. (1996): Ann Thorac Surg 62: p.1431f

Kochamba GS, Pfeffer TA, Sintek CF, et al. (1996): Ann Thorac Surg 61: p.900f

²³ Popovsky MA, Whitaker B, Arnold NL (1995): Transfusion 35: p.734f

²⁴ Cohen JA, Brecher ME (1995): 35, p.640f

²⁵ Kanter MH, van Maanen D, Anders KH, et al. (1996): JAMA 276, p.798f

²⁶ Linden JV, Kruskall MS (1997): Transfusion 37: p455f

²⁷ Renner SW, Howanitz PJ, Bachner P (1992): Arch pathol Lab Med 116: p613f

²⁸ Linden JV, Kruskall MS (1997): Transfusion 37: p.455f

2.4.5. Autologous blood salvage

22. Blood from intra-operative or post-operative surgery can be recovered and reinfused, with or without processing. The reporting of four deaths (a prevalence of 1 in 35,000 procedures) related to intra-operative recovery between 1990-1995 to the New York Department of Health has raised concerns. Post-operative re-infusion has been employed in cardiac and orthopaedic surgery, but its efficacy is controversial because:²⁹
- air embolism can occur;
 - there are elevated levels of cytokines, and the presence of bone fragments, fat and other debris;
 - Fibrin degradation products (FDPs) are present which can make coagulation interpretation more difficult;
 - cardiac enzyme levels are elevated and caution is needed when the laboratory results are interpreted; and
 - the presence of tumour cells in the operating field requires the need for leucocyte filtration and / or irradiation prior to re-infusion.
23. In spite of these problems, only a few complications were reported when blood was re-infused within six hours into patients who underwent joint arthroplasty.³⁰ Is this a procedure that should be considered routinely?

2.5. Screening requirements

24. Optimal use of erythrocytes is influenced not only by the therapeutic criteria but also by the procedures related to processing, distribution, and utilisation. Blood products that cannot be used for reasons of contamination or because they pass their expiration date are usually returned to the producing centre for documented disposal but in reality they may be considered to be wasted.

2.5.1. PCR

25. Scientific advances in the ability to detect viral contamination result in the reduction of pathogenic biologic materials that can be transmitted by blood transfusion from one person to another. While this has meant increased safety, which is paramount, it has also meant that donations tested positive by polymerase chain reaction (PCR) assays during the window period result in a greater number being rejected. This number could possibly rise when NAT testing is used to detect bacterial contamination of blood components. What will be the implications on the optimal use of blood and blood components with the routine requirement for PCR testing on mini-pools beginning in July and a potential similar requirement for single donations in the near future? What will be the cost implications for testing of blood products for viral contamination via PCR, given that currently the cost for a three virus testing via NAT is estimated at approximately 2-3 Euros for each donation ?

2.5.2. Filtration/ leucocyte depletion

26. Red blood cells can be separated by density centrifugation but still contain 25% - 45% of residual leucocytes.³¹ This generally accepted source of side effects can be eliminated by filtration, which is done prior to long term storage or in the clinical facility, immediately

²⁹ Goodenough LT, Brecher ME, Kanter MH, AuBuchon JP (1999): New Engl J Med Vol 340: p525f

³⁰ Farris PM, Ritter MA, Keating EM, et al. (1991): J Bone Joint Surg 73A: p.1169f

³¹ Council and Scientific Advisory Board of the German Medical Association, #3

before transfusion. Filtration of erythrocytes can reduce leucocytes as much as 4 orders of magnitude.

27. It has been suggested that leucocyte filtration should be used routinely. But should this be carried out in the blood bank or at the bedside? Is routine leucocyte reduction acceptable in terms of cost-effectiveness? Or should a list of clinical situations in which filtration is indicated be established?

2.6. Closing remark

28. In addressing issues related to the optimal use of erythrocytes, participants in the 'Wildbad Kreuth Initiative' should give consideration to all aspects of this issue, from the therapeutic indications and clinical practices that could be recommended to the cost-benefit implications of increased testing requirements using advanced technologies.

3. Platelet Concentrates

3.1. Introduction

1. As one of the main components of blood, platelets have been shown clinically to have significant therapeutic benefit. They are administered routinely to patients who are considered to be at serious risk of haemorrhage, or are actively bleeding, and have low platelet counts (thrombocytopenia) or severely decreased platelet function (thrombocytopathia). Prophylactic use is based mainly on the observed existence of a quantitative correlation between platelet count and bleeding. The decision as to whether or not prophylactic platelet transfusion should be carried out, however, may be difficult due to the problems in determining precisely those factors, in addition to thrombocytopenia, that may ascertain the patient's risk of bleeding. Platelet concentrates in addition are expensive and their administration carries associated risks. Given that there is increasing attention being given to the need to limit platelet transfusions and to optimise the use of the different types of platelet concentrates, discussion on the various aspects is needed.¹

3.2. Background

2. Platelet concentrates, which should be stored at room temperature for no more than 5 days, may be prepared from donated blood according to the platelet-rich plasma (PRP) or buffy-coat (BC) method. The mean platelet-count of a single donor PRP or BC platelet concentrate should contain on average 60×10^9 platelets. For a single platelet transfusion for adults, therefore, 4 – 8 units need to be pooled. Platelet concentrates may also be prepared by apheresis techniques resulting in single donor concentrates (apheresis platelet concentrates (APC)) containing on average $3 - 4 \times 10^{11}$ platelets.
3. Platelet concentrates may be irradiated in order to prevent proliferation of transfused lymphocytes in the recipient and thus preclude transfusion-related graft-versus-host disease, particularly in immunocompromised patients. They may also be filtered in order to decrease the number of leucocytes in the concentrate to be transfused. This may decrease the risk of transfusion-related transmission of infections as well as decrease the risk of allo-immunisation.
4. As transfusion-transmitted graft-versus-host disease may develop following platelet transfusion, irradiated platelet concentrates are recommended for patients with immunodeficiencies. There is also a risk of transmitting bacterial or viral infections from donor to recipient which may be enhanced if white blood cells are present in the platelet preparation. The presence of HLA molecules on leucocytes that remain in the platelet concentrate is the main reason for the development of HLA-alloantibodies and the resulting refractoriness to platelet transfusions. The use of leucocyte reduction-filters may reduce white blood cell-related risks associated with platelet transfusion.²
5. Transfusion-related acute lung injury, haemolytic reactions, febrile non-haemolytic transfusion reactions, and transfusion mediated immunomodulation are also risks associated with platelet transfusion that have to be considered. Platelet transfusion may be deleterious in situations with uncontrolled increased platelet turnover such as heparin-

¹ Murphy MF, Murphy W., Wheatley K, Goldstone AN. Survey of the use of platelet transfusions in centres participating in MRC, leukaemia trials. *British Journal of Haematology* 1998; 102: 875 - 876

² Kekomäki S, Volin L, Koistinen P et al, Successful treatment of platelet transfusion refractoriness: the use of platelet transfusions matched for both human leucocyte antigens (HLA) and human platelet alloantigens (HPA) in alloimmunized patients with leukemia. *European Journal of Haematology* 1998, 60: 112 – 118.

induced thrombocytopenia type II, microangiopathic haemolysis or disseminated intravascular coagulation.

3.3. Medical indications for transfusion

6. When dealing with platelet threshold levels for the indication for platelet transfusion, accurate counting of low platelet numbers in every day medicine may create difficulties when a range below 10×10^9 /platelets will be reached.³ Clinical experience has shown that the risk of haemorrhage appears to be considerably greater in neonates than in adults, indicating 2 – 3 fold higher platelet transfusion thresholds. Furthermore, the risk of bleedings seems to increase in patients with low haematocrit.
7. In patients with longstanding thrombocytopenia, such as in aplastic anaemia or autoimmune thrombocytopenia, there is often little evidence of bleeding and regular prophylactic platelet transfusion is not needed.
8. In thrombocytopenic and/or thrombocytopathic patients with spontaneous haemorrhage or bleeding during surgery, platelet transfusions are considered to be indicated. This may also be true in life-threatening bleeding in patients with increased platelet turnover such as autoimmune thrombocytopenic purpura, or thrombotic thrombocytopenic purpura. The indication to transfuse platelets in the bleeding patient may consider prognostic factors for patient outcome. As an example - a patient with far-advanced, end-stage liver disease without long-term treatment option with severe thrombocytopenia may not be considered an optimal candidate to receive platelet concentrates when actively bleeding. During relevant surgery the platelet count should be maintained above 50,000 / μ l in most patients.
9. In relation to the prevention of haemorrhage (prophylaxis), the main use for platelet transfusion is in patients with haematological or oncological diseases, most of whom are undergoing more or less intensive chemotherapy resulting in treatment-related thrombocytopenia. In addition, disease-related thrombocytopenia must be considered. The main aim of prophylactic platelet transfusion is to prevent bleeding-related morbidity and mortality in patients with bone marrow failure. There is a general agreement, supported by a few clinical studies, that a platelet threshold of 10×10^9 /l might be as safe as higher levels for most patients without additional risk factors for bleeding.⁴ These risk factors are poorly defined and may include sepsis, concurrent use of antibiotics, antipyretics or other abnormalities in haemostasis such as deranged plasmatic coagulation. In these cases, a higher platelet threshold, in the range of 20×10^9 /l, may be considered.
10. In addition to platelet count and risk factors for bleeding, there may be a different bleeding risk in patients with haematological malignancies and those with non-haematological cancers when treated with chemotherapy and becoming equally thrombocytopenic.^{5 6} In the latter, patients pre-chemotherapeutic parameters may help to estimate the patients risk of becoming severely thrombocytopenic.^{7 8}

³ Springer W, von Ruecker A, Dickerhoff R. Difficulties in determining prophylactic transfusion thresholds of platelets in leukaemia patients. *Blood* 1998; 92: 2183 - 2184

⁴ Blundell EL, Pamphilon DH, Fraser ID et al. A prospective, randomized study of the use of platelet concentrates irradiated with ultraviolet-B light in patients with hematologic malignancy. *Transfusion* 1996; 36: 296 – 302.

⁵ Goldberg GL, Gibbon DG, Smith HO et al. Clinical impact of chemotherapy-Induced thrombocytopenia in patients with gynecologic cancer. *Journal of Clinical Oncology* 1994, Vol. 12; 11: 2317 - 2320

⁶ Fanning J, Hilgers RD, Murray KP et al. Conservative management of chemotherapeutic-induced thrombocytopenia in women with gynecologic cancers. *Gynecologic Oncology* 1996; 59: 191 - 193

⁷ Blay JY, La Cesne A., Mermet C et al. A risk model for thrombocytopenia requiring platelet transfusion after cytotoxic chemotherapy. *Blood* 1998, Vol. 92, 2: 405 - 410

3.4. Reducing need for platelets

11. Depending on the clinical situation, some therapeutic strategies may help to reduce the bleeding risk and therefore the need for platelet transfusions in individual patients. These include:
- Pharmacological enhancement of haemostasis with aprotinin, tranexamic acid⁹, desmopressin;
 - Stimulation of bone-marrow production of platelets with recombinant thrombopoietin;
 - Avoidance of drugs known to impair platelet function such as non-steroidal anti-inflammatory drugs,
 - Control of patient's plasmatic haemostasis (e.g. avoidance of vitamin K deficiency, avoidance of large volume transfusions of hydroxyethyl starch or other volume expanders);
 - Extremely careful and styptic operations avoiding hypothermia.

3.5. Screening requirements

12. Optimal use of platelets and platelet concentrates is influenced not only by therapeutic criteria but also by the procedures related to their processing, distribution, and utilisation. Products that cannot be used because of complications during therapeutic administration, reasons of contamination, or because they pass their expiration date, should be returned to the producing centre for documented disposal. In reality these platelet concentrates may be considered to have been wasted.
13. Viruses are pathogenics that can be transmitted either intracellularly or attached to blood cell membranes by platelet transfusion. Tests that rely on the measurement of antibodies or antigens detect viruses after a period of replication and amplification and therefore have a 'window period' for undetectable infection. To minimise this 'window', the testing for viral nucleic acid sequences could be considered as the technology develops.
14. The rate of bacterial contamination of platelet concentrates, which is directly related to their length of storage, is considered to be greater than that of contamination by many viruses. To date, however, there is no accepted method, test, or device to identify bacterial contaminated platelet concentrates.

3.5.1. Filtration/leucocyte depletion

15. Leucocyte depletion by filtration can reduce leucocyte contamination of platelet concentrates to less than 1%. A pre-storage filtration of blood products may:
- prevent the disintegration of leucocytes;
 - reduce the leucocyte derived release of mediators;
 - eliminate intra-leucocytic agents such as protozoa or viruses;
 - eliminate HLA-bearing fragments of leucocytes.

⁸ Bolwell BJ, Goormastic M, Andresen S et al. Platelet transfusion requirements during autologous peripheral blood progenitor cell transplantation correlate with the pre-transplant platelet count. *Bone Marrow Transplantation* 1997; 20: 459 - 463

⁹ Shpilborg O, Blumenthal R, Sofer O et al. A controlled trial of tranexamic acid therapy for the reduction of bleeding during treatment of acute myeloid leukemia. *Leukemia and Lymphoma* 1995; Vol 19: 141 – 144

16. Prospective randomised clinical studies in support of leucocyte depletion by filtration are not available.

3.6. Recipients refractory to platelet transfusion

17. Refractoriness is the poor or even missing increment in platelet count after platelet transfusion. Refractoriness occurs in most patients receiving repetitive prophylactic platelet transfusions. Failure to achieve a satisfactory response to platelet transfusion becomes more probable as the number of transfusions the patient receives increases. In most cases, the development of refractoriness to platelet transfusion can be attributed to immunological reasons such as HLA-antibodies. Therefore, a satisfactory increment may be achieved by the transfusion of HLA matched or cross-matched compatible platelets but may increase the risk of graft-versus-host disease. The transfusion of patients with refractoriness should be considered only therapeutically.

3.7. Closing remark

18. In addressing issues related to the optimal use of platelets, participants in the 'Wildbad Kreuth Initiative' should give consideration to all aspects of this issue, from the therapeutic indications and clinical practices that could be recommended to the cost-benefit implications.

4. Albumin

4.1. Introduction

1. Plasma, the liquid component of whole blood, is used not only for transfusion purposes but can be processed further by fractionation in order to obtain concentrates of specific proteins. Developed by Cohn during World War II, human albumin preparations were first used to replace blood losses in the resuscitation of injured soldiers. Although, it has been used for decades with an excellent viral safety record, a recent meta-analysis¹ gave rise to discussions about the therapeutic benefit and potential hazards of human albumin. This at a time when questions are being raised with regard to the optimal use of blood and blood products.

4.2. Background

2. Human albumin (HA) preparations are produced from pooled plasma by alcohol precipitation (modifications of Cohn method) as solutions with 4 - 5% (isooncotic) or 20 - 25% (hyperoncotic) albumin content. Recently, chromatographic methods have also been introduced. HA is pasteurised in final containers for at least 10 hours at 60 °C.
3. Human albumin has significant effects on macro- and micro-circulation. Therefore stringent criteria for choosing to infuse human albumin, as well as careful clinical monitoring are advocated in order to avoid potential hazards, such as lung oedema. In contrast to the congenital deficiency of coagulation factors (as in haemophilia A and B), an inherited deficiency of albumin is associated with rather mild symptoms².

4.3. Current clinical use

4. For decades, the use of human albumin has been mostly empirical and clinical studies providing clear-cut evidence of therapeutic benefits are lacking. Consequently, only a general description of indications for its use is practical.
5. Isooncotic HA may be used to replenish blood volume. In contrast to crystalloid solutions, such as electrolytes and sugars, which are able to diffuse freely into the extravascular space, albumin remains and binds water (approx. 18 ml water per g HA) within the vasculature for a period of several hours, provided there are no disturbances of capillary permeability. Iso-oncotic HA has to be considered for such indications as part of a therapeutic regimen including blood cells, fresh frozen plasma (FFP), crystalloid solutions, or colloid volume expanders. Possible applications worthy of consideration are:
 - Acute blood loss;
 - Severe burns; in this state, the time pattern of complex vasomotor reactions and disturbances of capillary permeability³ needs particular consideration;
 - Shock or hypovolaemia due to various causes.
6. Hyperoncotic HA has the capacity to raise the colloid osmotic pressure (COP) in disorders with hypoalbuminaemia. The COP is an important counterpart to the hydrostatic pressure and is essential for the re-entry of water towards the venous end of capillaries and thus for maintenance of intra-vascular volume.

¹ Cochrane Injuries Group Albumin Reviewers: Brit Med J 317:235; 1998

² Watkins et al.: PNAS 91:2275; 1994

³ Goodwin et al.: Ann Surg 197:520; 1983

7. In many countries, the following indications are considered obsolete:
 - Replacement in chronic diseases with hypoalbuminaemia due to impaired synthesis or loss (e.g. chronic liver failure, nephrotic syndrome); and
 - Parenteral nutrition
8. The use of human albumin is heterogeneous as was shown by the Sanguis study. The Cochrane review raised the question as to whether there is sufficient evidence of benefit deriving from the use of human albumin in the above indications. Bearing this in mind, several questions could be posed:
 - What are suitable diagnostic criteria (concerning the underlying diseases, severity of complications, and parameters of circulation and fluid homeostasis) as a basis for the use of HA?
 - How is HA use justified in comparison to alternatives, and under which circumstances?
9. The dosage of HA may be based on the patient's clinical situation, physical data (e.g. blood loss, circulation parameters), and laboratory data. The amount and speed of administration depend on the patient's cardiovascular situation. For the aforementioned indications, is it possible to reach a consensus about diagnostic criteria in order to determine the starting HA dose and the parameters required to monitor further dosage?
10. Though HA is the most abundant physiologic blood protein, its use carries risks and side effects that have to be weighed against the expected benefits of its administration in any individual case:
 - Careful monitoring of the fluid homeostasis and circulatory functions is needed. HA infusion should be avoided or at least restricted in any hypervolemic state, and in cardiac decompensation of any cause. Is improved guidance and education of medical personnel necessary to avoid detrimental effects on macro- and microcirculation?
 - Anaphylactoid reactions may occur rarely;
 - An increased aluminium content of HA would be detrimental for premature infants, and patients with kidney failure; therefore, should the aluminium content be controlled?⁴⁷
11. In spite of the excellent viral safety record of HA, the theoretical risk due to new pathogens, e.g. nvCJD, can never be totally excluded.
12. HA is a 'very old' therapeutic preparation, and there might be a considerable underreporting of unwanted effects. Is an improvement of monitoring and reporting (Haemovigilance) necessary?

4.4. Outlook

13. The use of 'old' therapeutic products, such as human albumin, is characterised by a significant amount of individual experience and clinical tradition. However, studies satisfying contemporary requirements in order to establish true evidence-based criteria and therapeutic standards are lacking.

⁴ European Pharmacopoeia: Monograph on human albumin

14. Recognising that the judgement of the treating physician, based on his or her personal expertise and the particulars of the patient, is the decision-making factor in relation to the use of human albumin, it nevertheless would appear desirable to:
- develop generally accepted guidance for the ‘treaters’ on the basis of a critical review of currently available evidence;
 - intensify the education of medical personnel involved in the use of human albumin; and
 - formulate urgent topics for clinical research in this field.

5. Fresh Frozen Plasma

5.1. Introduction

1. The transfusion of whole blood has been widely replaced by the targeted use of blood components, one of which is plasma. While the use of plasma in clinical settings has increased in the course of the past twenty years, the growing awareness of the risks associated with the use of blood and blood products in general, has raised considerable interest in the rational basis for its administration.

5.2. Background

2. Plasma can be collected and stored as fresh frozen plasma (FFP) or used to manufacture specific protein concentrates by fractionation. FFP is the anticoagulated (usually with anticoagulants containing citrate) liquid part of blood which is obtained by separation from the blood cells (centrifugation of whole blood donations, or apheresis), and stored frozen until transfusion to patients. It contains all plasma proteins, e.g. the normal levels of stable coagulation factors, albumin, immunoglobulins, and inhibitors.¹
3. FFP is used for transfusion because it provides the entire spectrum of soluble blood constituents in physiologically balanced concentrations. Thus in complex disorders with impaired synthesis, or increased turnover or loss, FFP is considered to be suitable for replacement of plasma proteins. High fluid volumes, however, have to be given in order to replace them in sufficient amounts, and purified and virus-inactivated concentrates are preferred, where available.

5.3. Current clinical use

4. The use of FFP varies considerably depending e.g. on the availability of specific clinical and laboratory expertise in haemostasis, and to a great extent appears to be empirical. Typical indications may be:
 - Treatment (and prophylaxis) of complications (e.g. bleeding, disturbances of microcirculation) due to complex coagulation disorders. Such disorders are usually complications of severe underlying diseases, which determine the therapy. The administration of FFP, therefore, can only be a part of the therapeutic strategy;
 - Increased turnover (consumption) of coagulation factors and inhibitors, in thrombo-haemorrhagic syndromes, termed e.g. disseminated intravascular coagulation (DIC), or consumption coagulopathy;
 - Impaired synthesis of coagulation factors and inhibitors, e.g. in liver failure;
 - Replacement of coagulation factors and inhibitors after severe blood loss or dilution, e.g. surgery or trauma necessitating massive transfusions;
 - Replacement in congenital deficiency of specific coagulation factors (e.g. of factor V or XI) or other plasma proteins, where no concentrates are available;
 - Thrombotic thrombocytopenic purpura (TTP). The current hypothesis is that a protease cleaving high molecular weight von Willebrand factor has to be substituted;
 - Exchange transfusions.

¹ Council of Europe Recommendation R (95) 15: Guide to the preparation, use and quality assurance of blood components

5. The dosage of FFP may be based on the patient's clinical situation, physical data (e.g. blood loss, circulation parameters), and laboratory data. Is it possible to reach (for all aforementioned clinical indications) a consensus on diagnostic criteria to determine the starting FFP dose and parameters to monitor further treatment?
6. In many Member States of the European Community, the following indications are now considered to be obsolete, since FFP is not sufficiently effective, or alternatives are preferable:
 - Volume expansion;
 - Albumin (protein) substitution to increase oncotic pressure;
 - Immunoglobulin substitution;
 - Parenteral nutrition.
7. As there are no uniform guidelines on the use of FFP, however, several questions as to the adequate indications need to be addressed:
 - What are suitable diagnostic criteria (concerning the underlying diseases, the patient's characteristics and condition and the severity of complications) to establish the indication for the use of FFP in complex coagulation disturbances?
 - How can the trigger for FFP use be defined in the context of severe blood loss and massive transfusion?
 - Under what circumstances should FFP transfusion be replaced by alternatives, and what fluids should be used?
8. Though FFP is the physiologically fluid part of blood, its use carries risks and side effects, that have to be weighed against the expected benefits of FFP transfusion in any individual case because:
 - Transmission of (viral and other) infections may occur²;
 - Volume overload may lead to serious complications such as lung oedema. Careful monitoring of the patient's fluid homeostasis and circulatory functions is warranted;
 - Citrate intoxication may occur, if large amounts are transfused quickly, and may lead to serious problems like shock, acidosis and hypothermia in patients with impaired liver function (e.g. premature infants);
 - Reactions of host immune system against FFP constituents, e.g. anaphylaxis against IgA, development of inhibitors;
 - Reactions of FFP constituents versus host, e.g. Transfusion Associated Acute Lung Injury (TRALI), may occur.
9. For both preventing the transmission of infections through blood products, and protecting the donor's health, the proper selection and testing of donors is indispensable³. The risk of virus transmission may also be reduced by quarantine storage or virus inactivation steps. Quarantine storage involves the release of FFP only if the donor still tests negative after a time interval covering the diagnostic window period of certain pathogens. Is it necessary to introduce such measures generally in the European Community?

² Glück et al.: Infusionsther Transfusmed 24:167; 1997

³ Council Recommendation on the Suitability of blood and plasma donors and the Screening of donated blood in the European Community. O.J. No L203, 21.7.98, p.14.

10. FFP is a ‘very old’ therapeutic preparation, and there might be considerable underreporting of unwanted effects. Is an improvement in monitoring and reporting (haemovigilance) necessary ?

5.4. Concluding remark

11. Discussion on the various issues posed in relation to the use of FFP, could help to arrive at concrete recommendations regarding definitive indications for the use of FFP, conditional uses and indications where its use is not justified.

6. Coagulation Factor Concentrates / Factor VIII & IX

6.1. Introduction

1. Haemophilia is a congenital haemorrhagic disorder encountered in all countries and ethnic groups throughout the world. Although occurring primarily in males, it is the daughters of those with haemophilia that are the obligate carriers of the disorder. Caused by a deficiency of clotting factors VIII and IX, haemophilia causes recurrent bleeding in joints and muscles, often accompanied by considerable pain, and leads to a general deterioration of the musculoskeletal system. For physicians involved in the care of patients with haemophilia, safety is of paramount importance accompanied by a professional concern for their quality of life. While advances in therapeutic technologies over the last two decades have helped to improve the latter, unforeseen consequences impacted severely in the 1980s on the former. With increasing attention being devoted to the use of clotting factor products developed by recombinant technology, emphasis on the optimal use of blood products, and the ever present concern for safety, it is fitting that the treatment of haemophilia be considered from three aspects: therapeutic, organisational and economic.

6.2. Background

2. The incidence of haemophilia in the general population is estimated to be approximately 1 in 10,000, a figure that is supported by data from a number of Member States of the European Community.

	Haemophilia A	Haemophilia B
Germany	3 800	634
Greece	587	95
Italy	3 428	625
U.K.	5 393	1 152

As a consequence of improved care, the number of patients with severe haemophilia in developed countries is expected to rise over the first decade of the new century.¹

3. While the development of coagulation concentrates from plasma in the early 1970's transformed the quality of life for haemophilia patients, the manufacturing process, which involved the pooling of plasma from thousands of donors, introduced the risk of viral infection. Between 1979 and 1987, a significant number of patients with both haemophilia A and B were infected with HIV.² But an even greater number in the European Community were infected with hepatitis C. These two iatrogenic infections impacted significantly on the longevity of haemophilia patients over the past 20 years.
4. These past experiences have focused attention on the possibility that parvovirus may be transmitted by plasma-derived products that have been subjected to a combination of heat and solvent detergent treatment. Whilst normally of little clinical consequence, the fact that this hardy virus is resistant to such methods has drawn attention to the residual risk of viral transmission associated with plasma products. This has been brought further into focus by the identification of the new variant Creutzfeldt-Jacob disease (nvCJD) that has been linked to 'mad cow' disease – bovine spongiform encephalopathy³. As a result, the demand for recombinant factor VIII has increased in the United Kingdom while at the

¹ F. Rosendaal. 1990.

² SC Darby et al. 1995.

³ CA Ludlam. 1998.

same time, an estimated 600 tons of British volunteer donor plasma is being destroyed at a loss of approximately 100 million units of factor VIII.

6.3. Therapeutic aspects

5. The goals of haemophilia therapy are: to treat life-threatening bleeds, to prevent bleeding, to maintain or restore joint function, and to help to integrate haemophilia patients into a normal social life. These goals are influenced significantly by the age of the patient; the severity of the disorder; the development of inhibitors; and particular circumstances associated with each individual (e.g. frequent vs infrequent bleedings). The provision of therapy is also influenced by the social situation linked in part to the health care delivery systems, the patient's preferences, and the treating physician's experience.
6. Guidelines on the choice of products to treat patients with coagulation bleeding disorders have been issued by many countries. Although there is agreement on some aspects of haemophilia therapy, there are differing points of view as to what doses of clotting factors should be administered in treating various bleeding episodes. This is clearly reflected in the differences in products used (i.e. plasma-derived, recombinant, purified) and dosages administered in Community Member States. As the reasons for these differences remain controversial, further investigation on the basis of a prospective multi-centre Community-wide study would provide treating physicians not only with clarity on this issue but support their clinical decisions.

6.3.1. The role of prophylaxis

7. Pioneered in Sweden in the 1950s, the treatment of haemophilia on a prophylactic basis is gradually being adopted as the norm in most Member States of the European Community. Data from several studies suggest that administration in this way helps to reduce the development of joint damage and disability and may also reduce the incidence of intracerebral haemorrhage, which was a common problem in the past. A collaborative study between several European centres has focused on socio-economic aspects. Whilst there is no doubt that prophylaxis involves increased initial expenditure on blood products, this is offset by a reduction in the number of hospital visits and in-patient treatment episodes. Over the long-term, prophylaxis facilitates attendance at school, improves the prospect of employment, and thus income and tax generation. There is also evidence of increased patient well-being that cannot be quantified in economic terms. There are, however, potential problems with venous access and patient acceptability. An alternative strategy might prompt on-demand therapy at home.
8. If prophylaxis is to be generally recommended, several contentious issues need to be resolved including:
 - Time at which prophylaxis should start;
 - Place of central venous devices;
 - Age at which prophylaxis should be suspended; and
 - Dosage and frequency of injections.
9. In the case of haemophilia A, a regimen of 20 - 40 units / kg body weight is commonly employed. For haemophilia B, twice weekly infusions are usual.

6.3.2. Recombinant products

10. The development of recombinant factor VIII has been welcomed by patients and many physicians as offering a considerably greater margin of safety with regard to preventing the transmission of infections. Most of these products, however, contain human albumin and / or bovine proteins, so the risk of transmission of infection cannot be regarded as having been completely eliminated. Furthermore, although no comparative and prospective randomised studies have been conducted, there is some evidence that the risk of inhibitor development is increased in association with treatment with recombinant factor VIII. These products are also considerably more expensive than conventional plasma products. The Republic of Ireland is the only Member States in the European Community with a definite policy of treating all haemophilic patients with recombinant factor VIII.
11. Governmental policy on the use of recombinant products differs in the Community. In the UK, the Department of Health has sanctioned their use only for patients under the age of 16. In Italy and Spain, patients who have contracted HIV are often able to obtain them. In Germany, it is individual patient and physician preferences for plasma-derived products that have influenced recombinant product use.
12. Clear guidance is required on the choice of factor VIII products - recombinant vs plasma-derived. This could assist health care authorities, faced with increasing demands on their resources, in making decisions with regard to treatment priorities.

6.3.3. Patients with inhibitory antibodies

13. Following the significant reduction in the risk of viral infection transmission by available clotting factor concentrates, the development of inhibitory antibodies is now the most feared complication in severe haemophilia.
14. Recommendations are required on the treatment of bleeding episodes in patients with inhibitory antibodies as well as on the role of immune tolerance induction. Treatment guidelines for those haemophilia patients with inhibitors have been issued in several Member States. There is general agreement that the choice of product is determined by the severity of the bleed and the titre of antibody. There is also agreement that a recombinant factor product is the treatment of choice for the few patients with both haemophilia B and inhibitory antibodies. In acute bleeding situations in those patients with haemophilia A and inhibitors, treatment options for different clinical situations, such as proposed in the following scheme, are needed.

Clinical situation

Options

Low titre (< 5 BU) minor bleed

Human factor VIII (up to 200 units / kg

Low titre, serious bleed

FEIBA 50 - 100 units / kg

Porcine factor VIII 50 – 150 units / kg

High titre, serious bleed

FEIBA 50 - 100 units / kg

recombinant factor Iv

15. The regular administration of factor VIII over a prolonged period can often result in induction of immune tolerance. Guidance is required on dosage and duration of treatment, and the results of an on-going investigation combined with extensive experience in this area will help to define the indication, dosage and duration of immune tolerance treatment. Additional issues have to be given serious consideration e.g. choice of products. As many low-titre antibodies will often disappear spontaneously over a period of months, consensus is required as to when treatment should be withheld and for how long.

6.4. Organisational aspects

16. Haemophilia is a rare disorder and as such, it has been suggested, should be treated in a restricted number of designated centres. Delivery of haemophilia care through such centres could prove more cost effective in the long term and more likely to offer a better clinical outcome for patients. In Germany, the Federal Government has introduced in its transfusion law a requirement that the provision of clotting factors to patients within comprehensive haemophilia care must be carried out only by physicians experienced in haemostasis / haemophilia treatment.
17. The number and geographical distribution of comprehensive care centres varies considerably among the Member States of the European Community. The World Federation of Haemophilia and national member organisations have issued guidelines on criteria for designating a clinical facility as a Comprehensive Care Centre. A key criterion is that at least 50 patients with severe haemophilia be registered, reflecting the need for a high level of collective experience in treating patients with this rare disorder. These centres should be geographically distributed. A further aspect requiring consideration is the combining existing adult and paediatric treatment facilities into a single centre.

6.5. Economic aspects

18. Haemophilia is a life-long disorder and consequently is of particular socio-economic interest. Data clearly indicate that almost 90% of the money spent on haemophilia care is allocated to the purchase of coagulation factor concentrates. The considerable variation in factor VIII usage throughout the European Community, ranging from .5 – 5 units per capita, reflects the method of financing in the health services and in particular the contribution of social security institutions and governments.⁴ In the forthcoming years, demands for recombinant products are expected to increase resulting in a reduction in the use of plasma derived products with a concomitant increase in the costs for the remaining plasma products. This along with a continuing rise in the usage of both factor VIII and factor IX demands the attention of health care authorities.

⁴ W. Schramm. Towards the best use of safe clotting factor concentrates. *Haemostaseologie*. 1996, 16: 269-273

7. Quality Management

7.1. Introduction

1. Ensuring the highest level of quality and safety of blood and blood products in the European Community has become an integral part of Community legislation with the coming into force of the Treaty of Amsterdam.¹ Efforts towards this goal, however, have been underway for several years as reflected in Resolutions on blood safety and self-sufficiency, adopted both by the Council^{2 3} and the European Parliament⁴, as well as Council's Recommendation on the Suitability of blood and plasma donors and the Screening of donated blood in the European Community⁵. Recognising that the complex series of processes that comprise the blood transfusion chain must be controlled if quality and safety are to be ensured, the Federal Ministry of Labour, Health and Social Affairs of Austria convened in 1998 a Forum of experts to discuss 'key issues and best options for action related to quality management for blood collection, processing and distribution'.⁶ Although the therapeutic use of blood and blood products was not covered, it was identified as a crucial link in the 'chain' and needed to be considered within the framework of quality management.

7.2. Background

2. Quality management is 'an umbrella term that encompasses quality system development and implementation; quality assurance, good manufacturing practice and quality control; and continued quality improvement'.⁷ Although introduced initially in the production environment it has since permeated many health care sectors including areas related to blood collection, processing and distribution. But quality management has yet to become an integral factor in the use of blood and blood products.
3. In clinical transfusion practice, quality implies a safe, effective and appropriate transfusion. While this is the ultimate aim of recommendations, guidelines, and algorithms issued by several international and national organisations, the results have been shown to be less than satisfactory. The Sanguis Study⁸ reported that, among the 43 participating teaching hospitals, the proportion of patients receiving red cell units ranged from 29% to 100% for total hip replacement and from 17% to 100% for coronary artery bypass graft. The inter-hospital differences persisted even after adjustment for patient-related variables, suggesting that other factors, such as clinicians' preferences and habits, play a major role in the decision to transfuse blood. Inappropriateness, both with respect to over-transfusion

¹ Treaty of Amsterdam. Article 152. Public Health.

² Council Resolution on Blood safety and self-sufficiency in the Community. O.J. No C164. 30.6.95. p.1

³ Council Resolution on a Strategy towards Blood Safety and Self-sufficiency in the European Community. O.J. No C374. 11.12.96. p.1

⁴ O.J. No C268, 4.10.93, p.29. / O.J. No C329, 6.12.93, p.268 / O.J. No C249, 25.9.95, p.231. / O.J. No C141. 13.5.96. p.131.

⁵ O.J. No L203, 21.7.98, p.14.

⁶ Federal Ministry of Labour, Health and Social Affairs of Austria. Conclusions and Recommendations of meeting on Quality management for blood collection, processing and distribution in the European Communities. Baden/Vienna Austria 13-15 July 1998. European Commission.

⁷ Discussion document on quality management. for the meeting 'Quality management for blood collection, processing and distribution in the European Community: a way forward'. Federal Ministry of Labour, Health and Social Affairs. Commission of the European Communities. Baden/Vienna, Austria. 13-15 July 1998

⁸ The Sanguis study was a European Community concerted action carried out from 1990 to 1992 in 43 hospitals in 10 Member States. It was aimed at assessing the use of blood and blood products in six commonly performed elective surgical procedures. It concluded that the use of blood and blood products was far from optimal and not compliant with published guidelines, often exceeding true needs.

or under-transfusion, can imply risks for patients and the waste of resources. Consequently, clinical transfusion practice could benefit from an effective quality assurance programme.

4. One of the major consequences of a quality management system in relation to blood and blood products is optimal use. It can be viewed as the balance between the input (e.g. number of available units of blood components and products) and the output (e.g. benefits measured in terms of desired outcome including quality of life, and reduced adverse events). Maintaining this balance could help to ensure the appropriate use of resources and minimise wastage.

7.3. Provision of health care

5. The degree to which health services increase the likelihood of desired outcomes and are consistent with current professional knowledge is a measure of quality of care. But quality does not equate with positive outcome and disease often triumphs. On the other hand, human resilience enables patients to overcome illness in spite of poor quality care. Assessing quality, therefore, requires attention to both processes and outcomes.⁹
6. The provision of health care may be associated with under-use, overuse and misuse. Under-use is the failure to provide a health care service when it would have produced a favourable outcome for a patient. Overuse occurs when a health care service is provided under circumstances in which its potential for harm exceeds the possible benefit. Misuse occurs when an appropriate service has been selected but a preventable complication occurs and the patient does not receive the full potential benefit. While reducing overuse and solving misuse problems can improve quality and reduce costs, fixing under-use nearly always results in both increased costs and increased quality.¹⁰
7. In relation to blood, overuse, under-use and misuse are reflected in over-transfusion, under-transfusion and transfusion errors. Over-transfusion and under-transfusion are mistakes - rule-based and knowledge-based errors of conscious thought. A skill-based transfusion error¹¹ is known as a 'slip' – an unconscious glitch in a routine activity. These problems have helped to contribute to the current risk of ABO incompatible blood transfusion being three times greater than the cumulative risk of infection with HBV, HCV, and HIV.¹² They are also directly linked to the optimal use of blood.

7.4. Implementing quality management

8. Increasing attention is being directed to ensuring that blood and blood products are used optimally, reducing the variability in clinical practice, controlling costs, and improving patient care outcomes. As previously mentioned, this has led over recent years to the elaboration of numerous guidelines, recommendations, and algorithms. Yet systematic reviews have shown that their mere existence does not necessarily lead to changes in practice. The failure to implement best practices is a direct consequence of lack of awareness.

⁹ Consensus Statement: The urgent need to improve health care quality. JAMA 1998; 280:1000-1005

¹⁰ Ibidem

¹¹ 'An unintended act (either of omission or commission) or one that does not achieve its intended outcome'. L. Leape, Error in Medicine. JAMA, 1994; 272:1851-1857

¹² J P. Aubuchon, M.S. Kruskall. Transfusion Safety: realigning efforts with risks. Transfusion. 1997; 37: 1211-1216.

9. Consideration has to be given, therefore, as to how quality management could be introduced effectively into clinical practice so as to prevent overuse and under-use of blood and blood components, and minimise 'slips'.
10. It could be done through training courses in transfusion medicine and haemotherapy in which clinicians are exposed to recommended guidelines. Only those who had successfully completed such training would be authorised to prescribe blood products. Compliance with such guidelines to prevent over-use could be improved by requiring pre-verification of requests by blood product providers. Prevention of under-use through a prospective audit would be valueless, however, since no requests for blood would be forthcoming. This could be addressed by assigning a transfusion expert to work in the clinical wards with responsibility for assessing patient's needs.
11. The introduction of clinical guidelines is a complex process that involves: the creation of the guideline (development); its assimilation by the clinicians for whom it is intended (dissemination); and assurances that clinicians act on its contents (implementation). The development of guidelines, however, is not the task of Quality Management; their dissemination and implementation is.
12. Setting out a relevant organisational structure with clearly defined roles and responsibilities could also facilitate the introduction of quality management in order to ensure the optimal use of blood in clinical practice. Consideration could be given *inter alia* to:
 - Who should be responsible for accepting and implementing recommendations and guidelines concerning blood transfusion and haemotherapy in clinical practice at national level?
 - Who should be responsible at local level for developing and implementing standard operating procedures (SOPs)? Should this be a transfusion committee or a quality manager in the hospital?
 - Whether an expert in transfusion-medicine should be assigned to each clinical department which provides haemotherapy?
 - Should this person be responsible for these therapies and have the authority to issue instructions related to indications, organisation and documentation of haemotherapy?
 - Who should be responsible in a clinic for:
 - storage and maintenance of haemotherapeutic drugs;
 - comprehensive documentation (documentation of charges included);
 - notification of adverse effects and to whom?
 - structuring monitoring, feed-back and look-back;
 - instruction and training of relevant staff in haemotherapy;
 - maintenance of a list of all used blood and plasma products; and
 - Who should be responsible for quality assurance?
13. Recognising that the main actors in relation to the use of blood and blood components are the local providers of blood products (hospital-based transfusion service, pharmacy) and the final users (clinicians in the wards), their co-operation is essential if optimal use through effective quality management is to be achieved.

7.5. In-process control

14. Statistical quality control is one of the basic tenets of total quality management. It requires that errors and deviations be regarded not as failures but as opportunities to improve the process. A system to reduce transfusion errors could be the introduction of in-process control. Introduced within the clinical wards, such a system should encompass the process starting with the identified need for a blood product and end with the use of the product. As this process includes many steps, some of which are critical for ensuring blood transfusion safety, the introduction of appropriate checks could contribute to minimising undesirable events and maximising blood utilisation.
15. But what are the critical points within the process and how can the checks that should be introduced be defined? Are the following sufficient as critical points within the process to ensure the safe and optimal use of blood products: 1) identification of patient; 2) identification of blood samples for pre-transfusion testing; and 3) identification of the blood product assigned to the intended patient?
16. Could the use of computerised systems with pre-established algorithms, based on guidelines, improve the collection and analysis of data and provide indicators on the clinical appropriateness for each blood prescriber? What checks would be appropriate to verify that the critical steps have been correctly carried out? Would the use of bar codes, which could be used to check the identity code on the patient's wristband with those on the blood bags and blood samples preventing further action in the event of non-correspondence, contribute to this aim?

7.6. Concluding remark

17. 'Evidence demonstrates that the most effective method of stimulating awareness of and compliance with best practices is computer-generated reminders provided at the point of care'.¹³ If quality management is to be introduced so that optimal use can be achieved, data on the outcome of patients treated by clinicians is needed. Such data could help to improve guidelines and to carry out cost analysis of different treatment strategies. There is the need, therefore, to establish criteria for the evaluation of outcome following treatment with each of the blood components included in the agenda of the 'Wildbad Kreuth Initiative'.

¹³ R.D.Zielstorff. Online Practice Guidelines: Issues, Obstacles, and Future Prospects. Journal of the American Medical Informatics Association, 1998; 5:227-236

8. Economic Aspects

8.1. Introduction

1. The delivery of health care has associated costs. This fact has become all too apparent to Member States of the European Community as they struggle to contain mounting health care expenditures brought on by increasing public expectations regarding the provision of health services, significant advances in medical technologies, and growing demands of an ageing population. The treatment of patients with products derived from blood and plasma cannot escape these realities. Managing these resources appropriately, however, could contribute to minimising over-expenditure and maximising health care.

8.2. Background

2. From the moment a donor offers to provide blood and plasma for the benefit of others until after the product(s) derived from that donation has been given to a patient, expenses are incurred. The costs are associated not only with the collection, processing and distribution of the blood and blood products but also with their therapeutic use. Considerable outlay has to be made in terms of equipment, supplies, staffing etc. in order to ensure the administration of safe and effective products. Expenses associated with the therapy itself, whether for out-patient visits or hospital stays, need to be covered. In addition, indirectly related expenditures are incurred such as work-months lost, quality of life diminished etc.
3. The inappropriate use of blood, blood components and plasma derivatives has a direct bearing on health care budgets – whether they be those of the hospital, national health insurance services or private insurance companies. Products may be ‘over-used’ because they are administered under circumstances in which the possibility of harm to the patient exceeds the potential benefit. They may be ‘under-used’ when in spite of the fact that they could have produced a favourable outcome they were not given. They may also be ‘misused’ as in the case where an appropriate product is administered and a preventable complication results. In this situation the patient does not receive the full benefit of the product or is exposed to an additional and unexpected adverse outcome.
4. In all cases, there are cost implications whether reduced or increased. The identification of those areas where overuse, under-use and misuse occur, as well as methods and procedures to overcome them could help to contribute to improving quality of service, lowering the number of adverse events, and providing a basis for justifying associated costs. One only has to look at the tremendous socio-economic burden that has had to be faced following the transfusion of HIV-contaminated blood and blood products to realise the importance of this issue.

8.3. Assessing outcomes of blood product use

5. It is regrettable but a fact that clinicians who administer blood and blood products do not regularly document the efficacy of their use. As a consequence, data recording parameters measured both before and after the use of blood products, which could substantiate the benefits accrued, is lacking. Without such data, it is difficult to carry out economic analysis. There is, therefore, the need to define the outcomes of blood use and the parameters against which these are to be measured.

6. Those blood-related issues that have economic implications, as well as how they could be addressed and by whom, need to be identified. Alternative treatment strategies in which blood and blood products are used need to be examined not only with respect to therapeutic outcome but also in relation to cost-benefit, cost effectiveness and cost utility. Parameters, whether non-monetary such as haematocrit level or platelet count after transfusion, or monetary such as amount of product administered, duration of treatment, length of hospital stay etc., need to be identified. Methods for evaluating a more expensive therapy (e.g. leucocyte reduced red cells) against a cheaper one need to be considered given that the former may result in a shorter hospital stay and as a consequence reduced hospital charges.

8.4. Economic evaluation

7. Carrying out an accurate economic evaluation of expenditures related to the use of blood and blood products would involve not only the identification of the therapeutic use of blood and blood products but the recording of costs from the initiation of treatment to its discontinuation. This is relatively easy during clinical trials which are conducted under highly rigorous conditions. Under normal conditions, however, the medical outcomes of therapy may be quite variable due to different patient populations, time of onset of therapy, stage of disease, and treatment protocols. Therefore, determining the related financial disbursements is difficult.
8. Assessing the economic implications and effectiveness of therapeutic interventions could be facilitated by applying outcomes and effectiveness research. This involves analysing current disease management programmes and identifying what does and does not work. As an example: studies on 1) different transfusion thresholds in prophylactic platelet transfusion (10,000 versus 20,000) in patients with acute myeloid leukaemia and 2) the extent to which dosage and time interval of platelet transfusion had an influence on platelet recovery and the development of refractoriness in patients with haematological malignancies, showed that higher doses of platelet transfusion reduced the time interval and the development of refractoriness. The impact on costs were evident.
9. Prophylactic treatment and screening programmes are also areas that require examination given the initially high costs of the former in comparison with the latter. A cross sectional study which compared prophylactic versus on-demand treatment of haemophilia patients with clotting factors showed that those receiving prophylactic clotting factor therapy required less additional health care resources mainly due to the reduction of bleeding in the joints.

8.5. Cost-savings

10. Blood is a resource which is limited, is associated with risk and is expensive. In order to ascertain whether cost savings can be realised in limiting the use of blood and blood products, without depriving patients of essential care, it is necessary to identify those elements that are the driving force behind financial expenditures. These can be identified as the 'cost drivers'. They can be earmarked by examining the utilisation of resources, such as was done in the Sanguis study which looked at the use of blood in elective surgery, or the pre-operative demand for blood and blood products. Awareness of these 'cost drivers' could be facilitated through the development and implementation of surgical blood order schedules, computerised decision support systems, or other mechanisms. These include clinical practice guidelines which are aimed at:

- assisting clinical decision making by patients and physicians;
- educating individuals or groups;
- assessing and assuring the quality of care;
- guiding allocation of resources for health care, and
- reducing the risk of legal liability for negligent care.

8.6. Effectiveness of blood use

11. In order to demonstrate effectiveness of a therapeutic procedure, evidence is required that it does more good than harm when used in a specific clinical situation applicable to an individual patient. Efficacy implies that the clinical strategy can achieve its goal of improving outcomes when used under optimal circumstances. It is, however, effectiveness that is the real basis for making true long-term funding decisions in the delivery of health care. How can effectiveness best be ascertained with regard to the use of blood and blood products? Are there therapeutic and diagnostic options that are inappropriate or obsolete that should be identified in order that costs could be better managed? Will the introduction of nucleic amplification technology requirements not only for plasma pools but for single unit donations be a contributing factor to increasing up front costs but decreasing long-term expenditure associated with therapy?

8.7. Concluding remarks

12. In considering the economic implications associated with the use of blood and blood products, attention also needs to be given to the financial consequences of changing therapeutic procedures and products. The decreasing demand for a particular blood product (e.g. clotting factors, albumin) can have a direct impact on the pricing of others (e.g. prothrombin complex preparations, immunoglobulin). Experts at Wildbad Kreuth should draw upon their experience to identify areas where difficulties are encountered, recognise where problems may arise and propose alternatives to overcome them.



BLOOD SAFETY IN THE EUROPEAN COMMUNITY: AN INITIATIVE FOR OPTIMAL USE

*Under the auspices of:
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Syllabus

1. RED BLOOD CELLS

1. Guidelines and recommendations for red blood cell transfusion have changed over the past ten years tending to more restrictive practice strategies. Increasing knowledge of the associated risks and complications as well as growing economic constraints are providing a rationale for more efforts to define clear indications and transfusion policies. Nevertheless, there are still substantial national and international differences in the clinical use of red blood cells in Member States of the European Community as shown in the Sanguis study (1).

1.1. Studies and Articles

2. There are a vast number of articles and studies concerning red blood cell transfusion policies with wide variations in the strength of evidence. However, the number of randomised, controlled clinical trials, which provide the highest level of evidence, remains small. Further limitations are given by sometimes highly specialised or small study-populations that do not allow the transfer to generally applicable recommendations. An overview of recent international studies and articles, categorised according to topic and study design, is given in Table 1.1.

1.2. Guidelines and Recommendations

3. The indication for red blood cell transfusion is anaemia, with or without acute bleeding, mainly to increase O₂ delivery. Differences in guidelines and recommendations reflect the difficulty in defining clear evidence-based parameters such as a certain haemoglobin concentration as a uniform 'transfusion trigger' and emphasise the importance of clinical symptoms and severity of illness that can be assessed with the help of different morbidity- and organ-dysfunction scores (9 - 11). Indeed, several studies suggest that anaemia increases the risk of death after surgery especially in critically ill patients (12) and in patients with cardiovascular disease (13).
4. Only a few guidelines (see Table 1.2) at least recommend a minimum haemoglobin-threshold that – with regard to the patient's age, general physical condition and the severity of illness – should not be exceeded. For critically ill patients with cardiovascular or respiratory disease, a critical haemoglobin value between 12.0 and 11.0 g/dl is far accepted, whereas young and healthy subjects are considered to tolerate a decrease in haemoglobin until 7.0 – 6.0 g/dl. A recent randomised, controlled clinical trial showed a similar 30-day mortality for critically ill patients who were assigned to a liberal (transfusion at Hb below 10.0 g/dl and maintained at 10.0 to 12.0 g/dl) or a restrictive (transfusion at Hb below 7.0 g/dl and maintained at 7.0 to 9.0 g/dl) transfusion strategy respectively (2). However, mortality was significantly lower with the restrictive transfusion strategy among patients who were less acutely ill and among patients who were less than 55 years of age, suggesting that 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. In addition, patients with active coronary ischemic syndromes did not have more adverse outcomes when a transfusion threshold of 7.0 g/dl was used.

Table 1.1
Selection of recent studies concerning
red blood cell transfusion strategies,
categorised according to topic and study design.

Study	Study design	No. of patients	Study population	Interventions / Outcome measures	Outcome
Comparison of different transfusion strategies					
1 Hébert et al. 1999 (2)	prospective, randomised, clinical, multicentre-trial	838	'critically ill' ICU Hb $\leq$ 9 g/dl age: $\geq$ 16 (mean: 57/58)	restrictive (n = 418, Hb 7.0 – 9.0 g/dl) vs. liberal (n = 420, Hb 10.0 – 12.0 g/dl) transfusion strategy 30-day mortality.	Overall 30-day mortality similar in both groups. Subgroup analysis: Significantly lower mortality with restrictive transfusion strategy among patients who were - less acutely ill - under the age of 55 Similar mortality with restrictive transfusion strategy among patients with - clinically significant cardiac disease - severe infection /septic shock - trauma
2 Hébert et al. 1995 (3)	prospective, randomised, clinical, multicentre-trial (pilot study to 1)	69	'critically ill' ICU Hb $\leq$ 9 g/dl age: $\geq$ 16 (mean: 59)	intervention same as in 1 30-day mortality; (secondary: ICU morbidity ICU mortality, 120-day mortality)	No significant differences.
3 Carson et al. 1998 (4)	prospective, randomised, clinical trial (pilot study)	84	surgery (hip fracture) post-OP Hb < 10.0 g/dl (mean: 82)	'symptomatic'- (clinical symptoms or Hb < 8.0 g/dl) vs. 'threshold'- (Hb maintained > 10.0 g/dl) transfusion practice hospital-, 30-, 60-day mortality, morbidity, functional status, place of residence;	30-day mortality: 2.4% both groups 60-day mortality: 4.8% (thresh.) vs. 11.9% (sympt.) 60-day morbidity (death or inability to walk): 45% (thresh.) vs. 39% (sympt.) Other outcomes similar.
4 Johnson et al. 1992 (5)	prospective, randomised, clinical trial	38	surgery (CABG*) age (mean): 61 / 52	restrictive (n = 20, haematocrit < 25%) vs. liberal (n = 18, haematocrit < 32%) transfusion strategy; post-OP cardiac indices; post-OP complications; length of stay in ICU and hospital; physical exercise tolerance;	No significant differences for all outcome measures between the two transfusion strategies. No correlation between haematocrit and exercise capacity.

Study	Study design	No. of patients	Study population	Interventions / Outcome measures	Outcome
5 Carson et al. 1998 (6)	retrospective, multicentre, cohort study	8787	surgery (hip fracture) age: ≥ 60 (mean: 80)	Mortality with or without transfusion 30-day mortality; (secondary: 90-day mortality)	No significant difference in 30- and 90-day mortality with or without transfusion after adjusting for 'trigger haemoglobin level' before transfusion, cardiovascular disease and other risk factors for death.
<i>Relationship between anaemia and clinical parameters</i>					
6 Hogue et al. 1998 (7)	prospective, randomised, clinical trial	190	surgery (radical prostatectomy) age (mean): 63	relationship between haematocrit and myocardial ischemia (clinically asymptomatic, defined as ST $\downarrow$ for 1 minute, diagnosed by ECG monitoring);	Independent association of haematocrit $< 28\%$ and risk for myocardial ischemia.
7 Spiess et al. 1998 (8)	prospective, observational, multicentre study	2202	surgery (elective CABG*) age: ≥ 28 (mean: 65)	association between post-OP haematocrit (HCT) on entry to ICU and myocardial infarction / left ventricular failure; three groups: high: HCT $\geq 34\%$ medium: HCT $> 25-33\%$ low: HCT $\leq 24\%$	Rates of Q-wave MI / left ventricular failure lowest in patients with low HCT and higher in patients with high HCT (with equal distribution of clinical variables, morbidity and transfusion during OP). Mortality of whole study population similar in high and low HCT-group (5.2 / 5.6), lowest in medium HCT-group (2.6).

Abbreviation: * Coronary artery bypass graft.

Table 1.2
Selection of recent guidelines on red blood cell transfusion

Guideline	Sponsor	character	Setting	Recommendations / transfusion threshold	Contraindications for red blood cell transfusion	Comments
1 Practice guidelines for blood component therapy (1996) (14)	American Society of Anesthesiologists	based on controlled and uncontrolled observational clinical studies	perioperative, obstetrics	red blood cell transfusion rarely indicated when Hb > 10.0 g/dl, almost always indicated when Hb < 6.0 g/dl; when Hb between 6.0 and 10.0 g/dl, consideration of patient's individual general risk factors for complications of inadequate oxygenation; if possible, avoidance of red blood cell transfusion by use of further therapeutic measures to minimise blood loss (e.g. preoperative autologous blood donation, intraoperative blood recovery)		haemoglobin concentration alone is an inadequate measure of oxygen delivery", but suggestion of a range of haemoglobin (6.0 – 10.0 g/dl) '...to rely solely on vital signs is inappropriate for anaesthetised patients' most rigorously developed guidelines with: - systematic literature review - guideline development process evidence category II-2 / II-3 *
2 Surgical Red Blood Cell Transfusion Practice Policies (1995) (15)	none	consensus statement	perioperative	'case-by-case' and 'one unit at a time' transfusion-strategy; transfusion at a Hb level of: - around 10.0 g/dl in cardiopulmonary affected patients; - around 7.0 g/dl in healthy, low-risk patients with no evidence of cardiopulmonary disease; exposure to allogeneic blood should be limited to appropriate need;		further policies concerning: - prevention of peri-OP blood loss - autologous blood donation - treatment of underlying cardiopulmonary disease to increase oxygen delivery - increasing red blood cell mass by pre-OP iron or erythropoietin therapy - documentation - inclusion of patient in transfusion decision literature reviewed;

Guideline	Sponsor	character	Setting	Recommendations / transfusion threshold	Contraindications for red blood cell transfusion	Comments
3 Guidelines for therapy with blood components and plasma derivatives (1995) (16)	Ministry of Health ('Bundesministerium für Gesundheit')	Expert opinion	all patients	acute blood loss: - patients without reduction of vital functions: loss of blood volume up to 20 % should be restored with crystalloids; Hb ↓ until 7.0 – 6.0 g/dl sometimes tolerated without signs of hypoxic organ damage; <i>Hb below 5.0 – 4.5 g/dl "critical" !</i> - older patients and patients with cardiac pulmonary disease: transfusion earlier chronic anaemia: - transfusion only because of clinical symptoms	further recommendations: - late bone marrow transplantation expected and non-immunologically caused haemolytic anaemias: as few transfusions as possible	<i>'no universally applicable lower limits for haemoglobin or haematocrit can be given as an indication for erythrocyte transfusion'</i> <i>duration, severity and cause of anaemia, the clinical condition, age and sex of patient have always to be taken into consideration.</i>
4 Consensus statement on red cell transfusion (1994) (17)	Royal College of Physicians of Edinburgh	consensus statement	all patients	transfusion decision should be made by an experienced medical practitioner; consideration of the patient's individual risk factors for complications of inadequate oxygenation.	<u>only</u> indication for red blood cell transfusion: raising of oxygen-carrying capacity of blood to increase oxygen-delivery in the tissues.	'there is no single critical haemoglobin or haematocrit value applicable to all patients' no literature reviewed;

Guideline	Sponsor	character	Setting	Recommendations / transfusion threshold	Contraindications for red blood cell transfusion	Comments
5 Practice strategies for elective red blood cell transfusion (1992) (18)	American College of Physicians	expert opinion	all patients	indication for red blood cell transfusion: 'relieve symptoms related to blood loss'; if possible, avoidance of red blood cell transfusion by 'advance planning' (pre-OP autologous blood donation, erythropoietin), correction of intravascular volume depletion by crystalloid (acute anaemia), other therapeutic interventions like erythropoietin, iron replacement (chronic anaemia); in case of transfusion, consideration of the patient's individual risk factors for complications of inadequate oxygenation (e.g. patients at risk for myocardial or cerebral ischemia) red blood cell transfusion only in case of clinical symptoms or deterioration of vital signs, also for anaesthetised patients;	to enhance the general sense of well-being to promote wound healing prophylactically (in the absence of symptoms) to expand vascular volume when oxygen-carrying capacity is adequate	restrictive transfusion policy: 'regard elective transfusion with homologous blood as an outcome to be avoided' main focus on clinical symptoms and possible deterioration of vital signs; no transfusion threshold and: 'normovolemic anaemia (haemoglobin 7.0 – 10.0 g/dl) can be well tolerated in asymptomatic patients'; unit-by-unit transfusion strategy.

* Grading of evidence: I: randomised controlled trials; II-1: non-randomised controlled trials; II-2: controlled observational studies (e.g., case-control, cohort studies); II-3: uncontrolled observational studies; III: descriptive studies, expert opinion.

(From: U.S. Preventive Services Task Force: Guide to Clinical Preventive Services: An Assessment of the Effectiveness of 169 Interventions. Baltimore, Williams and Wilkins, 1989)

1.3. Glossary: Conservation, Documentation, Crossmatch and Side-Effects

1.3.1. Conservation

General

5. Blood is collected from a donor in general as a whole blood product¹. This product can be further separated or filtered in a blood bank facility. Units or bags with erythrocyte concentrates can be conserved at 2 - 6°C for a total period of 35 days². The last day of this period should therefore be written on the bag².

Erythrocyte products

6. The standard erythrocyte product for clinical substitution is the buffy-coat free erythrocyte concentrate in additive solution². The amount of plasma in this product is lower than 15 ml/260ml bag². Washing of erythrocyte preparates with physiologic saline is generally no longer affordable, because today there are only a very few clinical indications, like 'congenital IgA deficiency', where washed erythrocytes are still in common use². The viscosity of this product is relatively good.

Irradiated erythrocyte blood products

7. Irradiation of erythrocytes is necessary in order to kill lymphocytes in the blood product, so as to prevent immune compromised patients from transfusion-transmitted graft versus host disease (tt-GVHD) and febrile non-haemolytic transfusion reactions (FNHTR)³: the dose of irradiation is generally 25-30 Gy⁴. A leucocyte-filtration, even with third generation filters, is not sufficient to prevent these side effects⁵.

Blood donations from relatives

8. Blood donations from relatives have a higher risk for transfusion-transmitted graft versus host disease than allogeneic donations. This is caused by partly identical HLA antigens, leading to more difficult elimination of allogeneic leucocytes by the immune system⁶. In addition blood donations from relatives before allogeneic blood stem cell transplantation can lead to a higher graft rejection or GvHD⁶. On the same issue, safety of blood products from relatives is lower compared to allogeneic blood, because safety considerations are much less effective among relatives than unrelated healthy donors⁷. For these reasons, patients with leukaemia, myelodysplastic syndrome, or aplastic anaemia should be excluded from familial blood transfusions.
9. The standard erythrocyte bag has the following characteristics:⁸
 - volume at least 250 ml;
 - erythrocytes given as a buffy-coat free concentrate in additive solution;
 - haemoglobin approx. 65 grams;
 - haematocrit lies in the range of 50-70 percent;
 - total amount of leucocytes is lower than 1.2×10^9 cells;
 - plasma volume is lower than 15 ml.
10. The volume of an erythrocyte bag compares to about 9% of an adult person of 70kg. Expecting a 70% recovery rate after transfusion, the patient's haemoglobin value should rise at about 10 to 15 g/l. In a mathematical model, suggesting an average lifetime of erythrocytes of some 60 days, a patient with a hypo-regenerative anaemia is considered to achieve every two weeks a transfusion on a long-term medication basis.

1.3.2. Documentation

11. The request for an erythrocyte transfusion and documentation in the report has to be documented by a physician.⁸
12. The formula has to include:
 - patient's data;
 - ABO blood group, RH and Kell status as far as known;
 - diagnosis of patient;
 - CMV status in immunocompromised patients;
 - Necessities of special preparations;
 - Filtration;
 - Irradiation;
 - Other.

Bed side testing

13. To ensure a safe transfusion and to minimise administrative transfusion errors it is absolutely necessary to carry out an ABO-identity test prior to each substitution of erythrocytes, granulocytes and plasma.⁸

1.3.3. Side effects

Graft-versus-host-disease (GvHD)

14. Most transfusion-transmitted graft versus host diseases develop after donation of erythrocyte concentrates, but also thrombocytes, granulocytes and fresh plasma⁹. Rates of GvHD are estimated to be about 1 in 10⁶ transfusions¹⁰. For patients with immune deficiency, irradiated blood products are recommended, while leucocyte filtration is not sufficient to prevent GvH disease¹¹.

Transfusion-related acute lung injury (TRALI)

15. Transfusion-related acute lung injury is an acute respiratory distress syndrome that occurs within a few hours after transfusion. Its estimated frequency is approximately 1 in 5,000 transfusions. Therapy is supportive, at least 90% of patients with TRALI recover.¹²

Haemolytic reactions

16. Fatal acute haemolytic reactions to transfusion continue to occur in the range of 1 in 250,000 – 1,000,000 transfusions.¹³ Approximately half of all deaths from acute haemolytic reactions are caused by ABO incompatibility, due to mismatching of patient and blood unit.¹⁴ Furthermore, approximately 1 in 1000 patients has clinical manifestations of a delayed reaction to transfusion¹⁵ and 1 in 260,000 has an overt haemolytic reaction due to the development of antibodies to minor red-cell antigens that were not detected by a routine antibody assay before transfusion. These reaction rates are much higher in populations at increased risk, such as patients with sickle cell disease¹⁶.

Febrile non-haemolytic transfusion reaction (FNHTR)

17. Today, there is a general agreement that cytokines are responsible for inducing FNHTR¹⁷. Cytokine secretion can either be induced from donor lymphocytes via allo-antibodies of the recipient or are delivered by transfusion from destroyed white blood cells in the bag and function thereby as pyrogenes. First episodes of FNHTR are found at rates of 1 – 6.8%, with relapses in the same patient at 5%.¹⁸ The more leucocytes are in the bag and the longer the products are stored, the higher is the frequency of FNHTR. Prevention of FNHTR can be achieved when leucocyte concentrations are < 5 x 10⁸ cells per bag¹⁷.

HLA-immunisation

18. HLA molecules on transfused leucocytes are a primary source for the development of HLA-allo-antibodies in the recipient. The reaction is dependent on the concentration of leucocytes per blood bag. A critical level for transfusion of leucocytes is seen at $>5 \times 10^6$ cells per transfusion¹⁹. Using leucocyte reduction filters for erythrocytes, HLA-immunisation could be reduced from 16% to 2.3%²⁰. For erythrocyte transfusions, without leucocyte reduction, in pregnancy, rates for development of allo-antibodies are 16% and 31% respectively²⁰.

Transfusion-Mediated Immunomodulation

19. The immunosuppressive effect of allogeneic blood is related to exposure to leucocytes and subsequent sensitisation and has been found to be clinically important in patients who are undergoing renal transplantation²¹ and in women who have multiple miscarriages.²² A number of retrospective reports have described an association between allogeneic blood transfusion and both earlier-than-expected recurrences of cancer and increased rates of postoperative infection.²³ Only a few prospective studies have attempted to clarify the potential immunomodulatory effects of allogeneic transfusion but failed to demonstrate a significant difference between patients either treated with autologous blood or allogeneic blood.^{24,25,26,27,28}

1.3.4. Crossmatch

ABO compatibility

20. Before transfusion is started, blood group typing has to be done. Erythrocytes are transfused major compatible (donor erythrocytes versus plasma of the receiving person).²⁸ Because of relative low amounts of plasma in the erythrocyte concentrate in additive solution, the minor compatibility (donor plasma versus erythrocytes of the recipient) is not of significant clinical relevance.²⁸
21. For patients receiving erythrocytes after blood group non-identical allogeneic bone marrow transplantation, blood group typing should be made prior to each blood transfusion to optimise transfusion outcome in each individual situation.

Rhesus- and Kell- compatibility

22. To prevent patients from alloimmunisation, transfusions should be compatible to Rhesus antigens, because 80% of D-negative recipients produce Rhesus D antibodies after transfusion.²⁸ The clinical indication for rhesus incompatible transfusion should be very strict. Exceptions should only be practised in case of life-threatening anaemia or lack of Rhesus D-negative blood.
23. For rhesus negative women, the risk of developing a *morbus haemolyticus neonatorum* after transfusion is high in case of pregnancy. The risk of immunisation with other blood groups (e.g. Kell, Rh c or Rh E) is significantly lower than for rhesus antigens.²⁸

Antibody testing

24. To eliminate the risk of haemolysis of the donor's erythrocytes, the search for allo-antibodies in the patient's plasma is done routinely in some countries. The only exception, not to crossmatch blood, is a life-threatening disease.²⁸ Patients are transfused with Rhesus D negative, Kell negative erythrocytes, as far available. However, acute immunologic reactions can still occur, e.g. via Rhesus –c or –E, or other rare blood group antigens.²⁸

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2. PLATELETS

1. Platelet transfusion practices show wide variations in Europe, among different countries and even between hospitals in the same country (1). To date, the number of clinical guidelines remains small and the majority refer to different clinical settings. The initially simple purpose of preventing or treating haemorrhage in patients with thrombocytopenia or platelet function defects has become a challenging task with regard to the diversity of possible underlying causes. In addition, the evaluation of the correct indication and appropriate dose, as well as avoidance of possible risks, such as infections, GvHD in immunodeficient patients and refractoriness, are of fundamental importance for transfusion policies.

2.1. Indications, transfusion triggers, doses

2. Platelet transfusions are indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. The recommended therapeutic or prophylactic transfusion ‘trigger’ is, primarily, a distinct platelet count. Other predictors for bleeding like bleeding time or thromboelastography are either considered as unreliable (2 - 4) or are reserved for special indications (5). Clinical risk factors for bleeding on the one hand (6) and the extent of bleeding on the other are important parts of most recommendations and influence the decision when and how much to transfuse. For example, the consensus conference of the ‘Royal College of Physicians of Edinburgh’ recommends a symptom-oriented unit-by-unit transfusion practice, suggesting a transfusion threshold only for therapeutic platelet transfusions in massive haemorrhage ($50 \times 10^9 /l$) and for prophylactic transfusions in patients with haematological malignancies and bone marrow failure ($10 \times 10^9 /l$) (7). Recommendations for the calculation of an appropriate dose of platelets are only given in the guidelines of the ‘British Committee for Standards in Haematology’ (8). A selection of recent guidelines is shown in Table 2.2.
3. The indications for therapeutic platelet transfusions in most clinical settings, however, are based on observation or consensus, whereas there is little evidence from clinical trials. In contrast, for prophylactic transfusions there are a limited number of randomised as well as non-randomised clinical trials examining different transfusion thresholds in haematological and oncological patients - most of them undergoing cytotoxic chemotherapy (9 - 13, as shown in Table 2.1.). Taken together, there is no evidence that the lower transfusion trigger of $10 \times 10^9 /l$ is associated with a worse outcome than the traditional transfusion trigger of $20 \times 10^9 /l$. These results are in keeping with a recent prospective and randomised, multicentre-trial of 255 patients with acute myeloid leukaemia undergoing induction chemotherapy, that showed no significant difference in bleeding episodes, red cell usage, hospital inpatient days or mortality in patients randomised to a platelet trigger of $10 \times 10^9 /l$ or to a trigger of $20 \times 10^9 /l$ (14). A reduction in platelet transfusion could not only reduce transfusion-related risks, but also markedly diminish costs (13).

Table 2.1
Selection of recent studies investigating different platelet transfusion triggers.

Study	Study design	No. of patients	Study population	Interventions /Outcome measures	Outcomes
Comparison of different transfusion triggers					
1 Rebulla et al. (1997) (14)	prospective, randomised, clinical, multicentre-trial	255	acute myeloid leukaemia (1 st course of induction chemotherapy) age: 16 –76 (median: 51 / 49)	transfusion threshold of: ≤ 10,000 /µl (135 patients) vs. ≤ 20,000 /µl (120 patients) <u>primary:</u> frequency of major haemorrhage; <u>secondary:</u> transfusion rates; rates of complete remission; mortality.	no significant difference in total number of major haemorrhage; bleeding-type: similar distribution, exception: gastrointestinal bleeding, twice in 10,000-threshold-group; 21.5% fewer platelet transfusions in 10,000-threshold-group; no significant differences in rates of remission and mortality.
2 Heckman et al. (1997) (11)	prospective, randomised, clinical, single-institution trial	78	acute leukaemia (induction therapy)	transfusion threshold of: ≤ 10,000 /µl vs. ≤ 20,000 /µl bleeding episodes / number of platelet transfusions number of RBC transfusions / febrile days / days hospitalised / days thrombo-cytopenic / need for HLA matched platelets / remission rate / death during induction therapy	no significant difference in the total number of bleeding episodes; ≤ 10,000 /µl patients more platelet transfusions for bleeding, ≤ 20,000 /µl more prophylactic platelet transfusions; total number of platelet transfusions 'nearly significant' higher in the ≤ 20,000 /µl patient group; no significant differences in the other outcomes.
3 Wandt et al. (1998) (13)	prospective, clinical, multicentre trial	105	acute myeloid leukaemia (induction or consolidation therapy)	Transfusion threshold of: ≤ 10,000 /µl vs. ≤ 20,000 /µl bleeding complications / number of platelet transfusions / number of RBC transfusions costs for each transfusion strategy (cost-effectiveness-analysis)	no correlation between serious bleeding events and platelet count; significant lower number of platelet transfusions in the ≤ 10,000 /µl patient group; no significant difference in the number of RBC transfusions; costs: costs of platelet therapy one third lower in the ≤ 10,000 patient group;

Study	Study design	No. of patients	Study population	Interventions /Outcome measures	Outcomes
4 Gmur et al. (1991) (9)	prospective, clinical, single-institution trial	102	acute leukaemia	transfusion threshold of: ≤ 5,000 /μl (without risk factors) ≤ 10,000 /μl (with fever or minor bleeding) ≤ 20,000 μl (heparin therapy, coagulation disorders, invasive procedures) bleeding episodes	31 bleeding episodes on: 1.9% study days in the ≤ 5,000 /μl group; 0.07% study days in the ≤ 10,000 /μl group;
5 Gil-Fernandez et al. (1996) (10)	retrospective analysis	190	bone marrow transplant patients	comparison of: conducted transfusion policies major haemorrhage with different transfusion policies; number of platelet transfusions;	transfusion policies: - 1990 – 1991: transfusion threshold: 20,000 μl (87 patients) 12 patients with 14 major haemorrhages; - 1993 – 1994: transfusion threshold: 10,000 /μl in stable and 20,000 /μl with 'higher platelet consumption' (total: 103 patients) 12 patients with 13 major haemorrhages significant lower use of platelet units in the 10,000 /μl group.

2.2. Dosage

- A recent prospective clinical trial examined the dose response to platelet transfusions in adults and children with haematologic malignancies (15). The patients, 69 adults and 13 children, received a medium ($4 - 6 \times 10^{11}$ adults / $2 - 4 \times 10^{11}$ children), high ($6 - 8 \times 10^{11}$ adults / $4 - 6 \times 10^{11}$ children), or a very high ($> 8 - 10 \times 10^{11}$ adults / $6 - 10 \times 10^{11}$ adults) dose of fresh (< 24 h old) ABO-compatible platelets in the form of apheresis platelet concentrates. The end points were platelet increment, platelet recovery and the transfusion interval. High and very high doses of platelets led to a significantly better increment and significantly longer transfusion intervals in adults and children. In patients with clinical factors favouring platelet consumption, the proportion of transfusions yielding an optimal platelet increment and transfusion interval increased with the dose of platelets. Authors concluded that transfusion of high platelet doses can reduce the number of platelet concentrates required by thrombocytopenic patients and significantly reduce donor exposure.

2.3. Refractoriness

- An approach for the evaluation of different methods to prevent refractoriness due to alloimmunisation was made by the 'Trial to Reduce Alloimmunization to Platelets' (TRAP Trial) (16). Conclusions from the study were that either reduction of leucocytes by filtration or UV-B irradiation of platelets was equally effective in preventing alloantibody-mediated refractoriness to platelets during induction chemotherapy for AML. Platelets obtained by apheresis from single random-donors provided no additional benefit as compared with pooled platelet concentrates from random donors.

Table 2.2
Selection of recent guidelines and consensus statements for platelet transfusion
with emphasis on clinical indications and dose

Guideline	Sponsor	Character	Indications / recommendations	Comments
1 Consensus conference on platelet transfusion (1998) (17) / (7)	Royal College of Physicians of Edinburgh	consensus conference	indications, prophylactic: - main use: prevention of bleeding in patients with <u>haematological malignancies and bone marrow failure</u> caused by disease / treatment → without risk factors*: threshold of $10 \times 10^9 / l$ → with risk factors* or planned invasive procedures: 'higher threshold', no consensus - <u>neonates</u> with considerable danger of haemorrhage: 'higher threshold than in adults' indications, therapeutic: - <u>massive haemorrhage</u>: threshold of $50 \times 10^9 / l$ 'clinical criteria need to be considered' - 'most <u>major surgery</u> (cardiac and vascular included) can be successfully carried out without platelet transfusion. Patients who have taken <u>aspirin</u> 10 days prior Op should be evaluated' - <u>thrombocytopenic purpura</u>: intracranial or eye haemorrhage, severe bleeding from the gut; contraindications: - heparin-induced thrombocytopenia - thrombotic thrombocytopenic purpura - haemolytic uraemic syndrome refractoriness: - no explicit recommendations, 'HLA-matched or crossmatch-compatible platelets seem satisfactory for patients who are refractory to immunological reasons' dose: recommendation of a 'single therapeutic dose' / unit-by-unit – practice	broad review of literature with consideration of clinical studies as far as possible, concerning: - physiological backgrounds - different indications - refractoriness - 'trigger factors' - dose - safety, risks and quality of platelet concentrates conclusion: 'precise indications and optimal specification still need to be defined' 'need for prospective randomised trials' and 'clearly defined protocols'
2 Practice Guidelines for Blood Component Therapy (1996) (2)	American Society of Anaesthesiologists	based on controlled and uncontrolled observational clinical studies	prophylactic platelet transfusion is ineffective and rarely indicated: - when thrombocytopenia is due to increased platelet destruction (e.g. ITP) - in <u>surgical patients with thrombocytopenia due to decreased platelet production</u> when platelet count is greater than $100 \times 10^9 / l$ prophylactic platelet transfusion is usually indicated: - in <u>surgical patients with thrombocytopenia due to decreased platelet production</u> when platelet count is below $50 \times 10^9 / l$ transfusion decision at intermediate platelet counts ($50 - 100 \times 10^9 / l$) should be based on risk of bleeding	perioperative and obstetric setting;
continued				

Guideline	Sponsor	Character	Indications / recommendations	Comments
3 Practice Guidelines for Blood Component Therapy (1996) (2)	American Society of Anaesthesiologists		therapeutic transfusion: - surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if platelet count is less than $50 \times 10^9 /l$ and rarely require therapy if it is greater than $100 \times 10^9 /l$ - 'platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding' dose: no recommendation, but statement that 'one platelet concentrate will increase the platelet count by app. $5 - 10 \times 10^9 /l$ in the average adult'; 'usual therapeutic dose: one concentrate per 10 kg'	
<i>Continuation</i>				
4 Guidelines for therapy with blood components and plasma derivatives (1995) (18)	Ministry of Health ('Bundesministerium für Gesundheit')	expert opinion	'indications' - <u>primary or secondary bone marrow insufficiency</u>, rapidly developing bleeding tendency and low platelet count: → without additional risk factors transfusion if platelet count $< 10 \times 10^9 /l$ 'detering prophylactic replacement until the platelet count falls below this lower limit can be justified in patients who are haemostatically stable and without additional risk factors' → with additional risk factors transfusion if platelet count $< 20 \times 10^9 /l$ (fever, infection, signs of bleeding, plasma clotting disturbances, rapid decrease of thrombocytes) - <u>aplastic anaemia or myelodysplasia</u>: 'only in exceptional cases' because of the generally lower risk of bleeding and the long-term need for transfusions. Only leucocyte-depleted cellular blood components. - <u>acquired disorders of platelet function</u>: 'rarely indicated' - <u>DIC</u>: only in case of manifest bleeding and when DIC is of thrombocytic origin - <u>prophylactically in surgery, lumbar or epidural puncture, organ biopsy</u>: 'normal risk' $> 50 \times 10^9 /l$, 'high risk' (eye, brain surgery): $> 100 \times 10^9 /l$ - <u>thrombocytopenia following severe blood loss and/or massive transfusion</u>: 'may become necessary if platelet count $< 50 \times 10^9 /l$ + bleeding tendency - <u>severe bleeding following surgery</u>: 'higher numbers of thrombocytes may be required depending on the severity of the medical situation' special indications - <u>congenital thrombocytopathies/ -penias</u>: - <u>autoimmune thrombocytopenia</u>: 'normally not required', only in case of life-threatening bleeding - <u>foetal or neonatal alloimmune thrombocytopenia</u>: 'compatible thrombocytes are the most effective measure...' 'not indicated' - bone marrow biopsies, even in cases of marked thrombocytopenia - no generally platelet transfusion after cardiac surgery dose: desired increment ($\times 10^9 /l$) $\times$ blood volume (L) $\times 1.5$	recommendations for the choice of preparation: - no existing immunisation: → ABO-compatible concentrates, rhesus factor D should also be considered; - following alloimmunisation against HLA and / or platelet specific antigens: → apheresis concentrates according to the antigen pattern of selected single donors;
5 Guidelines	British	expert opinion	indications:	

Guideline	Sponsor	Character	Indications / recommendations	Comments
for platelet transfusions (1992) (8)	Committee for Standards in Haematology		- <u>bone marrow failure</u>: - therapeutic: no explicit recommendation, but statement that: 'serious spontaneous haemorrhage due to thrombocytopenia alone is unlikely to occur at platelet counts above $10-20 \times 10^9 / l$', 'minor bleeding may occur below $50 \times 10^9 / l$' - prophylactic: → without risk factors: $10 \times 10^9 / l$ reduces the risk of haemorrhage as effectively as keeping it above any higher level → 'associated factors' **: use of platelet transfusions might be considered to keep the platelet count above $20 \times 10^9 / l$ - 'long-term prophylactic transfusions for patients with <u>chronic failure of platelet production</u> due to <u>aplastic anaemia</u> or <u>myelodysplasia</u> not usually indicated' - <u>platelet function disorders</u>: '...rarely need platelet transfusions to prevent haemorrhage...' - <u>massive blood transfusion</u>: platelet count should be maintained $> 50 \times 10^9 / l$ - <u>cardiopulmonary bypass surgery</u>: no indication of prophylactic platelet transfusion - <u>disseminated intravascular coagulation (DIC)</u>: only indicated in case of bleeding, in addition to fresh frozen plasma - <u>thrombotic thrombocytopenic purpura (TTP)</u>: '...platelet transfusions should not be given...' - <u>autoimmune thrombocytopenia</u>: platelet transfusion only in patients with major haemorrhage - <u>prophylaxis for surgery</u>: $> 50 \times 10^9 / l$ ('normal'), $> 100 \times 10^9 / l$ for 'operations in critical sites' (e.g. brain, eye) dose: should be calculated with regard to desired increment and patient's estimated blood volume: Dose = desired increment x estimated blood volume of patient / 0.67^+	

Classification and structure of indications shown as depicted in the original papers.

* 'risk factors' defined as: 'sepsis, concurrent use of drugs (e.g. antibiotics), other abnormalities of haemostasis'.

** 'factors associated with bleeding' defined as: 'fever, infection, concurrent coagulopathy, rapid fall in platelet count'.

+ corrected recovery factor that allows pooling of approx. 33% of platelets in a normal spleen.

2.4. Glossary: thrombocyte concentrates - production and preparations ⁽¹⁸⁾

2.4.1. Production

6. Thrombocyte concentrates (TC) are produced either immediately after donation by healthy donors from whole blood units consisting of 450 ml blood and 63 ml CPD stabiliser (quadruple bag system); 500 ml blood and 70 ml CPDA-1 stabiliser (single or double bag system); or by mechanical thrombocytapheresis. Donors of whole blood should have abstained from taking any medications affecting platelet function (in particularly acetylsalicylic acid, indomethacin) for three days or (in the case of cytopheresis donors) one week. TC from whole blood is produced by centrifugation and isolating platelets from platelet-rich plasma or from the 'buffy coat'. In mechanical thrombocytapheresis thrombocytes from a single donor are separated using cell separators.

2.4.2. Preparations

Platelet rich plasma

7. Platelet rich plasma contains about 60 – 90% of the blood platelets present in a unit of whole blood ($5 - 8 \times 10^{10}$ blood platelets in about 180 ml – 250 ml fresh plasma). It is only used in exceptional situations, because sufficient thrombocytes often cannot be transfused due to unavoidable volume overload.

Pool thrombocyte concentrates (TC)

8. Pool TC are produced by combining 4 – 8 blood-group compatible single donor TC in a special blood bag. Additive nutrient solution can be added to improve shelf life.

Thrombocytapheresis TC

9. Thrombocytapheresis TC contain $2 - 4 \times 10^{11}$ platelets from a single donor in up to 30 ml stabilised fresh plasma as well as, depending on the production procedure used, about $0.1 - 5 \times 10^8$ leucocytes and up to 30×10^8 erythrocytes.

Leucocyte-depleted TC

10. Leucocyte-depleted TC can be produced both from pool-TC as well as from thrombocytapheresis-TC by filtration through a special filter. This enables over 99% of the leucocytes to be eliminated; the remaining leucocytes per unit should not exceed 1×10^7 . However, up to 20% of the platelets are lost, what must be taken into consideration when prescribing dosage.

2.5. Literature

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3. ALBUMIN

1. The physiological property of albumin to generate and to preserve colloid osmotic pressure is the reason for most of its clinical applications: haemodynamic regulation to prevent shock, intra- and extravascular fluid balance to prevent peripheral and lung oedema and substitution in case of thermal injury are only some of the possible indications for albumin solutions in different concentrations. However, the discussion about the clinical benefit of albumin remains controversial especially with the background of cost-calculation in which crystalloid solutions as well as non-protein colloids like hydroxyethyl-starch are competitors.

3.1. Indications and studies

2. Clinical trials evaluating the indications of albumin, non-protein colloids and crystalloids should be interpreted carefully with respect to date of publication, number of patients and outcome measures. Only trials not older than 1990 are listed below.

3.2. Surgery: peri-operative period

3. A recent trial from 1995 (1) investigated the effects of different treatment regimens on fluid balance, pulmonary functions and economics during and after coronary artery bypass (CAB) surgery. Ringer's acetate was compared with dextran 70, polygeline (35 mg/ml), or albumin (40 mg/ml) in 40 patients. At the end of the operation, fluid retention was significantly lower in patients receiving polygeline and dextran 70, compared with those receiving Ringer's acetate. At 48 hours there were no differences in cumulative fluid balance. Outcomes for pulmonary function (intrapulmonary venous mixture, arterial oxygen tension, time on the respirator) showed no significant differences between the groups. One fatal myocardial infarction was reported in the Ringer's acetate group a few hours after the operation.
4. Another clinical trial from 1994 (2) examined the effect of supplemental albumin (25 mg/ml) on the complication rate and mortality of surgical ICU-patients whose albumin concentrations at admission were < 3.0 g/dl. The first group of 116 patients received 37.5 g/day of albumin until the circulating albumin concentration increased to > 3.0 g/dl; the control group of 116 patients received no albumin. The complication rate was 44% in the albumin group versus 36.9% in the controls. The albumin patients had a mortality rate of 10.3% versus 5.8% in the control group. There were no significant differences between the groups in the number of days spent receiving mechanical ventilation or in the tolerance to tube feedings.
5. A similar study was conducted in 1990 (3) with 40 'critically ill' patients, 18 of whom received albumin (25 mg/ml) to maintain serum albumin above 2.5 g/dl. No clinical benefit from albumin therapy could be shown when assessing mortality (39% vs 27%, treatment vs control) or major complication rate (89% vs 77%). There were no differences in further outcomes (e.g. length of hospital stay, ICU stay). The trials are listed in Tables 3.1. and 3.2.

3.3. Thermal injury

6. The impact of crystalloids and colloids on pathophysiological mechanisms in burn injuries has been investigated in several animal studies (6, 7). However, recent randomised clinical trials evaluating the benefit of albumin administration in adult patients are lacking.

Table 3.1
Selection of recent studies with surgical setting, albumin vs no albumin

Study	Study design	No. of patients	Study population	Interventions / Outcome measures	Outcomes
<i>albumin vs no albumin</i>					
1 Golub et al. (1994) (2)	prospective, randomised, clinical trial;	219	surgical ICU in community hospital; albumin: < 3.0 g/dl; standard nutritional support;	supplemental albumin (25 mg/ml) (n = 116): 37.5 g/day vs no albumin (n = 103); - morbidity in ICU; - mortality in ICU;	complications: albumin: 44% control: 36.9% mortality: albumin: 10.3% control: 5.8% no significant differences in days spent receiving mechanical ventilation / tolerance to tube feedings;
2 Woods et al. (1993) (4)	prospective, randomised, clinical trial;	69	surgery: abdominal aortic aneurysm; aortoiliac or aortofemoral bypass graft;	albumin replacement to ≥ 3.5 g/dl (n = 37); vs no albumin (n = 32); - length of post-OP ileus (OP until 'first day of flatus')	no significant differences in: - length of post-OP ileus; - number of days until regular diet was begun; - length of post-OP hospital stay;
3 Foley et al. (1990) (3)	prospective, randomised, clinical trial;	40	'critically ill' albumin < 2.5 g/dl;	albumin (25 mg/dl) to maintain serum-albumin ≥ 2.5 g/dl; vs no albumin;	mortality: albumin: 39% control: 27% major complication rate: albumin: 89% control: 77% no significant differences in length of hospital stay, ICU-stay, ventilator dependence, tolerance of enteral feeding;

3.4. Hypoalbuminaemia in patients receiving parenteral nutrition

- In a recent clinical trial, the effect of albumin administration on patients receiving parenteral nutrition and serum albumin < 2.5 g/dl was examined (8). None of the patients had known consumptive disease or nephrotic syndrome, 16 received albumin, 15 placebo. There was no evidence for an improvement of morbidity or mortality by albumin. In addition, the authors concluded that on the basis of high albumin catabolic rates, albumin can be given to replace albumin stores.

3.5. Albumin administration in children

- Four recent studies investigating the effect of albumin administration in children and infants within different clinical settings are shown in Table 3.4. (9 – 12).

Table 3.2
Selection of recent studies with surgical setting, crystalloid vs colloid

Study	Study design	No. of patients	Study population	Interventions /Outcome measures	Outcomes
<i>crystalloid vs colloid</i>					
1 Tollofsrud et al. (1995) (1)	prospective, randomised, clinical trial;	40	coronary artery bypass surgery;	four treatment regimens: - Ringer's acetate - polygeline (35 mg/ml) - dextran 70 (60 mg/ml) - albumin (40 mg/ml) fluid balance; pulmonary functions; 'economics';	end of OP: fluid retention significantly lower in polygeline and dextran 70 vs Ringer's acetate; →48 hours: 'no differences in cumulative fluid balance' higher colloid osmotic pressure in colloid group; higher net lung capillary filtration pressure only on 2 nd post-OP day in colloid group; but no adverse effects on pulmonary parameters and time on respirator in the Ringer's acetate group; costs: albumin > \$230 than Ringer's acetate;
2 Prien et al. (1990) (5)	prospective, randomised, clinical trial;	18	surgery: Whipple's OP	three pre-OP treatment regimens: Ringer's lactate (n= 6); hydroxyethy-starch (10%) (n = 6); albumin (20 mg/ml) (n = 6); effect of regimens on the formation of intestinal oedema (jejunal specimens during OP; measurement of water fraction: g H ₂ O /g tissue dry weight);	colloid osmotic pressure (COP) prior anaesthesia: Ringer's lactate: 20.3 → 14.1 HES: 22.0 → 22.0 albumin: 20.7 → 28.1

Table 3.3
Randomised, double-blind study of intravenous albumin administration vs placebo
in hypoalbuminemic patients receiving parenteral nutrition
[Rubin et al. (1997) (8)]

Study	Study design	No.	Study population	Interventions/ Outcome measures	Outcomes
1 Rubin et al. (1997) (8)	prospective, randomised, clinical trial;	31	total parenteral nutrition; albumin < 2.5 g/dl;	at least 6 days: albumin: 25 g daily; vs placebo;	increase in serum-albumin level: ↑ 1.42 g/dl in albumin; ↑ 0.29 g/dl in placebo; mean albumin metabolism: start: 17.4 g/dl; end: 20.5 g/dl; death (within 30 days): - one in placebo - two in albumin sepsis / bacteriaemia: - one in placebo - three in albumin pneumonia: - four in placebo - seven in albumin

Table 3.4
Selection of studies investigating the effect of albumin administration
within different clinical settings in children and infants

Study	Study design	No.	Study Population	Interventions / Outcome measures	Outcomes
1 Green-Halgh et al. (1994) (9)	prospective, randomised, clinical trial;	70	age: < 19 burns > 20 % (total body surface)	low albumin (n = 36): albumin given when < 1.5 g/dl vs high albumin (n = 34): maintained at 2.5 – 3.5 g/dl;	no differences in: - length of stay; - complication rate; - mortality; - resuscitation needs; fluid maintenance requirements; urine output; tube feedings; days of antibiotic treatment;
2 Greenough et al. (1993) (10)	prospective, randomised, clinical trial;	30	premature infants; albumin levels ≤ 3.0 g/dl; median gestational age: 29 weeks; age (median): 2 days;	5 ml/kg albumin (20 mg/ml) vs placebo; albumin level; weight; ventilation requirement;	albumin: - significant increase in albumin level; - significant reduction in weight; placebo: - significant increase in weight; no significant changes in peak inspiratory pressure; modest reduction in inspiratory oxygen concentration (< 15 %) in both groups, significant only in the albumin group;
3 Boldt J et al. (1993) (11)	prospective, randomised, clinical trial;	30	cardiac surgery;	LMW-HES* (6%) (n = 15) vs albumin (20 mg/dl) (n = 16) from induction of anaesthesia until the start of cardiopulmonary bypass; haemodynamic and laboratory values;	no significant differences in haemodynamic data (MAP, HR, CVP), laboratory values (AT III, fibrinogen, platelet count, coagulation, creatinine) and urine output; colloid osmotic pressure (COP) similar in the two groups; albumin increased after infusion of albumin; no anaphylactic reactions;
4 Kanarek et al. (1992) (12)	prospective, randomised, clinical trial;	24	premature newborns with total parenteral nutrition; albumin < 3.0 g/dl; Cardioresp. Distress requiring assisted ventilation;	albumin vs no albumin;	increase in albumin concentration, MAP; albumin infants regained birthweight earlier than no-albumin infants;

* LMW-HES: 'low-molecular-weight hydroxyethyl-starch'

3.6. Randomised Clinical trials

9. In a recent retrospective meta-analysis (21) of 32 randomised clinical trials, the administration of albumin or plasma protein fraction (supplemental albumin or plasma protein fraction compared with no albumin or plasma protein fraction or with crystalloid solution) in critically ill patients (adults and children, a total of 1419 patients) with hypovolaemia from trauma or surgery, with burns, or with hypoalbuminaemia was reviewed. Studies that compared different levels of albumin supplementation were also included. The outcome measure of the meta-analysis was mortality from all causes at the end of the follow-up period scheduled for each trial. If a trial did not include the numbers of deaths within a study, data were sought subsequently from the respective authors. Data were extracted and analysed, and patients were categorised in three groups (hypovolaemia / burns / hypoalbuminaemia).
10. The following results were presented: 'For each patient category, the risk of death in the albumin treated group was higher than in the comparison group. For hypovolaemia, the relative risk of death after albumin administration was 1.46 (95% confidence interval 0.97 to 2.22); for burns, the relative risk was 2.40 (1.11 to 5.19); and for hypoalbuminaemia, it was 1.69 (1.07 to 2.67). Pooled relative risk of death with albumin administration was 1.68 (1.26 to 2.23). Pooled difference in the risk of death with albumin was 6% (95% confidence interval 3% to 9%) with a fixed effects model. These data suggest that for every 17 critically-ill patients treated with albumin there is one additional death.' The authors concluded that there is no evidence that albumin administration reduces mortality in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia and suggested that it may increase mortality.
11. However, the meta-analysis has created controversy (22 – 32) and a few points, among others, should be taken into consideration when interpreting the results: the publication dates of the included studies; the number of patients involved; the respective study-populations and underlying diseases; the outcome measures; and the different treatment arms. Table 3.5 shows an overview (modified from the original article) of the most important characteristics of all included trials.

3.7. Guidelines and recommendations

12. For vascular loading in peri-operative care, most current guidelines and authors recommend a first line treatment with crystalloids or artificial colloids and the administration of albumin when other colloids are contra-indicated or when their upper volume limit has been reached (13 - 17).
13. For thermal injuries, the 'Centre de Traitement des Brûles, Hôpital d'Instruction des Armées Percy, Clamart' recommends that 'human albumin should be reserved for severely burned patients whose albuminaemia falls to approximately 20 g/l, or proteinemia to 35 g/l. (18)

Table 3.5

Trials reviewed in the retrospective meta-analysis of the Cochrane Injuries Group
[BMJ 1998; 317 (7153): 235 – 140 (21)]

Trial / Authors	'Critical illness' / Patients	No. of patients	Intervention	Control	Length of follow up	No. deaths
➤ hypovolaemia						
Skillman et al. (1975) (33)	surgery; 'abdominal vascular reconstructive procedures'	16	25% concentrated salt-poor albumin 1 g/kg and 5% albumin in saline	Ringer's lactate with 5% dextrose	1 day	not known
Shah et al. (1977) (34)	trauma; <i>multiple trauma and shock</i>	20	5% salt-poor albumin in Ringer's lactate	Ringer's lactate	unspecified	5 i*: 2/9 c**: 3/11
Lowe et al. (1977) (35)	trauma; <i>laparotomy for acute abdominal trauma</i>	171	50 g albumin/200 ml Ringer's lactate	Ringer's lactate	5 days	6 i: 3/57 c: 3/84
Boutros et al. (1979) (36)	surgery; <i>major abdominal aortic operations</i>	24	albumin in 5% dextrose	5% dextrose in lactated Ringer's (n=9) 5% dextrose in 0.45% NaCl (n=8)	4 days	2 i: 0/7 c: 2/17
Virgilio et al. (1979) (37)	surgery; <i>abdominal aortic surgery</i>	29	5% albumin in Ringer's lactate	Ringer's lactate	21/2 weeks	2 i: 1/15 c: 1/14
Lucas et al. (1978) (38)	trauma; 'seriously injured patients, requiring massive transfusions'	52	150 g salt-poor albumin during operation, 150 g/day for 5 days postoperatively	No albumin	to positive fluid balance or oral intake	7 i: 7/27 c: 0/25
Zetterstrom et al. (1981) (39)	surgery; <i>elective major abdominal surgery</i>	30	20% albumin 100 ml at end of operation, 200 ml on day of operation, 100 ml/day for next 3 days	no albumin	unspecified	1 i: 0/15 c: 1/15
Zetterstrom (1981) (40)	surgery; <i>reconstruction of the abdominal aorta</i>	18	5% albumin to keep pulmonary arterial occlusion pressure equal to preoperative level	balanced electrolyte solution of Ringer's type to keep pulmonary arterial pressure equal to preoperative level	unspecified	2 i: 2/9 c: 0/9
Grundman et al. (1982) (41)	surgery;	17	human albumin and crystalloid	crystalloid only	5 days	1 i: 1/14 c: 0/6
Rackow et al. (1983) (42)	trauma and sepsis;	17	5% albumin	0.9% NaCl	to discharge	12 i: 6/9 c: 6/8
Gallagher et al. (1985) (43)	surgery; <i>coronary artery bypass grafting</i>	10	5% albumin	Ringer's lactate	1 day	0

Trial / Authors	'Critical illness' / Patients	No. of patients	Intervention	Control	Length of follow up	No. deaths
Nielsen et al. (1985) (44)	surgery; abdominal aortic surgery	26	80 g albumin in units of 100 ml 20% albumin on day of operation, 20 g daily for next 3 days	no albumin	4 days	0
Prien et al. (1990) (5)	surgery; Whipple's operation	12	20% albumin maintain central venous pressure at preoperative level	Ringer's lactate	unspecified	0
Boldt et al. (1993) (11)	surgery 'elective aortocoronary bypass grafting using cardiopulmonary bypass'	30	5% albumin	no albumin		0
McNulty et al. (1993) (46)	surgery; 'elective cardiac procedures'	28	5% albumin	isotonic crystalloid	unspecified	not known
Woods et al. (1993) (4)	surgery; abdominal aortic aneurysm resection / aortoiliac or aortofemoral bypass graft	69	albumin supplementation	no supplementation	to discharge	1 i: 1/37 c: 0/32
Pockaj et al. (1994) (47)	metastatic cancer and IL2-associated vascular leak syndrome	107	5% albumin in 0.9% NaCl	0.9% NaCl	unspecified	0
Tollofsrud et al. (1995) (1)	surgery; coronary artery bypass surgery	20	4% albumin when fluid required	Ringer's acetate	48 hours	1 i: 0/10 c: 1/10
So et al. (1997) (48)	hypotensive preterm infant, gestational age < 34 weeks, birthweight < 2 kg, mech. ventilated for RDS ^{###}	63	5% albumin 10 ml/kg over 30 minutes	0.9% NaCl 10 ml/kg over 30 minutes	to discharge	12 i: 7/32 c: 5/31
Woittiez et al. (1998) (49)	surgery; abdominal aortic surgery	31	20% albumin	0.9% NaCl	unspecified	12 i: 8/15 c: 4/16
➤ burns						
Jelenko et al. (1979) (50)	burns;	14	hypertonic crystalloid with 12.5 g/l albumin	Ringer's lactate	5 days	3 i: 1/7 c: 2/7
Goodwin et al. (1983) (51)	burns	79		Ringer's lactate	to discharge	14 i: 11/40 c: 3/39
Greenhalgh et al. (1995) (9)	burns; < 19 years, with burns > 20 % total body surface area	70	25% albumin to maintain serum levels between 2.5 and 3.5 g/dl	no albumin unless levels dropped below 1.5 g/dl	to discharge	10 i: 77/34 c: 3/36

Trial / Authors	'Critical illness' / Patients	No. of patients	Intervention	Control	Length of follow up	No. deaths
➤ hypoproteinaemia						
Bland et al. (1976) (52)	hypoprot. [#] high-risk premature infants	27	25% albumin 8 ml/kg	5% glucose 8 ml/kg	unspecified	5 i: 4/14 c: 1/13
Nilsson et al. (1980) (53)	hypoprot. (post-OP); elective surgery of colorectal cancer	59	20-25 g albumin/day for 3 days starting day after operation	no supplemental albumin	to discharge	1 i: 1/29 c: 0/30
Brown et al. (1988) (54)	hypoprot; 'patients who required TPN'	67	TPN*** with added albumin	no supplemental albumin	to discharge	10 i: 6/34 c: 4/33
Foley et al. (1990) (3)	hypoalbuminaemia (< 2.5 g/l); 'critically ill'	40	TPP with added albumin (25-50 g/day 25% albumin)	no supplemental albumin	to discharge	13 i: 7/18 c: 6/22
Kanarek et al. (1992) (12)	hypoalb. ^{###} (< 3.0 g/dl) 'premature newborn'	24	TPP with added albumin	no supplemental albumin	unspecified	5 i: 3/12 c: 2/12
Wojtysiak et al. (1992) (55)	hypoalb. 'patients who required parenteral nutrition'	30	TPP with added albumin	no supplemental albumin	5 days	0
Greenough et al. (1993) (10)	hypoalb. (≤ 3.0 g/dl); sick preterm infants (mean gestational age: 29 weeks)	40	20% salt-poor albumin 5 ml/kg with maintenance fluids	5 ml/kg maintenance fluid placebo	24 hours after infusion	10 i: 6/20 c: 4/20
Golub et al. (1994) (2)	hypoalb. (< 3.0 g/dl)	219	37.5 g/day albumin until serum albumin >3.0 g/dl	no supplemental albumin	to discharge	18 i: 12/116 c: 6/103
Rubin et al. (1997) (8)	hypoalb. (< 2.5 g/dl)	36	TPP with added albumin	no supplemental albumin	to discharge	3 i: 2/16 c: 1/15

Trials reviewed by Cochrane Injuries Group in (21). Number of patients, number of deaths in the intervention as well as in the control group, respective treatment and length of follow up are shown as in original article.

*Number of deaths in intervention group. **Number of deaths in control group. ***Total parenteral nutrition.

[#]Hypoproteinaemia. ^{###}Hypoalbuminaemia. ^{####}Respiratory distress syndrome.

14. In the context of decreased albumin synthesis in patients with cirrhosis and liver failure Moreau et al. recommend that 'albumin infusion should be reserved to the treatment of hyponatraemia or functional renal failure complicating cirrhosis with severe liver failure and marked hypoalbuminaemia, when the infusion of colloids failed to correct these anomalies'(19).

15. Two guidelines for the use of albumin are shown, as examples, in Table 3.6.

Table 3.6
Selection of Guidelines and recommendations for the use of albumin
(with focus on most important indications and description of recommended approach:
First-choice therapy → second-choice therapy.)

Guideline	Sponsor	Method	Indication	Recommendation
1 Guidelines for therapy with blood components and plasma derivatives (1995) (20)	Ministry of Health ('Bundesministerium für Gesundheit')	expert opinion	acute / severe blood loss (→ massive transfusion) / acute volume replacement	→ loss up to 20 %: of total blood volume: crystalloid electrolyte solutions / synthetic colloid volume expanders → 4 –5 % albumin, if upper dose limits for dextran or HES (1.5 g/kg body weight) are reached 'the use of albumin solutions should be reserved for those patients whose plasma albumin concentration has fallen below 30 g/l, e.g. when volume loss exceeds 50 %' '...or in cases where clotting disorders other than those due to dilution occur during replacement therapy with synthetic colloids' dosage: 'no upper dose limit' 'patient's water and electrolyte status should be monitored' 'speed of infusion depends on the individual's cardiovascular condition' contraindications: no absolute contra-indications known relative: hypervolemic state albumin is 'unsuitable' for parenteral nutrition
			'children, pregnant / nursing women'	'in pregnant and nursing women and in children, the primary use of 4 – 5 % albumin solutions is recommended instead of applying synthetic colloids because of lack of controlled safety studies'
			'plasma exchange therapy'	'for plasma exchange therapy, 4 – 5 % albumin solutions are the exchange medium of choice'
			20- 25% albumin solution for raising colloid osmotic pressure in chronic albumin deficiency	'in hypalbuminemia with serum concentrations below 45 g/dl and a corresponding COP below 18 mmHg with coexisting oedema, 20 - 25 % albumin solutions may be indicated to increase COP for a limited period of time' 'administration of human albumin solutions is <u>never indicated</u> in diseases accompanied by chronic hypalbuminaemia <u>due to failing synthesis or to damage of capillary permeability</u>, since the underlying cause remains unchanged'

Guideline	Sponsor	Method	Indication	Recommendation	Comments
2 Vermeulen et al. (1995) (13)	University Hospital Consortium (UHC)	Delphi Round	haemorrhagic shock: non-haemorrhagic shock: cardiac surgery:	} crystalloids → colloids (with preference to non-protein colloids)	literature-based; however, no review of literature possible; Delphi-round with specialists from: critical care / transfusion medicine / surgery / neurosurgery / traumatology / pathology / gastroenterology / hepatology / clinical nutrition / pharmacotherapy / pharmacoeconomics;
			nephrotic syndrome:	short-term use in patients with acute, severe peripheral or lung oedema	
			plasmapheresis:	large plasma exchange (> 20 ml/kg): albumin small plasma exchange: albumin / crystalloid	
			thermal injury:	crystalloids: initial fluid resuscitation colloids if: > 50% of body surface affected / at least 24 hours since injury / crystalloid failed	
			cirrhosis and paracentesis:	'albumin should be avoided'	
			nutritional intervention:	'albumin should not be used'	
			severe hypoalbuminaemia: impending hepatorenal syndrome: increasing drug efficacy:	} 'indications with limited or inconclusive published supportive evidence, considered inappropriate based on the results of the consensus exercise'	
			hyperbilirubinaemia in newborn:	'should not be administered in conjunction with phototherapy'	

3.8. Glossary: albumin - production and effective components ⁽²⁰⁾

3.8.1. Production

16. Albumin preparations are produced from a human plasma pool by alcohol precipitation. Two preparations are available for therapy: 4 – 5% isooncotic and 20 – 25% hyperoncotic solutions for intravenous infusion.
17. Albumin is free of isoagglutinins and blood group substances and thus can be administered independent of the recipient's blood group. It is pasteurised for at least ten hours at minus 60 degrees centigrade to inactivate viruses. The main effective component is human albumin with a molecular weight of about 66 kDa.

3.8.2. Effective components

18. Preparations intended for clinical use may contain monomers along with dimers and, in small amounts, polymers of albumin. According to the German Pharmacopoeia, a maximum content of 5% polymers is permissible. Aside from human albumin, preparations currently available have an almost isotonic electrolyte content with a sodium concentration between 130 nmol/l and 169 nmol/l and a potassium concentration below 2 nmol/l, as well as containing up to 50 g glucose/l. Up to 3.2 g/l sodium octanoate and up to 4.29 g/l acetyltryptophan are added as stabilisers.

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4. FRESH-FROZEN PLASMA

1. The wide variety of ingredients made fresh-frozen plasma a tempting ‘drug’ for the treatment of different, but not always the right indications. Now, with scarce resources and increasing availability of alternative products and specific concentrates, the indications for fresh-frozen plasma are decreasing. However, the number of recommended clinical indications did not change too much in the nineties and contraindications are clearly defined.

4.1. Clinical trials

2. Most recommendations are based on pathophysiological considerations and clinical observations. A selection of clinical trials evaluating the use of fresh-frozen plasma for different populations is shown in Table 4.1.

Table 4.1
Selection of clinical studies evaluating
the use of fresh-frozen plasma for different settings

Study	Study design	No. of patients	Study population	Interventions / Outcome measures	Outcomes
1 Consten et al. 1996 (1)	randomised, clinical, single-institution trial	50	surgery, elective cardiopulmonary bypass mean age: 63 years; 35 men, 15 women;	group I (n =24): 3 units of FFP after OP group II (n=26): equal amount of plasma substitute; peri-OP blood loss; peri-OP transfusion requirements; coagulation parameters; platelet count;	No significant differences in blood loss, transfusion requirement, coagulation parameters and platelet count;
2 NNNI Trial Group 1996 (2)	prospective, randomised, clinical, multicentre-trial	776	preterm babies at gestational age < 32 weeks	three treatment regimens: - 20 ml/kg FFP (within 2 hours) +10 ml/kg (24 hours after first infusion) - equal volumes of gelatin-based plasma substitute or - glucose primary outcome: survival without identifiable major disability 2 years after birth;	No significant differences in primary outcome, deaths and developmental quotients.

Study	Study design	No. of patients	Study population	Interventions / Outcome measures	Outcomes
3 Dumont et al. 1996 (3)	observational study	28	surgery, orthotopic liver transplantation	group I (n = 13): pre-OP factor V > 10 % - < 60 %; group II (n = 15): pre-OP factor V > 60 %; bleeding during OLT and up to 48 hours after OP; coagulation factors;	group I: total intra-OP bleeding: 3460 ± 2700 ml; group II: total intra-OP bleeding: 3470 ± 2110 ml; lowest levels of clotting factors after reperfusion; 36 h post-OP all levels of clotting factors > 50 %; no reintervention in both groups necessary;
4 Leese et al. 1991 (4)	prospective, randomised, clinical, multicentre-trial	72	patients with 'predicted severe pancreatitis' (Glasgow prognostic scoring system)	two treatment groups: - FFP: 8 units / day over 3 days; - control group: same volume of colloid; mortality within hospital stay;	'no significant difference in clinical outcome' mortality: FFP group: 20 %; colloid control group: 18 %;
5 Leese et al. 1987 (5)	randomised, clinical, multicentre-trial	202	patients presenting acute pancreatitis	two treatment groups: - FFP: 2 units /day over 3 days; - control group: same volume of colloid;	no significant differences in clinical outcome.

4.2. Guidelines and recommendations

- Tables 4.2 – 4.5 show a selection of recent guidelines. Even though there are slight differences in the recommended dosage, the major part of the recommendations match between the different guidelines. The indication of cardiopulmonary surgery occurs solely in the guidelines of the British Committee for Standards in Haematology (9), in which platelet concentrates are recommended as a first-line treatment. Accordingly, Consten et al. (1) conclude that 'the routine use of fresh frozen plasma in operations with cardiopulmonary bypass is not justified'. All guidelines emphasise the importance of clinical symptoms.

Table 4.2
Guidelines for the use of fresh frozen plasma. 1998
[National Blood Transfusion Council South Africa (6)]

Guideline	Sponsor	Character / methods setting	Recommendations I	Recommendations II (details / further remarks)	Contraindications	Dosage / application comments
1 Guidelines for the use of fresh frozen plasma (1998) (6)	National Blood Transfusion Council South Africa	expert opinion, peer review	immediate reversal of warfarin effect	} 'in the emergency situation pre-operative reversal of the warfarin effect may also be accomplished by FFP infusion'	same as in 4 (see below)	dosage recommended
		setting/patients: all				starting dose: 10 – 15 ml / kg
		recommendations follow the Guidelines of the British Society of Blood Transfusion (→4). Only additional or differing remarks are listed:	DIC	} 'in chronic DIC or in the absence of haemorrhage in acute DIC, there is no indication for blood components to normalise laboratory results'		infusion immediately after thawing (within 2 hours)
			massive transfusion			} - 'if: microvascular bleeding + platelet count < 50 x 10⁶ /l → platelet concentrates' - 'if: fibrinogen < 1.0 g/l → cryoprecipitate' - 'if: PT or PTT > 1.5 x + fibrinogen >1.0 g/l →FFP'
	liver disease	} 'a PT > 2.0 control value is likely to be associated with excessive haemorrhage at surgery'				

Table 4.3
Practice guidelines for blood component therapy. 1996
[American Society of Anesthesiologists (7)]

Guideline	Sponsor	Character / methods setting	Recommendations I	Recommendations II (details / further remarks)	Contraindications	Dosage / application comments
2 Practice guidelines for blood component therapy (1996) (7)	American Society of Anesthesiologists	based on controlled and uncontrolled observational clinical studies setting/patients: perioperative, obstetric;	- urgent reversal of warfarin therapy - correction of known coagulation factor deficiencies for which specific concentrates are unavailable - correction of microvascular bleeding in the presence of elevated (> 1.5 times normal) PT or PTT - correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when PT and PTT cannot be obtained in a timely fashion	'Four to five platelet concentrates, one unit of single-donor apheresis platelets, or one unit of whole blood provide a quantity of coagulation factors similar to that contained in one unit of FFP (except for decreased, but still haemostatic, concentrations of factors V and VIII in whole blood)'	'augmentation of plasma volume or albumin concentration'	<i>dosage</i> 'FFP should be given in doses calculated to achieve a minimum of 30 % of plasma factor concentration' → 'usually achieved with administration of 10 – 15 ml/kg of FFP, except for urgent reversal of warfarin anticoagulation, for which 5 – 8 ml/kg of FFP usually will suffice.'

Table 4.4
Guidelines for therapy with blood components and plasma derivatives. 1995
 [Council and Scientific Advisory Board of the German Medical Association (8)]

Guideline	Sponsor	Character / methods setting	Recommendations I	Recommendations II (details / further remarks)	Contraindications
3 Guidelines for therapy with blood components and plasma derivatives (1995) (8)	Ministry of Health ('Bundesministerium für Gesundheit')	expert opinion	<i>indications</i> - 'emergency treatment of clinically dangerous bleeding tendencies or overt bleeding in cases of complex haemostatic disorders of the haemostatic system:' → liver parenchyma damage → DIC - coagulation disorders due to severe blood loss and/or blood dilution - replacement therapy in factor V and factor XI deficiencies - TTP - exchange transfusion	in an adult at least 3-4 units FFP are required initially. If more than 50 ml/min are applied, additional calcium application is required. 'FFP should not be administered for a loss of less than 65 % of blood volume' (also see <i>dosage</i>)	'FFP should not be given' - for volume expansion - as albumin or protein substitution to influence colloid osmotic pressure - for parenteral feeding - as a substitute for immunoglobulins
					<i>dosage</i> 'rule of thumb': 1ml FFP/kg body weight increases the factor content by about 1 – 2 % → emergency treatment: 15 ml/kg initially, followed by further clinical and laboratory monitoring → coagulation disorders caused by blood loss and/or dilution, e.g. massive transfusion: 1 FFP per 3-2-1 EK, depending on the clinical situation. → factor V replacement: in spontaneous bleeding plasma levels of 5 –15% / for surgery at least 20 % (20 ml FFP/kg /12h) → factor XI replacement: trauma or surgery: 10 ml FFP/kg (goal > 20%) → TTP: immediate infusion of 30 ml/kg, exchange with 3 – 4 l/d → chronic TTP: 10 ml/kg/3 weeks 'FFP should be infused rapidly'

Table 4.5
Guidelines for the use of fresh frozen plasma. 1992
 [British Committee for Standards in Haematology (9)]

Guideline	Sponsor	Character / methods setting	Recommendations I	Recommendations II (details/ further remarks)	Contraindications	Dosage / application comments
4 Guidelines for the use of fresh frozen plasma (1992) (9)	British Committee for Standards in Haematology	expert opinion	'definite indications'		'no justification'	dosage
		setting/patients: all	- replacement of single coagulation factor deficiencies, where a specific or combined factor concentrate is unavailable - immediate reversal of warfarin effect - acute disseminated intravascular coagulation - thrombotic thrombocytopenic purpura	'replacement of factor II and X with PCC* recommended' 'deficiency of von Willebrand factor should not be corrected with FFP' first-line: if available PCC* and factor VII first-line: treatment of underlying cause; + FFP + cryoprecipitate + platelet concentrate 'at least 3l/day' only indicated in the presence of bleeding and disturbed coagulation	- hypovolaemia - plasma exchange procedures - 'formula' replacement (e.g. '1 unit of FFP following each 4 –6 units of blood') - nutritional support - treatment of immunodeficiency states	„depends on the clinical situation“ recommended starting dose: 12 – 15 ml / kg ABO compatibility Rh D compatibility in females of child-bearing age infusion immediately after thawing monitoring of response (clinical / PT / PTT) alternatives presented
			- massive transfusion - liver disease - cardiopulmonary bypass surgery - 'special paediatric indications'	if: PT/PTT > 1,5 – 2 x and fibrinogen > 0,8 g/l prior surgery: „a PT of 1.6 – 1.8 times the control value is probably realistic“ no routine peri-OP use intra-OP bleeding: first-line: platelet conc. FFP: proven abnormalities of coagulation others than heparin-effect * Prothronbin complex concentrate		summary 'fresh frozen plasma should only be used to treat bleeding episodes or prepare patients for surgery in certain defined situations'

4.3. Glossary: FFP - production, quarantine storage, quality criteria and effective components⁽⁸⁾

4.3.1. Production

4. Fresh frozen plasma (FFP) is produced from a single blood donation. After centrifugation, the plasma from a whole blood donation is transferred to a transfer bag in a closed system. This procedure should be completed within six hours, but not later than 18 hours after whole blood donation. Alternatively plasma can be extracted mechanically by plasmapheresis. The plasma should be frozen without delay.

4.3.2. Quality criteria

5. The quality of FFP is especially high if shock freezing has taken place within six hours after donation. This freezing technique should guarantee complete freezing of plasma within one hour to a temperature below -30 degrees centigrade. Factor VIII is a good indicator of the quality of FFP because it reacts most sensitively to inactivating influences. FFP may contain the following amounts of residual cells: Erythrocytes $< 1000 /\mu\text{l}$, leucocytes $< 500 /\mu\text{l}$, thrombocytes $< 20,000 /\mu\text{l}$.

4.3.3. Quarantine storage

6. Before a donor's plasma can be released for clinical application, the donor must test 'negative' for infective markers after a period of quarantine storage of FFP. The FFP from plasmapheresis and whole blood donors must be stored over six months. The protein content depends on the donor's serum protein content. This must be at least 60 g/l in serum of plasmapheresis donors.

4.3.4. Effective components

7. The activity of coagulating factors is given in units. One unit of a coagulation factor corresponding to '100%' is defined as the activity present in 1 ml plasma from a plasma pool. It is subject to individual variations of between 60% and 140%, corresponding to 0.6 to 1.4 U/ml. The activity of coagulation factors and inhibitors in thawed FFP must be at least 70% of the original individual activity in donor plasma: when stored correctly the FFP contains, in addition to the coagulation and fibrinolysis enzymes, their inhibitors such as anti-thrombin III, protein C, protein S, alpha-2-macroglobulin, alpha-2-antiplasmin and PAI/-1 in their active forms.

4.4. Literature

- 1) Consten EC, Henny CP, Eijssman L et al. The routine use of fresh frozen plasma in operations with cardiopulmonary bypass is not justified. *J Thorac Cardiovasc Surg* 1996; 112 (1): 162 – 167.
- 2) The Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; 348 (9022): 229 – 232.
- 3) Dupont J, Messiant F, Declercq N et al. Liver transplantation without the use of fresh frozen plasma. *Anesth Analg* 1996; 83 (4): 681 – 686.
- 4) Leese T, Holliday M, Watkins M et al. A multicentre controlled clinical trial of high-volume fresh frozen plasma therapy in prognostically severe acute pancreatitis. *Ann R Coll Surg Engl* 1991; 73 (4): 207 – 214.
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- 6) National Blood Transfusion Council of South Africa. Guidelines for the use of fresh frozen plasma. *South African Medical Journal* 1998; 88 (10): 133 – 134.
- 7) Practice Guidelines for Blood Component Therapy. A Report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 1996; 84: 732 – 747.
- 8) Council and Scientific Advisory Board of the German Medical Association. Guidelines for therapy with blood components and plasma derivatives. *Deutscher Ärzte-Verlag* 1995.
- 9) British Committee for Standards in Haematology. Guidelines for the use of fresh frozen plasma. *Transfusion medicine* 1992; 2: 57 – 63.

5. Coagulation Factor Concentrates (Factor VIII & IX) *

5.1. General remarks and recommendations ^{(CA) **}

1. Haemophilia and severe von Willebrand disease are rare life-threatening bleeding disorders with potentially serious complications associated with the disease and treatment. These patients should be followed in comprehensive care centres that offer expertise in diagnosis, assessment and management of bleeding and related complications, and that can meet the educational and counselling needs of patients, family members and health care providers.
2. The comprehensive care centre(s):
 - must work closely with family physicians and other health care providers;
 - the centre's haematologist should be consulted before any dental or surgical procedure;
 - all patients with haemophilia or von Willebrand disease should be registered with a haemophilia treatment centre, possibly with a comprehensive care centre;
 - eligible patients should be enrolled in a home self-infusion programme; and
 - eligible patients should attend comprehensive care centres for routine follow-up examinations.
3. 'Optimal therapy provides the patient with immediate access to treatment for correction of the haemostatic defect at the first sign of haemorrhage. For most patients with severe or moderate haemophilia, this means a home therapy programme.'
4. 'Haemophilia and von Willebrand disease are the most common congenital bleeding disorders. The optimal management of patients with these disorders, especially those with severe disease, requires more than the treatment and prevention of acute bleeding. Patients who have repeated episodes of bleeding will need long-term management of joint and muscle damage and other sequelae as well as attention to education, employment and psychosocial needs.'
5. An additional concern is that blood products used in the past in the treatment of bleeding disorders have been associated with devastating viral complications such as hepatitis and AIDS. The aim of management should be to prevent disease and treatment-associated morbidity and mortality, and to optimise quality of life. These goals can usually be met through the provision of comprehensive care, including home therapy, with the effective and safer treatments that are now available.
 - Plasma-derived concentrates are now of high purity and are subjected to effective viral attenuation procedures.
 - Recombinant Factors VIII and IX, which are currently thought to provide the greatest degree of safety from viral transmission, are now available.
6. Modern management of haemophilia and von Willebrand disease is expensive, but it is cost effective and of considerable benefit when long-term outcomes are examined.

* with support from J. Etzler, assistant to the Director, World Federation of Haemophilia (WFH), Information Clearinghouse

** Country Codes, as shown in chapter 5.9. 'References and Literature'

5.2. Choice of concentrates

7. Clinicians should have a choice of plasma-derived or recombinant concentrates having an adjusted specific activity of at least 50 IU FVIII per mg protein. (Australia)

Table 5.1
Choice of Concentrate according to National Treatment Guidelines

Country	General remarks	Haemophilia	Haemophilia A	Haemophilia B	VWD	Immune tolerance
AUSTRIA	p-d and recombinant used; for PUPs with severe haemophilia recombinant is to be preferred; for pre-treated pts. no specific recommendations - all products are used;	recombinant products preferred for short-term treatment of mild or moderate haemophilia				
BELGIUM	—					
DENMARK	—					
FINLAND	—					
FRANCE	—					
GERMANY	recombinant predominantly for children - but available for all pts.		- p-d high-purity FVIII - recombinant FVIII	- p-d high-purity FIX - recombinant FIX	FVIII concentrate rich in VWF NOT cryoprecipitate!	
GREECE	—					
IRELAND	recombinant offered to all pts. with haemophilia A / B		recombinant FVIII	recombinant FIX		
ITALY	recombinant is the best choice for all pts.		recombinant FVIII	- p-d high-purity FIX - recombinant FIX when licensed	FVIII concentrate rich in VWF NOT cryoprecipitate!	
LUXEMBOURG	—					
NETHERLANDS	p-d and recombinant products used - <u>pts. are informed about the products and then make their own choice;</u> (end 1997: 30% recombinant)					
PORTUGAL	—					

Country	General remarks	Haemophilia	Haemophilia A	Haemophilia B	VWD	Immune tolerance
SPAIN			p-d & recombinant products are all regarded as safe and efficient for haemophilia A	- PCC not contra-indicated; - high-purity mono FIX - recombinant FIX for: - PUPs - „risk surgery“ - chronic hepatitis - preceeding thromboembolism - ITT - hypercoagulative states (diabetes, septic processes)		- p-d high-purity mono FIX or - recombinant FIX
SWEDEN	p-d and recombinant products are all regarded to have a high degree of safety		- high-purity FVIII - monoclonal FVIII (mainly Octonativ-M); switching to - recombinant FVIII is successively; market share of rFVIII is 50% (1998)	- purified FIX only	- intermediate-purity FVIII (Haemate-P) exclusively recommended;	any FVIII or FIX product (except Haemate-P);
UNITED KINGDOM	trend towards recombinant for virus safety reasons		recombinant FVIII is likely to be used widely	- p-d high-purity FIX - recombinant FIX may become licensed	- intermediate-purity FVIII (*Alpha VIII, Haemate-P, 8Y) - higher-purity FVIII (*Alphanate) - VWF concentrate (*VWF-VHP) * named-patient basis NOT cryoprecipitate	
ICELAND			recombinant FVIII for <u>on-demand</u>			
LIECHTEN-STEIN	—					
ROMANIA				high-purity FIX	- FVIII concentrate rich in VWF - (platelet concentrate) - recombinant FVIII for pts. with inhibitor	
SWITZER- LAND			recombinant FVIII for <u>short course</u> of treatment of <u>mild to moderate haemophilia A</u>			

Country	General remarks	Haemophilia	Haemophilia A	Haemophilia B	VWD	Immune tolerance
AUSTRALIA	recombinant is likely to be used widely	recombinant for pts. hitherto least exposed to conc.	- p-d high-purity FVIII - recombinant FVIII	- p-d high-purity FIX - PCC only for short course (2-3 days), if longer + heparin prophylaxis - recombinant FIX should be licensed	- p-d intermediate - purity FVIII - purified VWF conc. - cryoprecipitate only very rarely when justified	
CANADA	recombinant and p-d very high-purity products are mostly used		- recombinant FVIII - p-d very high-purity FVIII (immunoaffinity chromatography)	- pd high-purity mono FIX - recombinant FIX - PCC	- p-d intermediate-purity FVIII (Haemate-P) - very rarely cryoprecipitate & platelet concentrate cryoprecipitate NOT in general	
NEW ZEALAND			- p-d intermediate-purity FVIII - recombinant FVIII (especially for mild haemophilia PUPs)	- PCC - p-d high-purity mono FIX (monoclonal antibody-purified) - mono FIX-VF	- p-d intermediate-purity FVIII - cryoprecipitate !!	
UNITED STATES (NHF-MASAC)	recombinant products are considered to be the safest - with plasma-derived virus-attenuated products remains the possibility of virus transmission;		- recombinant FVIII (as the first choice) - p-d high purity FVIII (immunoaffinity) - p-d intermediate purity FVIII	- recombinant FIX - p-d high-purity FIX (immunoaffinity) - PCC	- FVIII concentrate that is known to contain the higher molecular weight multimers of VWF (Alphanate Haemate-P Koate HP) - NOT cryoprecipitate - only in emergency situations if concentrates not available;	
UNITED STATES (Georgia)			- recombinant FVIII - p-d monoclonal antibody purified FVIII - p-d high-purity FVIII	- p-d pure FIX conc. - PCC	- p-d intermediate-purity FVIII (Haemate-P, Alphanate, Koate-HP) - cryoprecipitate NOT in general - only if 'directed screened repeated donor';	

5.3. Comprehensive care ^(CA / US-G)

8. Comprehensive care, including home therapy, is the mainstay for treatment for patients with haemophilia or von Willebrand disease. The composition of the comprehensive care team reflects the fact that management involves more than the treatment of acute bleeding episodes. The multidisciplinary care team devises a coordinated plan for the patient and relies on his private (family) physician for follow-up:

'Primary' care team	'Referral' support team	Also available should be
– haematologist – nurse coordinator (first contact for patients with acute problem or requiring follow-up) – orthopaedist – physical therapist – genetic counsellor – social worker	– rheumatologist – orthopaedic surgeon – dentist – clinical geneticist – infectious disease specialist – hepatologist – gynaecologist	– physiatrist – psychologist – psychiatrist – dietician – occupational therapist – vocational rehabilitation specialist

9. Essential components of comprehensive care include:

- Genetic counselling;
- Care of patients with HIV infection supervised by infectious disease specialists in specialised multidisciplinary clinics;
- Patients with HCV/HBV infections managed in conjunction with specialists in liver disease.

10. Specialised services which must be available include:

- blood banks with specific expertise in coagulation factor concentrates; and
- laboratory capable of performing the full range of haemostasis tests.

5.4. Continuous infusion

11. Continuous infusion

- should be used instead of short-interval multiple dosing schedules; and
- be used when higher levels of FVIII or IX have to be maintained over longer periods.

Table 5.2
Indications for continuous infusion
(AU / IT / NL / NZ / ZA / SE)

especially used in:	may be used in:	comments
- intracranial bleeding - cerebral contusion - major surgery	- major head injury - acute bleeding in high-titre inhibitor patients	see below

Table 5.3
Continuous infusion treatment regimens
(NZ / US-G)

clearance rates	infusion rates	administration details
Estimated: adults: 4 mls/kg/hr children: 5 mls/kg/hr	Formula: Infusion rate (IU/kg/hr) = clearance (mls/kg/hr) x steady state concentration (IU/ml)	Give a bolus dose sufficient to achieve a plasma FVIII activity of 80%;
clearance rates fall during infusion;	<u>Initial infusion rate (IR):</u> Example: The infusion rate to achieve a steady state concentration of 80% (0.8 IU/ml) on the first day is on the basis of the given clearance rates: adult: IR (IU/kg/hr) = 4 (mls/kg/hr) x 0.8 = 3.2 IU/kg/hr child: IR (IU/kg/hr) = 5 (mls/kg/hr) x 0.8 = 4.0 IU/kg/hr Initial infusion rates can be approximated: adult: 3 IU/kg/hr child: 4 – 5 IU/kg/hr <u>Infusion rate on subsequent days:</u> Pro rata reductions in the infusion rates can be calculated for lower target concentrations on subsequent days; For example a 50 kg patient, for whom a target level of approx. 40% is desired on a subsequent day, should receive an infusion of 3 mls/hr subject to confirming appropriate response by ex-vivo factor levels;	⇒ factor level must be monitored to confirm that target level is achieved; ⇒ continuous infusion of purified FIX should only be used by experienced haematologist; <u>Reconstitution of factor for continuous infusion:</u> Reconstitute each 250 IU vial of factor VIII with 10 ml of sterile water for injection to achieve concentration of 25IU/ml <u>Storage of reconstituted factor:</u> FVIII concentrates are stable in i.v. solutions for at least 12 hrs. at room temperature so that 12-hr. bags can be prepared by the pharmacy; <u>Administration of factor:</u> - paediatric drip chamber using a metriset or - syringe driver and a 50 ml plastic syringe; depending on the administration system used and the weight of the patient, sufficient reconstituted product can be prepared for up to 24 hours as stability is maintained at room temperature for this period;

5.5. Inhibitor treatment (CA / NL / NZ / ZA / CH / UK)

- In principle, inhibitors may develop in any blood coagulation disorder. The development of factor VIII inhibitor is a serious complication of factor VIII replacement therapy. Inhibitors reduce the half-life of factor VIII, causing relative or complete refractoriness to factor VIII. This causes a dramatic reduction in quality of life and may reduce life expectancy, since the alternative treatments used in inhibitor patients are not as clinically effective as factor VIII concentrate is in patients without an inhibitor. Inhibitors may

develop not only in newly treated patients, but also in previously multitransfused patients in response to specific products, and result in a greatly reduced recovery of infused FVIII and a shortened half-life in vivo. Therefore, regular screening for inhibitors and monitoring of diagnosed inhibitors is required in all treated patients.

13. Factors contributing to inhibitor formation are:

- severe haemophilia;
- type of genetic defect;
- family history of inhibitors;
- greater predisposition in black patients;
- use of particular blood coagulation products; *
- individual characteristics of the immune system;
- additional stress on the immune system during replacement therapy.

** Recently, there was some concern that previously untransfused patients receiving rFVIII may be at higher risk of inhibitor development than those receiving a plasma-derived product.*

14. Usually, inhibitors develop within the first 25 treatment exposure days (after a median of 9-11 treatment days) - in newly treated patients within the first 50 exposure days or within a few months after starting replacement therapy. After 200 treatment exposure days the risk of inhibitor development is reduced to nil. Frequently, inhibitors are transient and disappear within several weeks or months. However, transient inhibitors may reappear again. Most inhibitors develop in patients with haemophilia A - and here mostly in severe haemophilia A, inhibitors in mild to moderate haemophilia A are rare. Overall, 35 - 45% of patients with haemophilia A receiving FVIII concentrate develop an inhibitor which remains detectable for some time. Persisting inhibitors develop in approx. 10 - 20% - the majority of them (>75%) being high responders. Inhibitor development in haemophilia B is approx. 6%. However, severe anamnestic response may occur in patients with haemophilia B. Therefore, children with haemophilia B should receive the first replacement therapy in hospital. In Von Willebrand disease (VWD) an incidence of less than 10% has been reported.

15. Screening for inhibitors in severe haemophilia A should be carried out

- if patient is unresponsive or has a poor response to appropriate replacement therapy screening for inhibitors is indicated;
- in children every 3-6 months for new inhibitor formation up to the age of 10;
- for 2 years after any change to regular use of a new blood product; and
- before surgery.

- Initial screening should be performed by means of Bethesda assay or an inhibitor screening test, which may be more sensitive;
- Inhibitor should be confirmed on at least 2 occasions by Bethesda assay.

16. Haemophilia centres managing inhibitor patients should be in a position to measure factor VIII levels 24 hrs. a day (availability of laboratory night and day) and to measure the inhibitor level within 24 hrs. of patient admission.

5.5.1. Inhibitor treatment – acute bleeding

17. Conventional immunosuppressive regimens are not successful in patients with inhibitors, but about 50% respond favourably to infusion protocols. *Low responders* (< 5 BU) respond to treatment in general without problems. *High responders* (> 5 BU) may respond to factor replacement by a rapid and marked increase of the inhibitor level and may show this anamnestic response in 3 days. *Non-responsive patients* require continued management with bypassing substances.

Mild bleeding

18. Mild bleeding may be treated empirically, using a product to which the patient is known to respond, or the product that is most effective according to past inhibitor measurements. In a few countries PCC is then used. Bypassing agents are usually used if there was a considerable anamnestic response to human and porcine FVIII in the past.

Major bleeding:

19. For severe bleeding (muscle bleeds, intra-abdominal or intracranial bleeding) or surgery the product most likely to be immediately effective should be used. Choice and dose should be based upon the current inhibitor titres to human and porcine FVIII. The inhibitor titre and the cross-reactivity to porcine FVIII have shown to vary independently of replacement therapy. Patients may react to human FVIII with briskly increasing inhibitor titres. This should be avoided in children.
20. The anamnestic response to human factor VIII does not predict the anamnestic response to porcine FVIII. Some high responders who are refractory to human FVIII but are lacking significant cross-reactivity to porcine FVIII, and who have little anamnestic response to treatment with porcine FVIII may be treated regularly with this product, even for relatively minor bleedings.
21. High-dose neutralising FVIII may be effective in low responders. High responders cannot be treated with human FVIII. For these patients bypassing concentrates, such as activated prothrombin complex or recombinant FVIIa is the recommended initial therapy. Porcine FVIII may be appropriate for both low responders and high responders with non cross-reacting antibodies. .

22. Formula for dosing human or porcine FVIII:

Initial dose	=	neutralising dose + incrementing dose
Neutralising dose	=	plasma volume x inhibitor titre
Plasma volume	=	40 x bw (kg)

5.5.2. Inhibitor treatment – immunoadsorption (CA / DE / IT / NL / NZ / SE / CH / UK)

23. The antibody-removal protocol is performed by means of extracorporeal immunoadsorption with a staphylococcal protein A column.

Table 5.4
Recommendations for the treatment of acute bleeding in patients with inhibitors
(CA / NL / NZ / ZA / CH / UK)

Inhibitor titre	Bleeding	Treatment approach	Comments
< 5 BU		human FVIII - high dose 100-200 IU/kg porcine FVIII - high dose 50-100 u/kg – 8-12 hourly or 25-100 u/kg by continuous infusion; aPCC - high dose 100 u/kg - 12 hourly	⇒ human FVIII is product of choice for < 5 BU; - 2-3 times normal dose FVIII may be sufficient; ⇒ if > 5 BU FVIII may not be effective; - test dose porcine FVIII is 100 u; - inhibitors may increase considerably with human or porcine FVIII; - with aPCC (FEIBA or Autoplex) risk of thrombosis – no more than 3-4 doses); - total daily dose of FEIBA should not exceed 200 u/kg;
5 - 10 BU	minor	PCC may be tried - 50-100 IU/kg - 12-24 hourly	- max. single dose 200 IU/kg
	major	human FVIII may be tried aPCC - 50-100 u/kg - 12-24 hourly porcine FVIII - high dose - bolus of 50 u/kg rFVIIa - 60-120 µg/kg - 2-3 hourly + tranexamic acid may be used 15-25 mg/kg orally or i.v. 6-8 hourly;	⇒ can usually not be treated with human FVIII; - infuse aPCC at 2u/kg/hr; - infuse porcine FVIII at 3-10 u/kg/hr.;
	life-threatening	aPCC - high dose rFVIIa human FVIII or porcine FVIII - high dose + immunoadsorption or plasmapheresis;	
5 - 20 BU		human FVIII - high dose	⇒ FVIII not effective if ≥20 BU;
5 - 50 BU		porcine FVIII + antihistamines or corticosteroids; aPCC - high dose + antifibrinolytic	⇒ porcine FVIII not effective if anti-porcine > 5 BU;

Table 5.5
Indications for immunoadsorption in patients with inhibitor

Inhibitor patient group	Indication	Further details
high responders >10 BU	- acute major bleeding - life-threatening bleeding - prior to surgery	- only for adults - patients refractory to human FVIII - additionally to high-dose porcine FVIII <u>alternative</u> plasmapheresis

5.5.3. Inhibitor treatment – immunosuppression ^(CA / NZ)

24. Conventional immunosuppressive regimens are not successful in inhibitor treatment in haemophilia as they are disappointing for alloantibodies. Immunosuppression is used for autoantibodies.

5.5.4. Inhibitor treatment - Immune tolerance treatment (ITT)

25. The treatment of high responder inhibitor patients is problematic and costly. Therefore, when patients develop high titres of persisting inhibitors induction of immune tolerance (ITT) to their therapeutic concentrate should be started as soon as the inhibitor has been confirmed by a second assay and 'when a spontaneous remission cannot be expected'. The cost of factor use in ITT protocols is less than if patients were continued to be treated on demand.

26. ITT can be induced by means of high-dose or low-dose regimens over longer periods, using the human FVIII concentrate to which they respond best. Overall, about 50 - 80% of high responders will respond favourably to ITT protocols. For high responders with lower inhibitor titres (<10 BU) a response rate of 85% has even been reported. In high-responders with higher inhibitor titres (>10 BU) a 30% rate has been reported for low-dose ITT and a 84% success rate with high-dose ITT.

ITT protocols

Bonn high-dose FVIII in combination with activated prothrombin-complex concentrate (aPCC):

100 IU /kg bw 2 x daily + 50 U/kg bw aPCC 1 x daily

Malmö high-dose FVIII in combination with gammaglobulin and cell-growth inhibitor:

100 IU/kg bw daily + i.v. IgG + cyclofosamide

Utrecht low-dose FVIII concentrate:

25 IU/kg bw daily

- ITT should be initiated promptly after the inhibitor has been confirmed by a second assay.
- ITT should preferably be started when inhibitor titre is <10 BU;
- In children ITT can be started without clinical symptoms and should be initiated as soon as age allows it.
- Intensive replacement therapy under ITT requires central venous access (Port-A-Cath) in children.
- As ITT is demanding for both patients and parents written informed consent must be obtained before starting with an ITT protocol.
- Low-dose ITT is recommended for patients with inhibitor titres <10 BU.
- High-dose ITT is recommended for patients with new inhibitors persistently >10 BU. Duration of treatment will extend from 6 - 18 months.

- For patients with very high titres of inhibitors or with long-established inhibitors ITT may be necessary for a period in excess of three years before immune tolerance is achieved. The general recommendations are, however, to discontinue ITT after 18 months unless the inhibitor is not declining by that time.
- ITT treatment should not be interrupted.
- Immediate availability of bypassing substances is required to which therapy has to be switched if inhibitors do not respond to ITT.

Table 5.6
Immune tolerance treatment regimens

Inhibitor patient group	ITT regimen	Comments
high responders >10 - 40 BU	low-dose protocol	
high responders >10 BU	high-dose protocol	⇒ especially for children; - current thinking is that most patients respond <u>eventually</u> to FVIII alone; If peak inhibitor is <50 BU and duration of inhibitor was < 5 yrs., there is a >90% response rate to FVIII alone;
high responders >10 BU	high-dose protocol	if the peak titre is >50 BU and duration >5 years, the response rate to FVIII alone is < 50%; (NZ) <u>combination possibly with</u> – aPCC – rFVIIa – immunosuppressive – gammaglobulin start with FVIII alone for a minimum of 3 months, only add IVIG as a second option – cyclophosphamide is a last resort; if inhibitor titre is not decreasing IVIG and cyclophosphamide can be repeated monthly for up to 3 cycles;
	all protocols	<u>administration of FVIII</u> 2-3 x weekly start with bolus of 50 u/kg bw - follow recovery and half-life by achieving trough level - when recovery is > 50% and T _{1/2} is at least 4 hrs., decrease the daily dose to 25 u/kg bw, then back down to every other day; in <u>children</u> without Port-A-Cath infusion 2 x weekly if child is in hospital - bolus and then continuous infusion inhibitor control 1-2 x weekly immune tolerance is induced when the BU titre is near zero

5.6. Product / treatment material use in general ^(KE / NZ / UK)

27. Basic principles

- Licensed products should be used in preference to unlicensed products.
- Unlicensed products should be used, if possible, under formal clinical trial conditions rather than on a 'named patient basis'.
- Each patient should be considered individually regarding product usage (e.g. HIV+, HCV+).

Table 5.7
Product / treatment material use in general

product	indication	Further details	dosage / application
cryoprecipitate / FFP	only when may not be avoided	because FFP and cryo are not virus-inactivated;	
recombinant FVIII	haemophilia A	<u>product of choice</u> for PUPs; mild/moderate haemophilia non-responsive to DDAVP;	
porcine FVIII • Hyate:C	porcine FVIII	low responders with non-cross reacting inhibitor;	<u>test dose</u> for inhibitor cross-reactivity: 100 u with adrenalin and hydrocortisone at hand;
porcine FVIII • Hyate:C	porcine FVIII		<u>therapeutic dose</u> : 25 - 100 u/kg bw by constant infusion or intermittent administration 8 - 12 hourly; resistance tends to develop at 4 - 5 days; thrombocytopenia may occur;
prothrombin complex (PCC)	<u>contraindicated</u> for pts. with FVIII inhibitors;	not to be used in life-threatening bleedings;	
high-purity monocomponent FIX	haemophilia B <u>contraindicated</u> for pts. with FVIII inhibitors;	• PUPs; • <u>product of choice</u> for surgery;	
activated prothrombin complex (aPCC) • FEIBA • Autoplex	haemophilia A inhibitor pts.;	• major bleeds • life-threatening bleed • surgery FEIBA has been used for joint, muscle and soft tissue bleeding in patients with both high and lower inhibitor titres (> 5 BU);	<u>dosage</u> : independent of inhibitor 50-100 u/kg bw every 6 - 12 hrs.; lower doses more frequently by intermittent infusion may be preferable in some circumstances; total dose of FEIBA should not exceed 200 u/kg bw per day; clinical trial efficacy rates reported are 80 - 90%;
recombinant FVIIa • NovoSeven	haemophilia A inhibitor pts.	high-titre inhibitor pts. non-responsive to aPCC - severe bleed - life-threatening bleed	<u>dosage</u> : usually 90 µg/kg 2 hourly for 36 hrs. frequent intermittent injection; frequency reduction to 3 and then 4 hourly as indicated by clinical progress;

5.7. Prophylaxis (AU / CA / DE / IS / IT / NL / NZ / SE / CH / UK)

28. Prophylaxis may be primary prophylaxis (long-term prophylaxis), secondary prophylaxis (limited-term prophylaxis) or single-dose prophylaxis.

- Long-term prophylactic treatment should be made readily available to all children prone to haemarthrosis.

Table 5.8
Long-term prophylaxis

Patients	Indications / details	Treatment goals / comments
severe haemophilia A/B infants 1-2 yrs. of age 1-3 yrs. of age children 2 - 3 yrs. of age	⇒ after first joint bleeding or frequent other bleedings; ⇒ 1 - 2 bleedings in the same joint (target joint); ⇒ long-term prophylaxis should not start until it is apparent that the child is likely to suffer from frequent recurrent haemorrhages; <u>Selection criteria for prophylaxis:</u> * after 3 spontaneous joint or muscle bleedings * newly diagnosed boys * older boys treated on demand * adequate venous access (Port-A-Cath may be used) * informed written consent from parents * information of the boy appropriate for his age	to prevent haemarthrosis prophylaxis is given until the end of the growth period through the high risk years of early childhood and into teenage years, usually finishing around 18 – 20 years of age life-long factor administration usually 2 x wkly. FVIII or 3 x wkly. FIX aim is to <u>maintain the trough factor level</u> - at or above 1%; - level should not fall below 1-3 %; factor usage corresponds to 2,000 - 3,000 IU/kg/year; <u>Treatment frequency:</u> - <u>with a target joint</u> start initially daily - then during each 7-day period: haemophilia A: day 1, 3, and 5 (3 x wkly) haemophilia B: day 1 and 4 (2 x wkly) - <u>without a target joint</u> on every alternate day during each 7-day period: haemophilia A: day 1, 3, and 5 (3 x wk) haemophilia B: day 1 and 4 (2 x wk) <u>dose reduction:</u> after 6 months dose reduction can be considered for those pts. who had no breakthrough bleeding; <u>breakthrough bleeding during prophylaxis:</u> ⇒ without breakthrough bleeding → dose reduction ⇒ breakthrough bleeding at reduced dose → dose increase to initial dose after treating the acute bleeding; - regular pharmacokinetic studies required to optimise therapy - should be done 1-2 times per year, especially in children; - development of a continuous infusion technique for prophylactic treatment may result in further improvement of prophylaxis; <u>Inhibitor pts.</u> High-bolus + low-dosage regimen has proven to be successful in young children & adults with inhibitors up to a max. of 40 BU - pts. have shown a relatively rapid response; since the introduction of ITT persisting inhibitors are rare in young pts. with haemophilia A;

Patients	Indications / details	Treatment goals / comments
adults	⇒ bleeding frequency >1 x in 2 weeks; ⇒ recurrent bleeding in the same joint; ⇒ chronic synovitis; ⇒ established arthropathy;	As people with factor VIII or IX levels >1% of normal rarely develop disabling arthropathy, primary prophylaxis is usually reserved for the very severe cases with ≤1% factor levels; decision to start prophylaxis involves balancing the decreased number of bleeds with the inconvenience of the regular injections required in prophylaxis; if high-titre inhibitors develop during prophylaxis pts. are switched to on-demand FVIIa therapy; <u>products</u> - p-d high-purity - recombinant FVIII
Moderate haemophilia A pts. with higher FVIII levels	frequent bleedings	
children & adults		

Table 5.9
Short-term prophylaxis

Prophylaxis	Indications	Treatment goals / comments
secondary prophylaxis	- often in chronic synovitis; - to break the cycle of frequent bleedings into specific joints (target joint) - during recovering from a large bleed - pre- & post surgery	Refers to limited-term prophylaxis when there is a high requirement for on-demand therapy (frequent regular injections over a limited time period to reduce the frequency of bleeding or rebleeding from a target joint)
short-term prophylaxis	- before activities that carry a high risk of provoking a bleed - particularly during intensive physiotherapy - during rehabilitation - social indication (school excursions, special social events with dancing etc.) - in any non-haemophilia related disease with symptoms of inflammation or fever pts. with haemophilia are extremely at risk of bleeding - therefore, prophylactic treatment is mandatory;	to prevent bleeding occurring in relation to a particular demanding/stressful activity;
single-dose prophylaxis	may be given prior to special events such as sports	an injection of product may be given prior to the event;

5.8. Treatment at home ^(CA / IS / NL / SE / US-G)

29. Optimal therapy provides the patient with immediate access to treatment for correction of the haemostatic defect at the first sign of haemorrhage. For most patients with severe haemophilia and moderate haemophilia this means a home therapy programme. Eligible patients should be enrolled in a home self-infusion programme and be required to maintain records of blood product use. The comprehensive care team must assess the family's ability to undertake home therapy and should provide ongoing supervision, encouragement and support. In home-treatment for children it is essential that both parents are involved. In the event of trauma or bleeding the treating physician at the patient's haemophilia centre must be immediately contacted; if treatment is provided at a local hospital, the haemophilia centre physician in-forms the local doctor.

Table 5.10
Self-treatment at home

Indicated for:	At age:	Child should learn self-infusion	Parent issues
newly diagnosed pts.			'new' haemophiliacs are first treated at hospital, but when parents feel confident they are trained for home-treatment
younger children	1-2 yrs. of age if Port-A-Cath is used		parents learn self-infusion technique for very young children;
children	3-5 yrs. of age 4-5 yrs. of age	- at school-age - at the age of 15 yrs. or in the early teens	child should participate in his factor infusion at an early age;

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5.10 National Treatment Guidelines

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AT Austria	<i>Österreichische Hämophilie-Gesellschaft (ÖHG) - Wissenschaftlicher Beirat.</i> Konsensus über die Verwendung bestimmter Faktorenkonzentrate bei Patienten mit Hämophilie. 18. Oktober 1997
CA Canada	<i>Association of Hemophilia Clinic Directors of Canada (AHCDC).</i> Hemophilia and von Willebrand's disease: Part 1: Diagnosis, comprehensive care and assessment 2nd edition - April 18, 1998 <i>Association of Hemophilia Clinic Directors of Canada (AHCDC).</i> Hemophilia and von Willebrand's disease: Part 2: Management. 2nd edition - May 11, 1998 <i>Teitel, J M.</i> National haemophilia treatment protocols: Canada. <i>Haemophilia</i> (1998) 4:422-423
DK Denmark	<i>Clausen, N; Scheibel, E. in cooperation with the Danish Haemophilia Society.</i> Behandlingsprotokol for born med blodersygdom. 1. udgave 1998
DE Germany	<i>Schramm, W. Deutsche Hämophiliegesellschaft (DHG) - Ärztlicher Beirat.</i> Konsensus-Empfehlungen zur Hämophiliebehandlung in Deutschland. 11. März 1993 <i>.Haemostaseologie</i> (1994) 14:81-83 + version on homepage of IHTC Munich <i>Bundesärztekammer - Vorstand und Wissenschaftlicher Beirat.</i> Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten. Juni 1995. Köln: Deutscher Ärzte-Verlag <i>Deutsche Hämophiliegesellschaft (DHG) - Ärztlicher Beirat.</i> Medikamente bei Hämophilie. DHG Sonderdruck - 20. März 1997 <i>Deutsche Hämophiliegesellschaft (DHG) - Ärztlicher Beirat.</i> Basisleitlinien zur Überwachung der Hämophiliebehandlung. 1998
IS Iceland	Homepage of the Icelandic Hemophilia Society. as of end 1998
IT Italy	<i>Associazione Italiana dei Centri Emofilia (AICE).</i> Linee guida per la terapia sostitutiva dell'emofilia e dei difetti ereditari della coagulazione. February 5, 1997 <i>Gringeri, A.</i> Treatment protocol of haemophilia and other congenital bleeding disorders in Italy. <i>Haemophilia</i> (1998) 4:423-424
KE Kenya	Guidelines for Treatment of Bleeding Haemophiliac and Related Bleeding Disorders. no date. (received from Dr. Mwanda)
MY Malaysia	<i>Duraisamy, G - National Blood Services Centre.</i> Recommended Dosage Schedule. Cabaran Challenge, May 1997, p. 11 <i>Duraisamy, G - National Blood Services Centre.</i> Investigations for Cranial Bleeds. Cabaran Challenge, May 1997, p. 11 <i>Haemophilia Society of Malaysia.</i> Haemorrhagic states (identification card for patients) no date. (received as new card from Dr. Duraisamy in 1997)

NL Netherlands	<i>Nederlandse Vereniging van Hemofilie-Patiënten (NVHP). Nederlandse Vereniging van Hemofiliebehandelaars (NVHB). Syllabus - Hemofilie: Behandeling en verantwoordelijkheid. October 31, 1996</i> <i>Mauser-Bunschoten, E P; Roosendaal, G; Van den Berg, H M; Treatment protocols in the Netherlands. Haemophilia (1998) 4:428-430</i>
NZ New Zealand	<i>New Zealand Society for Haematology - Haemostasis and Thrombosis Subcommittee. National Guidelines for Factor Replacement in Haemophilia. updated version - December 1998</i>
RO Romania	<i>Asociatia Romana de Hemofilie. Protocol pentru tratamentul hemofiliei si bolii von Willebrand. no date</i>
SA South Africa	<i>South African Haemophilia Foundation (SAHF) - Medical Advisory Committee. Treatment Guidelines For Haemophilia in South Africa. 1997</i>
ES Spain	<i>Grupo de trabajo de coagulopatias congenitas. Recomendaciones sobre la eleccion de concentrados de factor VIII y IX 1996</i> <i>Grupo de trabajo de coagulopatias congenitas. ADDENDUM a las recomendaciones terapeuticas adopted April 22, 1998</i>
SE Sweden	<i>Socialstyrelsen. Vård och behandling av blödarsjuka - nationellt vårdprogramme 1997. 1997.</i> <i>Swedish Hemophilia Society / Förbundet Blödarsjuka i Sverige (FBIS). The Care and Treatment of Hemophilia - Swedish National Programme 1997. 1997</i> <i>Berntorp, E. Guidelines on treatment of haemophilia in Sweden. Haemophilia (1998) 4:425-426</i>
CH Switzerland	<i>Schweizerische Hämophiliegesellschaft (SHG) - Ärztliche Kommission. Richtlinien für die Behandlung einer hämophilen Blutung. April 1996</i> <i>Schweizerische Hämophiliegesellschaft (SHG) - Ärztliche Kommission. Hemmkörper gegen Gerinnungsfaktoren .1/1998</i> <i>Schweizerische Hämophiliegesellschaft (SHG) - Ärztliche Kommission. Fragen rund um neue Gerinnungspräparate. September 1998</i> <i>Schweizerische Hämophiliegesellschaft (SHG) - Ärztliche Kommission. Medikamente gegen Schmerzen. Dezember 1991</i> <i>Schweizerische Hämophiliegesellschaft (SHG) - Ärztliche Kommission. Notfälle bei Hämophilen. Wie vermeiden? Wie richtig handeln? September 1998</i> <i>Schweizerische Hämophiliegesellschaft (SHG) - Ärztliche Kommission. Notfallkarte für Bluter: Grundregeln der Hämophilie-Behandlung. ohne Datum</i> <i>Meili, E O. Schweizerische Hämophiliegesellschaft (SHG). Reise-Notfallblatt: Richtlinien für die Substitutionstherapie mit Faktor VIII- und Faktor IX-Konzentraten bei Hämophilie A und B. September 1994</i>
UK United Kingdom	<i>United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO)</i> <i>Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders.. October 3, 1996</i> <i>United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO) - Inhibitor Working Party. Recommendations for the treatment of factor VIII inhibitors. 1996</i> <i>United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO) - Working Party on Chronic Liver Disease in Haemophilia. Guidelines on the diagnosis and management of chronic liver disease in haemophilia. 1995</i> <i>United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO)</i> <i>Prophylaxis in the treatment of haemophilic boys. 1994</i> <i>Ludlam, C A. Haemophilia care within the United Kingdom. Haemophilia (1998) 4:427-428</i>

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6. QUALITY MANAGEMENT IN HAEMOTHERAPY

1. There has been increasing concern among the Member States of the European Community about the safety of blood products over recent years. As a result, legislative requirements for medicinal products derived from blood and plasma have been put in place for the European Community and relevant guidelines have been issued by the European Commission. The Guidelines for the preparation, use and quality assurance of blood components, prepared by the Council of Europe¹, are drawn upon for these blood products.
2. In order to exploit the full potential of the blood products that are available in the European Community, efforts need to be focused on their optimal use. The establishment of common quality management criteria throughout the European Community would greatly contribute to ensuring the quality of haemotherapy, from optimal supply to optimal use.

6.1. Quality management

3. 'Quality' as defined by the International Organisation for Standardization (ISO) is 'the totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs'.² Another definition is 'the level of agreement between a supplied service and the criteria set for this service'.³ A 'quality system' as defined by the ISO is 'the organisational structure, procedures, processes, and resources needed to implement quality management'.² 'Quality management' is defined as the sum of activities that together ensure the effective functioning of a quality system.
4. The term quality management comprises quality assurance as well as further quality-related aspects: 'quality assurance' is defined as 'all the planned and systematic activities implemented *within* the quality management system, and demonstrated as needed to provide adequate confidence that an entity will fulfil requirements for quality'.² Most authors understand quality management more comprehensively than quality assurance: 'quality assurance has a long tradition in medicine and public health care. Internal and external measures aim at improving *clinical* quality. But classic quality assurance ignores *economic efficiency* as well as weaknesses in *interprofessional communication and co-operation*. Total quality management aims at creating these conditions'.⁴ Taken together, quality assurance means the determination and documentation of the status quo in order to compare with the standard and provides measures how to minimise differences between how it is and how it should be.⁵ Quality management – as mentioned above - additionally takes into account how a quality system can be established, maintained and improved. An important tool of quality assurance and thus of quality management is 'quality control' that 'involves operational techniques and activities aimed both at monitoring a process and at eliminating causes to unsatisfactory performance at all stages of the quality loop....'²

6.2. Quality in haemotherapy: clinical guidelines

5. Quality in haemotherapy implies administering the right quantity of the right blood component in the right way at the right time. Clinical guidelines could be a valuable tool for conveying current knowledge and creating uniform transfusion standards within the Member States of the European Community. To what extent clinical guidelines are able to influence clinical practice, however, depends on their quality, the provided strength of evidence and how they are implemented.

6.2.1. Quality criteria of clinical guidelines:

6. Different approaches have been developed to judge the quality of published guidelines.^{6/7/8/9/10} For clinical guidelines, the following quality criteria are essential:

Table 6.1
Most important quality criteria of clinical guidelines^{11/12/13/14}

– validity	proven effectiveness and efficiency
– reliability	applicable with similar results for different clinicians in similar clinical circumstances
– reproducibility	confirmation of recommendations by independent experts
– multi-discipline-based development	involvement of specialists of possibly all user-disciplines
– flexibility	‘pathway’, reasonable deviations should be possible
– clarity	unambiguous recommendations, clear terminology and language
– transparency	reconstruction of development process should be possible
– control of effectiveness and efficiency	examination of acceptance and implementation with regular revision and adaptation to new conditions
– cost-benefit ratio	improvement of medical treatment at acceptable costs

6.2.2. Level of evidence

7. Whenever possible, clinical guidelines should be based on evidence and provide it at the highest level. Two different classification systems for grading evidence-based data underlying the development of clinical guidelines, are shown in Tables 6.2 and 6.3. Quality criteria of the studies themselves – e.g. date of publication, number of patients, study design – , particularly the person responsible for handling of the meta-analyses should always be taken into consideration.

Table 6.2
Grading of evidence as proposed by
U.S. Preventive Services Task Force¹⁵ and used by
the American Society of Anesthesiologists in
‘Practice guidelines for blood component therapy’ (1996)¹⁶

I	randomised, controlled trial
II – 1	non-randomised, controlled trial
II – 2	controlled observational studies (cohort or case-control studies)
II – 3	uncontrolled observational studies
III	descriptive studies, expert opinion

Table 6.3
Grading of evidence as proposed –among others – by
Scottish Intercollegiate Guidelines Network⁸

I a	Evidence obtained from meta-analysis of randomised controlled trials
I b	Evidence obtained from at least one randomised controlled trial
II a	Evidence obtained from at least one other type of well-designed controlled study without randomisation
II b	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience or respected authorities

6.2.3. Development of clinical guidelines

8. There are different ways possible for the development of clinical guidelines and a considerable number of guidelines that can be referred to for assistance. The preferred method for developing clinical guidelines is through consensus conferences. They offer the opportunity for direct discussion between a relatively large group of participants with the aim of arriving at broad consensus. In the optimal case, a consensus conference should provide the synthesis of existing knowledge ('the science base') and user experience ('the experience base'). It should include:¹⁷ a 'preparation group' that decides on the topics to be discussed, and a panel of experts knowledgeable in the topics, and potential users. The topics should be distributed among the panel of experts who then take inventory of the existing knowledge ('science base') and user experience ('experience base') in a comprehensible way with the aim of providing the highest strength of evidence (see Table 6.2. and Table 6.3.). This should be followed by the presentation and discussion among experts of different disciplines having current knowledge and experience with the aim of arriving at consensus.
9. Consensus conferences can be held in several meetings or can be combined with delphi methods. If a consensus cannot be found, this and the underlying reasons should be stated. At the end of the process stands the publication and implementation of the results. Additional periods and modalities for the revision of guidelines should be discussed and fixed.

6.2.4. Central versus decentral development of clinical guidelines

10. The central development and co-ordination of clinical guidelines seems advantageous for several reasons and is practised in different countries of the European Community, e.g. in the Netherlands by the 'Nederlands Huisartsen Genootschap' (NHG) and in Germany by the 'Zentralstelle der deutschen Ärzteschaft zur Qualitätssicherung in der Medizin'⁶ and the 'AWMF'.¹¹ However, flexibility and the possibility of adopting clinical guidelines that are pertinent to distinct regional conditions is crucial for their implementation and their impact on clinical practice.¹⁸ A comparison of advantages and disadvantages of the central or the decentral development of clinical guidelines is shown in Table 6.4.

Table 6.4
Central versus decentral development of clinical guidelines.
Selection of possible advantages and disadvantages

	advantages	disadvantages
central	broad process possible: - involvement of specialists of different disciplines: → professionalism → coordination	no 'ownership': - lower acceptance, consideration of all regional conditions not possible - expensive
decentral	'ownership': - better acceptance ¹⁸ - better consideration of regional conditions	process limited to a single institution: - narrow spectrum of specialists

6.3. Quality of structure, processes and outcome in haemotherapy

11. The first step when implementing a quality system is to define quality or, in other words, to set criteria for a product or a service. The definition of structure-, process-, and outcome-related quality has been proven to be a useful instrument for this purpose: quality of structures (personnel and/or material) and quality of processes (e.g. co-ordination of sub-processes) are necessary to yield quality of a certain outcome (e.g. clinical outcome).
12. The definition of suitable structures and processes to maintain and improve quality in haemotherapy can be made either by guidelines or legislation. For example, in Germany the 'Transfusionsgesetz' ¹⁹ establishes in law the use of blood and blood products by defining principle demands on: the personnel structure, the qualification of involved clinicians and staff, and documentation and communication between the respective authorities. Further details focusing on the process of transfusion itself are given by the instructions for haemotherapy that are published by the scientific board of the 'Bundesärztekammer'.²⁰
13. General recommendations for the development of national transfusion policies and guidelines on the clinical use of blood have also been developed by the WHO, proposing the establishment of a National Committee on the Clinical Use of Blood in each country.²¹ The central matter of interest will be whether, how and to what extent the development of uniform structures and processes makes sense and how different national conditions can be co-ordinated within the European Community. Finally, considerations have to be made about how to assess the quality of the respective outcome, e.g. the impact of clinical guidelines on clinical practice, the clinical outcome itself, economic aspects.

6.4. Glossary: Quality

efficacy*	‘the extent to which a specific intervention produces a beneficial result under ideal conditions’
efficiency*	‘the extent to which the resources used to provide a specific intervention of known efficacy and effectiveness are minimised’
effectiveness*	‘the extent to which a specific intervention, when deployed in the field, does what it is intended to do’
quality**	‘the totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs’
quality assurance**	‘all the planned and systematic activities implemented within the quality management system, and demonstrated as needed to provide adequate confidence that an entity will fulfil requirements for quality’
quality control**	‘operational techniques and activities that are used to fulfil requirements for quality’; ‘quality control involves operational techniques and activities aimed both at monitoring a process and at eliminating causes to unsatisfactory performance at all stages of the quality loop’
quality system**	‘the organisational structure, procedures, processes, and resources needed to implement quality management’

* definition from: Ovretveit J. Health Service Quality. An Introduction to Quality Methods for Health Services. 1992. Blackwell Scientific Publications. Oxford.

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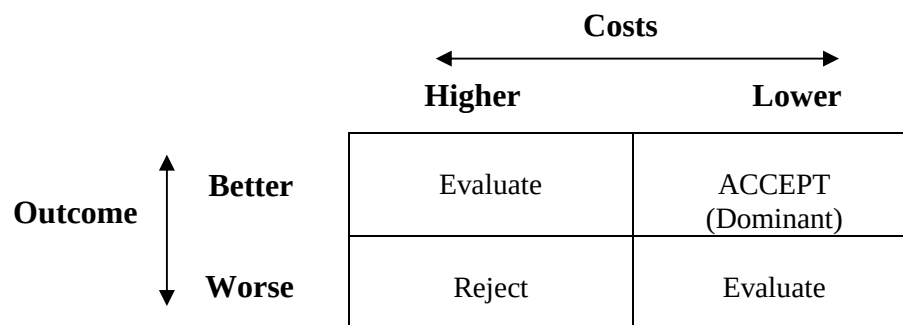
7. ECONOMIC ASPECTS IN MEDICINE

7.1. Economic evaluations in medicine

1. During the last decade, there has been growing interest in the economic evaluation of healthcare programmes. New as well as established therapies and diagnostic approaches are increasingly being assessed by the various techniques used in health economic evaluations. One of the main reasons for this development is that cost-containment programmes in most European countries cannot manage the expanding demands arising from the availability of new and more expensive medical technologies, a growing elderly population, and from national, political and social problems such as high unemployment rates. Another factor is that in most European countries there are no incentives to contain costs because the services and treatments are covered by taxes or health insurances.^[1]
2. With economically behaviour rationing of healthcare should be avoided. Rationing is focused on the limitation of resources. But the focus of rational decision-making is to guarantee and improve the productivity of our healthcare system.
3. The scholarly discipline of economics offers a wide range of concepts and instruments regarding the use of limited resources. According to Samuelson and Nordhaus,^[2] ‘Economics is the study of how people and society choose to employ scarce resources that could have alternative uses in order to produce various commodities and distribute them for consumption, now or in the future, among various persons and groups in society’. Clinicians, pharmacists, economists, epidemiologists and those involved in operational research have begun to apply the theories, tools and concepts of economics to health and healthcare, and thus the discipline ‘economic evaluation in medicine’ has developed.
4. Purchasers of healthcare are increasingly requesting proof of the monetary value of competing alternatives, i.e. of different therapy strategies, in order to decide on their reimbursement status. In competitive marketplaces the price of good or services set through the interaction of supply and demand is a factor for scarcity and the price expresses the value for money. Regulated markets such as the health sector are immune to price competition, and price is an indicator of neither scarcity nor value. Therefore, instruments of evaluation are used to determine the value of services, treatments and prevention programmes.
5. An economic evaluation (i.e. cost-benefit-analysis, cost-effectiveness-analysis and cost-utility-analysis) is an analysis of all costs and consequences over a relevant time-period for a particular healthcare intervention. Socioeconomic evaluations can be used to answer a number of important questions and may be of interest to government regulators, reimbursement authorities, payers, patients and providers.
 - Which diagnostic procedure or therapy should be included in the list of services?
 - What effect will the results of a particular medical intervention have on a patient’s quality of life?
 - Which of several alternatives is the most cost-effective?
 - What is the cost per quality year of life saved by using a specific medical intervention?

7.2. When do we need a socioeconomic evaluation?

6. Under what circumstances should a technology, treatment or healthcare programme be the subject of an economic appraisal? The following figure shows a simple decision tool for considering the two main dimensions of a potential evaluation: the costs and the outcome. In circumstances where a drug is more costly and leads to better results, an economic evaluation is advisable. When a medical intervention yielding better outcomes is available at a lower cost, this therapy should be accepted. In contrast, a more costly medical intervention producing less favourable outcomes should be rejected. Economic evaluation may, however, assist in identifying cheaper interventions with worse outcomes, because this will determine the potential for rationalisation within the constraints of an expenditure ceiling.



7.3. Concept of costs and consequences

7. All economic studies investigate the balance between input (the consumption of resources) and outcome (changes in the health status of an individual and/or society).

7.3.1. Costs

8. In decision-making, a prime factor is often the unit price of a treatment or service; economic analyses provide a more comprehensive interpretation of costs. This is accomplished by determining the overall cost of a given diagnostic or therapeutic process from the initiation of diagnosis until a final outcome is achieved. Often the concepts of price and costs are seen as equal. The following equation shows how costs are defined:

$$\text{Costs} = \text{Price} * \text{resource consumption}$$

9. To assess costs, all relevant resources used must first be identified. Second, they have to be quantified in physical units, such as number of days in a medical ward or intensive care unit, and the frequency of diagnostic tests and treatments, number of physician visits, etc. In a last step, the price per resource has to be identified. The perspective from which the study is conducted determines whether charges or acquisition prices will be of interest (Table 7.1). If the chosen perspective is that of a third-party payer, the provider bills the payer for a service or product. If the study is conducted from the provider's perspective, then the hospital purchase price (e.g. for drugs, devices or other healthcare interventions) will be of interest.^[1, 3]

Table 7.1
How perspective determines costs

Societal	All medical and non medical costs Productivity losses Intangible costs
Third party payer	Charges that pertain to reimbursement of providers
Health care provider	Variable costs that influence the expenses of providing health care
Patient	Costs that affect out-of-pocket payments Lost wages
Employer	All insurable direct costs Lost wages

10. The various types of costs can be grouped under the following categories:

- direct medical costs
- direct non-medical costs
- indirect costs.

Direct Medical costs

11. Direct medical costs are defined as costs or resources used for the delivery of medical care and they include costs associated with the following:

- medications
- laboratory tests
- medical supplies
- use of diagnostic equipment (e.g. magnetic resonance imaging and x-ray)
- medical staff time for personnel such as physicians, nurses, pharmacists, physical therapists and laboratory technicians
- room and board (i.e. the cost of supplies, equipment and personnel required for routine patient-related services such as food, laundry, and housekeeping).

12. These are examples of costs that can be directly related to the medical care of a patient. Other costs of operating a hospital or a practice include those for plant maintenance and repairs, utilities, telephones, accounting, legal fees, insurance, taxes, real estate and interest expenses. These costs are difficult to relate to the medical cure of a patient and in general, most economic studies do not incorporate general operating costs into the costs of a given medicine.

Direct Non-Medical Costs

13. Economics literature generally defines direct non-medical costs as out-of-pocket expenses paid by a patient for items outside the healthcare sector. This category includes costs for the following:

- travel to and from the hospital, clinic, or doctor's office
- travel and lodging for family members who live elsewhere
- domestic help or home nursing service
- patients' out-of pocket expenses

14. Although these costs are generally classified as ‘non-medical’ because they are not directly incurred by the healthcare provider and are somewhat difficult to measure, they represent both real and often substantial medical-care costs for a patient. For example, a patient’s inability to afford competent follow-up care at home may result in poor compliance with drug therapies and eventual treatment failure. This may lead to additional hospital stays or office visits, and could affect the final cost to the provider. High transportation costs may lead to a patient missing appointments for necessary follow-up visits, which can result in the deterioration of a patient’s medical condition and increased treatment costs for the provider. Therefore, even though these costs may not be directly incurred by the provider, it is important that the provider is made aware of their potential economic impact. It may also be possible to use these costs to encourage payers (e.g. employers, insurance companies) to discuss with the healthcare provider the use of a more cost-effective test or therapy.

Indirect Costs

15. Indirect costs are defined as costs of reduced or lost productivity due to morbidity or premature mortality. These include:
- loss of earnings due to temporary, partial, or permanent disability;
 - loss of income and productivity to family members who forfeit paid employment in order to remain at home to care for a patient;
 - loss of productivity to employers and society.

Opportunity Costs

16. Health economists recommend, whenever possible, that opportunity costs should be calculated (i) because market prices often do not indicate the real value of medical interventions, and (ii) because allocating resources to one health programme means sacrificing the benefit that the resources might have produced in another programme. Opportunity costs estimate the value of forgone benefits because a healthcare resource is not available for its best alternative use.^[6]

7.3.2. Consequences

17. Monetary consequences can be divided into the subgroups described previously: direct medical, direct non-medical and indirect consequences. Non-monetary consequences include medical parameters, i.e. blood pressure, blood glucose levels or outcome parameters. Outcome measures include objective measures of morbidity, health status, mortality, and of a patient’s perception of quality of life and satisfaction. The use of outcomes research represents an important advance in medical economic analysis because of the relationship between the final health status of the patient or the result of diagnosis and therapy and overall cost effectiveness. *Outcomes and effectiveness* research is focusing on the evaluation of services and products not with the means of a controlled, randomised clinical trial, but rather by analysing the effectiveness in a practical setting i.e. in observational studies. Demonstration of effectiveness requires evidence that the clinical strategy does more good than harm when used in the specific clinical setting applicable to an individual patient. Efficacy implies that the clinical strategies can achieve their goals of improving outcomes in optimal circumstances. But the effectiveness is the only real basis for making rational long-term funding decisions in health care delivery.

7.3.3. Discounting

18. Because of their different time-frames, costs and effects should be discounted so that a direct comparison can be made between different time-periods. Discounting is a technique that allows a comparison of costs and benefits occurring at different times. This is particularly important in healthcare, where costs often occur immediately, while benefits may occur at a later stage (e.g. prevented complications due to an avoided infection). Discounting is not a correction for inflation. Rather, it reflects time preference (i.e. individuals prefer to have benefits today rather than in the future) and the opportunity cost of capital (i.e. the returns that could be earned if the resources were invested in alternative programmes).
19. The discounting of health benefits is controversial. For practical purposes, many economic evaluations will present results both with costs and benefits discounted and not discounted^[9]. Also, the discount rate is quite variable in economic evaluations. Table 7.2. provides the recommendations of published guidelines on economic evaluation studies. The chosen discount rate, the time horizon, as well as the decision of whether to discount benefits at all, will greatly influence the results of an economic evaluation.^[15] Sensitivity analysis using different discount rates is a common approach.

Table 7.2
Discount rate for different countries

Country	Discount-rate
Australia [12]	5%
Canada [15]	5%
Ontario [11]	5%
England [6]	6% ¹
Germany (Hannover Guidelines) [8]	5%
USA (US Panel on Cost-Effectiveness in Health and Medicine) [7]	3%

7.4. Marginal and Incremental Costs

20. Consideration of average costs generally leads to incorrect interpretations. Marginal and incremental analyses identify where additional resources should be targeted, where reductions should be made if expenditures must be cut, and how resources can be reallocated to achieve an overall gain in health benefit with no overall change in expenditure. Marginal costs are the costs of producing one extra unit of a healthcare intervention. However, for practical purposes, marginal costs often refer to the cost of producing the next logical batch of output, rather than just 1 extra unit. Important issues that can be addressed with marginal and incremental analyses include defining the most appropriate patient population and the optimal duration of treatment for a drug or technology or health care programme.

¹ The currently treasury rate.

7.5. Externalities

21. Externalities (external influences) or spillover effects occur when healthcare programmes or medical interventions inflict costs on, or deliver benefits to, individuals who did not pay for them. For example, the avoidance of infections exert positive external influences because individuals will not infect other individuals. An example of a negative spillover effect is the development of antibiotic resistance as a result of the inappropriate prescribing of antibiotics.

7.6. Conclusion

22. The reality of scarce healthcare resources puts immense pressure on medical decision-makers to examine additional criteria in deciding whether and when to use and pay for medical interventions. The initial response to the problem of limited resources in Europe was healthcare rationing through political cost-containment programmes. In most European countries, this behaviour yielded a very short term success and, in less than 5 years, these efforts were nullified. For a long time, socioeconomic evaluations that pursued rational strategies were viewed negatively, since they were regarded as simply marketing instruments for the pharmaceutical industry. One reason for this was that the methods used in many published economics studies were neither transparent nor validated. For some years, politicians, medical decision-makers and administrators showed a growing interest in studies using a global economic and clinical approach, i.e. studies that combine efficiency, safety and effectiveness parameters. Socioeconomic evaluations are currently based on these key parameters, and socioeconomic studies are now published in reputable medical journals. Indeed, it has become acceptable to add economic dimensions to large clinical trials.^[3] With these kinds of studies, innovative interventions can be assessed in terms of their incremental and marginal costs, and inappropriate and obsolete therapies, preventive strategies or diagnostic options can also be identified.
23. Results from socioeconomic studies cannot be used as an absolute criterion on which to base decisions. Economic data should be assessed on the basis of relative value for money in order to guarantee an appropriate allocation of resources. Therefore, in recent years comparisons between healthcare interventions in terms of their relative cost effectiveness per life-year saved or per quality-adjusted life-year gained have become fashionable. However, to avoid unthinking decisions, a certain homogeneity in study concepts and methods must be guaranteed. The concepts presented above are already fixed components of published guidelines^[10-12, 14, 17, 18] and need to be considered when conducting a socioeconomic analysis. Finally, there need to be guarantees that appropriate comparisons will be made. An understanding of these key concepts, as well as the relevance and integrity of economic data will contribute greatly to the overall effort of socioeconomic analyses to determine the optimal allocation of resources.

7.7. Glossary: Health Economics

(Source *International Society for Pharmacoeconomics and Outcomes Research: ISPOR-Lexicon, 1st Edition, ISPOR, 20 Nassau Street, Suite 307, Princeton, NJ 08542*)

ACQUISITION COST

Purchase price of a drug, device, or other healthcare intervention to an institution or a person. Acquisition cost for the same product or service typically varies depending on the purchaser and arrangements made between the manufacturer or provider of the service and the ultimate practitioner who delivers or provides the product to the patient.

ANCILLARY COST

Fee associated with additional service performed prior to and/or secondary to significant procedure, such as lab work, x-ray and anaesthesia.

AVERAGE COST

Total cost of healthcare intervention provided divided by the total quantity of the intervention (i.e. product or service) provided.

AVERTED COST

Financial outlay (for resource utilisation) avoided by using an alternative healthcare intervention, typically compared to standard care.

CAPITAL COST

The cost attributable specifically to the capital used in the production of goods and services.

CLINICAL OUTCOME / CLINICAL ENDPOINT

Consequence of the use of healthcare products, services or programmes that affect patients' clinical well-being.

COST

In the most limited sense, expenses incurred in the provision of healthcare products and services. More broadly, the sacrifice of alternative benefits made when a given resource is consumed (or healthcare intervention is used) in a given clinical situation.

COST-BENEFIT-ANALYSIS

An analytical technique that enumerates and compares the net costs of a healthcare intervention with the net benefits, or cost savings, that arise as a consequence of applying that intervention. Results of both the costs and the health outcomes are expressed entirely in monetary units. A key disadvantage of this type of analysis is the difficulty of converting or translating non-monetary clinical and quality of life outcomes, such as lives or years of life saved, into financial units.

COST-BENEFIT-RATIO

The ratio of the total monetary cost of a programme divided by the benefits as monetary savings in projected expenditure

COST-EFFECTIVE

A healthcare product or service is cost-effective when, compared to alternatives, it requires relatively fewer resource inputs for the same unit of output.

COST-EFFECTIVENESS-ANALYSIS

The cost of attaining a unit of health effect, commonly expressed in marginal terms. Therefore, the numerator is the change (or difference) in resource use measured in monetary terms (i.e. the cost) of the healthcare intervention compared to its alternative, while the denominator is the change (or

difference) in health effect (i.e. clinical or quality of life outcome), measured in natural units, due to the intervention compared to its alternative.

COST-UTILITY ANALYSIS

A form of cost-effectiveness-analysis in which values are assigned to different kinds of health outcomes, reflecting the relative importance of the different kinds of health outcomes to people, and results are expressed in units such as cost per quality adjusted life-year (QUALY). Expressing results in this way facilitates comparisons across health care interventions with very different effects, for example saving lives versus reducing disability. The values may be obtained either from persons with the disease in question and presumably eligible for the healthcare intervention, or from the general population.

DIRECT MEDICAL COST

Fixed and variable costs associated directly with a medical condition or healthcare intervention. These include the costs of services and products used in the care of the patient, and may include expenditures for: hospital stays, physician and other health professional visits or encounters, emergency department visits, home health care visits, prescribed medicines, and medical equipment and supplies.

DIRECT NON-MEDICAL COST

The cost of providing to the patient all non-medical assistance, food, lodging and transportation because of the illness or healthcare intervention.

ECONOMIC OUTCOME

Financial consequence, due to medical or non-medical resource utilisation and the inability to the use of resources for other useful purposes, that results from the choice of a particular healthcare intervention, such as a drug, device, procedure, service or programme. Also known as a cost-outcome.

ECONOMIC OUTCOME ANALYSIS

The analysis of the inputs and consequences of a health care intervention, such as a drug, device, procedure, service or programme usually relative to alternatives. Also known as an economic evaluation.

EFFECTIVENESS

The degree to which a therapeutic outcome is achieved in a general patient population from a medical technology applied for a given medical problem under actual or average conditions of use. Alternatively, the probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under average or actual conditions of use.

EFFICACY

The degree to which a therapeutic outcome is achieved in a general patient population under rigorously controlled and monitored circumstances, such as randomised clinical trials. Alternatively, the probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use. Efficacy is generally evaluated in controlled trials of an experimental therapy and a control therapy, and is the standard for drug approval by regulatory authorities.

EFFICACY VERSUS EFFECTIVENESS

The choice of whether to evaluate use of a technology in an ideal manner (i.e., in a rigorously defined patient cohort being treated in a specified type of clinical setting) versus in „typical“ or ‘average’ circumstances (i.e., among typical patients in standard practice across a variety of clinical settings). Simplistically, efficacy outcomes are meaningful to the FDA when assessing the value of a product for approval, while effectiveness outcomes are typically useful to healthcare providers and payers (i.e. the marketplace) when assessing the technology’s value for standard use and coverage.

EFFICACY

The degree to which a therapeutic outcome is achieved in a patient population under rigorously controlled and monitored circumstances, such as randomised controlled clinical trials.

FIXED COST

A cost which does not vary with quantity or volume of output provided in the short run (typically, within one year). These costs usually vary with time, but not with quantity or volume of service provided, and may include rent, equipment lease payments and some wages and salaries.

HEALTH OUTCOME

Ambiguous term with multiple possible meanings. The more limited definition includes quality of life factors (i.e. symptoms such as back pain, dispense, blindness) that the patient perceives. A broader definition also includes clinical endpoints (e.g. blood pressure, blood glucose level, etc.).

INCREMENTAL COST

The additional cost that one healthcare product or service imposes relative to a competitive intervention compared with the additional benefits it provides.

INDIRECT COST

Cost of lost or reduced productivity resulting from morbidity or premature mortality due to a medical condition or treatment, as well as informal care-giving costs. Morbidity costs include goods and services not produced by the patient because of the illness. Mortality costs include goods and services the person could have produced had the illness not been incurred and the person not died prematurely. The third aspect of indirect cost relates to lost productivity incurred by an employee (and his/her employer) who leaves work to provide care for the patient, usually a family member. Also known as productivity cost.

INTANGIBLE COST

Costs assigned to amount of suffering that occurs because of the disease or healthcare intervention. Increasingly these are being included in utility assessments.

INTENTION-TO-TREAT OR AS TREATED

Placement and analysis of patients in the cohort of origin (i.e. intention-to-treat, or intent-to-treat) versus their placement and analysis in a separate cohort of those who received whatever their particular mix of therapies was. Intent-to-treat also refers to inclusion in an analysis of all patients randomised.

INTERMEDIATE OUTCOME / ENDPOINT

Outcome that can be measured in the short-term (e.g., laboratory value or vital sign), which suggests but does not directly measure ultimate outcomes. Alternatively an outcome that cannot be perceived by the patient (e.g. cholesterol level, blood pressure), but that is often associated with a precursor to such a health outcome. Also known as surrogate outcome/endpoint.

MARGINAL COST

The extra cost of producing one extra unit of a healthcare intervention. For example, the additional cost of a healthcare provider doing ten MRI screenings instead of nine on a given day.

MEASUREMENT AND MODELING

Alternative analytical approaches to determine outcomes. Proponents of „measurement“ strategies support using clinical trials to measure effectiveness directly(i.e., effectiveness trials). Proponents of 'modelling' strategies support incorporating the results of clinical trials measuring efficacy into models which then are used to estimate effectiveness. Increasingly, both approaches are used in tandem as part of comprehensive research programmes.

OPPORTUNITY COST

The value of forgone benefits because a healthcare resource is not available for its best alternative use. The value of forgone benefits because a healthcare resource is not available for its next best alternative use.

OUTCOME

Any result or consequence that stems from exposure to a causal factor, such as a preventive or therapeutic health care intervention.

OUT-OF-POCKET COST

The portion of payments paid for by an individual with his or her own money as opposed to the portion paid for by the insurer. Co-payments, deductibles and coinsurance are out-of-pocket costs.

PRIMARY ENDPOINT

The most important outcome measure to be used to evaluate a given health technology. Clinical trial protocols will identify that outcome, and it will be specified to the regulatory authority in advance to the conduct of that trial.

PROTOCOL-INDUCED COST

Additional costs incurred delivering a healthcare intervention due to the inclusion of that activity within a clinical study. These costs are typically not incurred in routine medical practice.

QUALITY OF LIFE (QOL) OUTCOME / ENDPOINT

A consequence of the use of a health care intervention that affects the patients' physical functioning (including extent and severity of symptoms and physical capacity), social functioning (including role function or employment), and/or psychological or emotional functioning or functional status, as well as the patients' perceptions of these.

REFERENCE PRICING

Reimbursement of a class of pharmacologically or therapeutically equivalent drugs according to the price of a single 'reference' drug in the group, which is frequently the least expensive.

TRANSFER PAYMENT

A payment (transfer of money) from one group to another without consumption of any physical resource; not recognised as a cost to society (e.g. taxation).

ULTIMATIVE OUTCOME

Endpoint that is of major long-term significance in evaluating the process of disease or the success of a given health technology. Examples may include survival duration, extent of morbidity, quality of life, or cost of care. Also known as long-term outcome.

VARIABLE COST

Costs that vary with changes in output volume. Examples include drugs, devices, supplies, and procedures provided under a fee-for-service reimbursement system.

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List of Tables

Table 1.1. Selection of recent studies concerning red blood cell transfusion strategies	86
Table 1.2. Selection of recent guidelines on red blood cell transfusion.....	88
Table 2.1. Selection of recent studies investigating different platelet transfusion triggers.....	97
Table 2.2. Selection of recent guidelines and consensus statements for platelet transfusion.....	99
Table 3.1. Selection of recent studies with surgical setting, albumin vs no albumin.....	105
Table 3.2. Selection of recent studies with surgical setting, crystalloid vs colloid	106
Table 3.3. Randomised, double-blind study of intravenous albumin administration vs placebo in hypoalbuminemic patients receiving parenteral nutrition.....	107
Table 3.4. Selection of studies investigating the effect of albumin administration..... within different clinical settings in children and infants.....	108
Table 3.5. Trials reviewed in the retrospective meta-analysis of the Cochrane Injuries Group.....	110
Table 3.6. Selection of guidelines and recommendations for the use of albumin.....	113
Table 4.1. Selection of clinical studies evaluating the use of fresh-frozen plasma for different settings	119
Table 4.2. Guidelines for the use of fresh frozen plasma 1998.....	121
Table 4.3. Guidelines for the use of fresh frozen plasma 1996.....	122
Table 4.4. Guidelines for the use of fresh frozen plasma 1995.....	123
Table 4.5. Guidelines for the use of fresh frozen plasma 1992.....	124
Table 5.1. Factor Concentrates: Choice of Concentrate according to National Treatment Guidelines	128
Table 5.2. Factor Concentrates: Indications for continuous infusion.....	131
Table 5.3. Factor Concentrates: Continuous infusion treatment regimens.....	132
Table 5.4. Factor Concentrates: Recommendations for the treatment of acute bleeding in patients with inhibitors.....	135
Table 5.5. Factor Concentrates: Indications for immunoadsorption in patients with inhibitor	135
Table 5.6. Factor Concentrates: Immune tolerance treatment regimens	137
Table 5.7. Factor Concentrates: Product / treatment material use in general.....	138
Table 5.8. Factor Concentrates: Long-term prophylaxis.....	139
Table 5.9. Factor Concentrates: Short-term prophylaxis.....	140
Table 5.10. Factor Concentrates: Self-treatment at home	141
Table 6.1. Most important quality criteria of clinical guidelines	146
Table 6.2. Grading of evidence as proposed by U.S. Preventive Services Task Force	146
Table 6.3. Grading of evidence as proposed by the Scottish Intercollegiate Guidelines Network	147
Table 6.4. Central versus decentral development of clinical guidelines	148
Table 7.1. How perspective determines costs	153
Table 7.2. Discount rate for different countries	155