Clinical Aspects of Blood Transfusion and Plasma Protein Therapies

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Agenda

- Introduction (Blood components and safety)
- Transfusion of Red Blood Cells and “Patient Blood Management” (PBM)
- Transfusion of platelet concentrates and some Swiss peculiarities
- Transfusion of plasma
- Treatment with plasma proteins – short overview and some examples
- Closing remarks
One of the first documented transfusions, Bellevue Hospital, New York, 1876
Donor Components:
- Red Blood Cells
- Platelets
- Plasma / -factors
- (Stem-) Cell products

Patient Conditions:
- Anemia
- Low count / dysfunction
- Coagulopathy

Therapeutic Apheresis:
- SC-TX / Cell-therapy

Safety, Availability, Compatibility, Optimal Use

Clinical Blood Transfusion & Plasma Protein Therapies / B. Mansouri Taleghani
Some Definitions First…

- **BLOOD PRODUCT**
  Any therapeutic substance prepared from human blood

- **WHOLE BLOOD**
  Unseparated blood collected into an approved container containing an anticoagulant preservative solution

- **BLOOD COMPONENT**
  A constituent separated from whole blood, mainly
  - Red cell concentrate
  - Platelet concentrate
  - Plasma
Prerequisites of Blood Transfusion and Blood Component Therapies

- Availability of different blood components
- Components used separately or in combination can meet most patients’ specific needs and keep the risk of treatment to minimum
Separation of blood components are desirable because it allows ...

- Optimal survival for each component
- Transfusing specific blood components according to the need of the patient
- Avoiding unnecessary components, which may be contraindicated in a patient
- To treat several patients from one unit of donated blood
- To supplement blood supply and add to the blood inventory
Blood Donation and Component Preparation

www.blutspende.ch

www.baxter.de/presseforum
Blood constituents (plasma, cells) show differences in size and density.
Principles of Transfusion Therapy

- Transfusion of individually needed blood components
- Carefully weighing up benefits and risks
Blood Safety = Process safety, not only a product safety!

Transfusion Chain

- donor acquisition
- blood donation
- donor screening
- product manufacturing
- product storage
- product delivery

- Taking blood sample for pre-transfusion testing
- pre-transfusion testing
- delivery

- indication to transfuse
- medication

- Evaluation effect
- Follow-up patient

- reception & handling
- controlling BP & pat ID
- Transfusion of BP
- Monitoring of patient

Blood Donation Service ↔ IH-laboratory ↔ Nursing staff ↔ Doctor
FVP: Fachtechnisch verantwortliche Person
HVP: Hämovigilanz-verantwortliche Person
BMA: Biomedizinische Analytiker/in
AKST: Antikörper-Suchtest
Transfusion Safety and Haemovigilance

- Establishment and monitoring of transfusion standards
- Reporting of adverse events (donation → transfusion)
  - Infections (TTI)
  - Immunological side effects
  - Other adverse events
- Evaluation of results
- Implementation of corrective measures
~ 42 Mio Blood units issued in 1996 - 2009
with 6653 Severe Adverse Events

Serious Hazards of Transfusion (= SHOT, UK), Homepage: www.shot.demon.co.uk

Introduction, Blood Safety
## Current estimated residual risk (UK)*

**Frequency for hospitals with \( \approx 20.000 \) transfusions / year**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Residual risk</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>1 : 0.36 Mio</td>
<td>1 / 20 Y</td>
</tr>
<tr>
<td>HCV</td>
<td>1 : 10.8 Mio</td>
<td>1 / 500 Y</td>
</tr>
<tr>
<td>HIV</td>
<td>1 : 4.3 Mio</td>
<td>1 / 200 Y</td>
</tr>
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</table>

*Niederhauser C; personal communication*
Risks of transfusions in CH (2008-13), all BP, grade 3&4

- Total risk of TR: ~1:15'000
- Allergic TR: ~1:30'000
- TACO: ~1:80'000
- TRALI: ~1:300'000
- Acute HTR: ~1:350'000
- Hypotensive TR: ~1:400'000
- Bacterial infection: ~1:400'000
- TAD: ~1:500'000
- Hyperkalemia: ~1:2.5 Mio
- Delayed HTR: ~1:2.5 Mio

Risk of IBCT in 2014:
~1:7’000 transfusions
Adverse effects of RBC transfusion contrasted with other risks

- HIV
- HCV
- HBV
- Life-threatening reaction
- Fatal hemolysis
- TRALI
- TACO
- Fever
- CHD
- Motor vehicle fatalities
- Firearm homicide
- Airplane fatalities
- Fall fatalities
- Lightning fatalities
- Death from medical error


©2012 by American College of Physicians
In the United States, medical error is the third leading cause of death. According to data from 2014, there were approximately 251,000 deaths from medical errors annually, which translates to 1 in 1,271 residents per year.

Data source: http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf

Makary M, Daniel M: Medical error - the third leading cause of death in the US. BMJ 2016;353:1-5
## Specifications of Red Blood Cell (RBC) Units

<table>
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<tr>
<th>RBC out of whole blood donations</th>
<th>RBC out of apheresis blood donations</th>
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<tbody>
<tr>
<td>Whole blood donations → Processing within 48 h</td>
<td>“Online“ collection by cell separators</td>
</tr>
<tr>
<td>Variable Volume 275 ± 75 mL</td>
<td>Standardized: e.g. 275 mL</td>
</tr>
<tr>
<td>Hemoglobin &gt; 40 g/Unit</td>
<td></td>
</tr>
<tr>
<td>Hematocrit 0.6 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Leukocytes &lt; 1 x 10^6</td>
<td></td>
</tr>
<tr>
<td>Storage: 42 - 49 days, 4 ± 2° C;</td>
<td></td>
</tr>
</tbody>
</table>
Rational of RBC Transfusion…

Avoid anaemia induced hypoxemia, in order to

- Reduce anaemia-associated mortality
- Reduce anaemia-associated morbidity
  - Cardiovascular complications
  - Cerebrovascular complications
  - Pulmonary complications
... Therefore the Goal of Blood Transfusion is to

- Improve Tissue Oxygen Delivery
- Avoid Critical Tissue Hypoxia
Determinants of Oxygen Delivery (DO$_2$) to Tissues

- **In Health:**
  - DO$_2$ 2 to 4-fold greater than requirements

- **Determinants of DO$_2$:**
  - Hb level
  - Oxygen saturation
  - Cardiac output
  - Microcirculation
  - Hb O$_2$ release

Hebert PC, CMAJ 1997; Tinmouth et al, Transfusion 2006
Blood use in elective surgery: the Austrian benchmark study

n=2600 TKP & THP; 04/2004 – 02/2005; Transfusion 2007;47:1468-80

![Bar chart showing transfused patients (%) across different hospitals with potential for improvement highlighted.](chart.png)
A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care (TRICC)


- Intensive care patients of 25 Canadian hospitals, 11/94 – 11/97
- Inclusion criteria:
  - Hb ≤ 90 g/L within 72 h of hospitalization
  - Normovolemic

Total patients n = 6451

Randomized n = 838

Restrictive strategy
  n = 420
  Hb ≥ 70 g/L ≤ 90 g/L

  Median RBC 2.6 ± 4.1

Liberal strategy
  n = 418
  Hb ≥ 100 g/L ≤ 120 g/L

  Median RBC 5.6 ± 5.3
The TRICC Trial

liberal transfusion strategy
(Hb 100-120 g/L)

restricted transfusion strategy
(Hb 70-90 g/L)

RBC 2.6 ± 4.1

RBC 5.6 ± 5.3


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RBC Transfusion in Intensive Care

Patients < 55 Y

B

APACHE II <= 20

Restrictive strategy

Liberal strategy

$ p = 0.020$

C

Survival (%)

Restrictive strategy

Liberal strategy

$ p < 0.02$

Time (Days)
“How low can we go”
Mortality rate (% & #) and postop Hb-Nadir

<table>
<thead>
<tr>
<th>Haemoglobin g/L</th>
<th>Carson et al 2002; n=300</th>
<th>Shander et al 2014; n=293</th>
</tr>
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<tbody>
<tr>
<td>7/7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/16</td>
<td></td>
<td></td>
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<tr>
<td>7/10</td>
<td></td>
<td></td>
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<tr>
<td>11/17</td>
<td></td>
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<tr>
<td>5/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/2</td>
<td></td>
<td></td>
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</tbody>
</table>
Randomized Transfusion-Trigger-Studies for RBC (n>40)

TRICC

TRIPICU

Villanueva

FOCUS

TRISS

TRACS

TITRe2

Almeida

MINT

(pilot)

3yr follow up

e etc., etc., ...

Rationale for Transfusion
The conclusion is that **in the majority of clinical settings a restrictive RBC transfusion strategy is cost-effective, reduces the risk of adverse events specific to transfusion, and introduces no harm.**

In anemic patients with **ongoing hemorrhage, with risk of significant bleeding, or concurrent ischemic brain, spinal cord, or myocardium, the optimal hemoglobin transfusion trigger remains unknown.**

Broad-based **adherence to guideline** approaches of therapy **must respect the individual patient condition ...**

RESULTS:

… A Hb level of less than 7 g/dL (intensive care unit patients) or less than 8 g/dL (postoperative patients) were the only thresholds based on high-quality evidence. Only four of 32 recommendations had a high-quality evidence base.

CONCLUSION:

…. More high-quality trials are needed to provide a stronger scientific basis for RBC transfusion guidelines that recommend more restrictive transfusion thresholds.
Data analyzed
31 randomized trials testing “restrictive” (< 70 or 80g/L, sometimes <90) vs. “liberal” transfusion triggers between 1950-2016, involving 12,587 participants

Conclusions
- restrictive transfusion decreased exposure to RBC transfusion by 43%
- restrictive strategy without impact on 30-day mortality or morbidity
- Good evidence that transfusions with allogeneic RBCs can be avoided in most patients with haemoglobin thresholds above 70 g/L to 80 (to 90) g/L
- insufficient data in acute coronary syndrome, myocardial infarction, acute neurological disorders, neurological injury/traumatic brain injury, stroke, thrombocytopenia, solid/hematological malignancies, bone marrow failure


RESULTS: Thirty-one trials …

In patients undergoing cardiac/vascular procedures, restrictive strategies seemed to increase the risk of events reflecting inadequate oxygen supply (risk ratio [RR], 1.09; 95% CI, 0.97 to 1.22), mortality (RR, 1.39; 95% CI, 0.95 to 2.04), and composite events (RR, 1.12; 95% CI, 1.01 to 1.24-3322, 3245, and 3322 patients, respectively).

Similar results were found in elderly orthopedic patients …, but not in critically ill patients. …

CONCLUSIONS:
Restrictive transfusion strategies should be applied with caution in high-risk patients undergoing major surgery.
“The delivery of good medical care is to do as much nothing as possible”

Samuel Shem, M.D., 1978
“Hip”: Patient Blood Management

“The three pillars of PBM”

- Management of Anemia & Coagulation
- Minimizing blood loss
- Improved patient care
- Optimal blood use
PBM – “old fashioned” synonym may be Optimal Hemotherapy & Blood Saving Measures*

- Optimal blood component use (as much as needed / as little as possible)
- If planning elective surgery
  - Treat iron-deficiency ± anemia in advance → iron ± Erythropoetin
  - Treat possible coagulopathies in advance
  - Consider autologous donation ± Erythropoetin
  - (Consider acute normovolemic Hemodilution)
- Optimize surgical techniques → „bloodless surgery“
- Intra-operative blood salvage
- Local and/or systemic measures for improving hemostasis
- Minimizing the volume of withdrawn blood samples (saving blood loss!)
- ...

“Three Pillars of PBM”

1. Pre-operative Management of Anemia & Coagulation
   PBM-ambulatory: Diagnosis and treatment of anemia and coagulopathy in elective surgery (risk of transfusion >10%). Utilization of waiting time until surgery.

2. Optimal Blood Use / Use of RBC
   Adherence to implemented guidelines for transfusion

3. Further Blood Saving Measures
   Restrictive taking of blood samples, blood-less surgery, Cell-Saver, management of body temperature, point-of-care diagnostic, management of coagulation
“Three Pillars of PBM”

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**FINDINGS:** … 227,425 patients, of whom 69,229 (30·44%) had **preoperative anaemia**….  
**INTERPRETATION:** Preoperative anaemia, even to a **mild** degree, is independently **associated** with an increased **risk of 30-day morbidity and mortality** in patients undergoing major non-cardiac surgery.

**FUNDING:** Vifor Pharma.
```
Pre-operative Patient Pathway in PBM

„Non-elective“ Surgery ≤ 4 d

Probability of Transfusion < 10%*

Probability of Transfusion ≥ 10%*

Signs / symptoms of Coagulopathy

*S has to be analyzed for individual hospital

♂ Hb ≥ 130 g/L
♀ Hb ≥ 120 g/L

♂ Hb ≤ 130 g/L
♀ Hb ≤ 120 g/L

Surgery

PBM-Ambulatory

„Elective“ Surgery Planning > 4 (ideally ≥ 14) days
```
Surgical Procedures with Transfusion Probability ≥ 10%
Inselpital 2014

Herz- und Gefäßeingriffe
- Eingriffe an Herz, Perikard, Aorta ± ECC
- Re-Sternotomie, Rethorakotomie
- Transkatheter-Klappenimplantationen
- Aorteneingriffe (offen, endovaskulär)
- Iliaco-femoro-politeale Eingriffe

Orthopädie
- Wirbelsäulen-OP (offen)
- Becken-OP (Prothetik, Osteosynthese, Re-OP)
- Hüft-OP (Prothetik, Osteosynthese, Re-OP)
- Femur- oder Knie-OP (Prothetik, Osteosynthese, Re-OP, Amputation)

Thoraxchirurgie
- Erweiterte Pleuropneumonektomie

Urologie
- Offene Tumorchirurgie der Nieren, Nebennieren
- Radikale Zystektomie
- Blasenersatzplastik
- Suprapubische Prostatektomie

HNO, Schädel-, Gesichts- und Kieferchirurgie
- Free-Flap-Chirurgie großer Tumoren

Säuglings- und Kinderchirurgie
- Skoliose Aufrichtung
- Kraniosynostosen

Viszeralchirurgie
- Lebertransplantation
- Offene Leberteilresektion großer Tumoren
- Resektion großer retroperitonealer Tumoren
- Resektion großer intraperitonealer Tumoren ± intraoperativer Chemotherapie-Perfusion
- Ösophagusresektion

Neurochirurgie
- Tumoren
- Tumoren nahe eloquente Zentren
- Aneurysmen

H.U. Rieder, 15.01.2015; ergänzt / modifiziert B. Eberle 20.9.16
**Surgical Consultation:**
anemia and/or coagulopathy? Transfusion probability ≥ 10%

- **yes**
  - **Patient referred to PBM-Ambulatory**

- **no**

**Pre-operative Administration**

**Anesthesiological Consultation:**
anemia and/or coagulopathy? Transfusion probability ≥ 10%

- **yes**
  - Same day referring to our PBM-ambulatory by the surgeons/anesthetists (beeper PBM-nurse) possible
  - The patient is ideally seen at the PBM-ambulatory on the same day or very contemporary
  - Reporting to referring physicians and involved units
  - In case of follow-on surgeries or multiple surgeries the process starts again from the beginning

- **no**

**Pre-operative surgical consultation**

**Hospital Admission**
“Three Pillars of PBM”

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## Adopted* Recommendations of RBC Transfusions in Normovolemic Surgical Patients

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Compensation capacity risk factors</th>
<th>Transfusion: YES/NO</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 60 g/L (≤ 3,7 mmol/L)</td>
<td>–</td>
<td>YES (exceptions possible)</td>
<td>1 C+</td>
</tr>
<tr>
<td>&gt; 60 – 80 g/L (&gt; 3,7 – 5,0 mmol/L)</td>
<td>Adequate compensation and no risk factors</td>
<td>NO</td>
<td>1 C+</td>
</tr>
<tr>
<td>Reduced compensation risk factors present</td>
<td>YES</td>
<td>1 C+</td>
<td></td>
</tr>
<tr>
<td>Signs and symptoms of anemic hypoxemia</td>
<td>YES</td>
<td>1 C+</td>
<td></td>
</tr>
<tr>
<td>&gt; 80 – 100 g/L (&gt; 5,0 – 6,2 mmol/L)</td>
<td>Signs and symptoms of anemic hypoxemia</td>
<td>YES</td>
<td>2 C</td>
</tr>
<tr>
<td>&gt; 100 g/L (&gt; 6,2 mmol/L)</td>
<td>–</td>
<td>NO (exceptions possible)</td>
<td>1 A</td>
</tr>
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* „Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten; Herausgeber: BÄK; 2017“ (under review)
MANAGEMENT MASSIVER BLUTUNGEN

Diagnostik
- Airway? Breathing? Circulation?
- CT? Sonographie? Angiographie? (Lokalisation identifizieren)
- Hb, Te, Gerinnungsstatus, ROTEM, BGA, ion Co, Lactat
- Koagulopathie? Hypothermie? Azidose?

Persistierend? Ern. Bilgegung?
- Hb, Te, Gerinnungsstatus, ROTEM, BGA, ion Co, Lactat
- Hypothermie? Azidose?

Behandlung
- Antishockie
  - Große ven. Zugänge, 10-15 C2
  - Cyclokapron 1g i.v. 8-stöll, balancierte Kristallsäulen
  - 4 EK, 4 FFP parent
  - RSI-Intubation, Schnelltransfusionsystem, Arterie

Identifizierung behandlbarer Ursachen und sofortige mechanische Kontrolle zugänglicher Blutungsquellen (Kompression, Tourniquet?)

Chirurgie/Interventionen

Sofortige Blutungskontrolle:
- Chirurgie, Interventionelle Radiologie, Endoskopie

Potenzielle Blutungen:
- Cell salvage
  - 4 EK, 4 FFP
  - Cell salvage

Identifizierung behandlbarer Ursachen

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- Hb, Te, Gerinnungsstatus, ROTEM, BGA, ion Co, Lactat
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Priorse Intervention?
- Intravenös? Bikarbonat? Wärme?

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- Hypothermie? Azidose?

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Persistierend? Ern. Bilgegung?
- Hb, Te, Gerinnungsstatus, ROTEM, BGA, ion Co, Lactat
- Hypothermie? Azidose?
Postpartale Hämorrhagie bei vaginaler Geburt

**Geburtsheiler**

- Geburtshilfliche Betreuung
- Tonus (Uterotonika)
- Trauma (insbesondere Geburtswege, Uterusruptur auszuleiten)
- Reflektorische (Uterusflecken)

**Massnahmen**

- Cyclopropan 1 g in 100 ml NaCl i.v. (19)
- Systolen 10-20/20 g im Second, e.g., nicht bei Hypovolämie/Praktikament
- Nadalor 100-500 mg i.v. im Anfall

**Anästhesie**

- Ventil eingesteckt in geöffnete Anschlussstelle
- Oxy 10-20/20 min. Prothesen-Maske

**Volumen/Blutprodukte**

- Voluven > max. 50 ml/kg
- Cyclopropan 1 g/m 10-20/20 min. Prothesen-Maske

**OPS**

- Curettage
- Geburtshilfliche Betreuung
- Blasenruptur
- Geburtshilfliche Betreuung

**Evt. Interventionelle Radiologie im frühen/ersten Stadium**

- Embolisation, z.B. Arteria

**Persistierende Blutung**

- Blutungsstopp, z.B. Membra
- 4 ml Coagulase
- 1, 4 ml Novo Seven
- 1, 4 ml FFP
- 1, 4 ml FFP
- 1, 4 ml FFP

**Volumen/Blutprodukte**

- Volumenverlust max. 50 ml/kg
- Cyclopropan 1 g/m 10-20/20 min. Prothesen-Maske

**Autolog Säuge!!**

**Sedio**

- Blutung...

**Kompression, evtl. Gefäßligaturen**

**Persistierende Blutung**

**Evt. Interventionelle Radiologie**

- Embolisation, z.B. Arteria

**Hysterektomie**

**Persistierende Blutung unter transfusioneller TRANSFUSION**

- Blutungsstopp, z.B. Membra
- 4 ml Coagulase
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**Volumen/Blutprodukte**

- Volumenverlust max. 50 ml/kg
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- 4 ml FFP

**RBC, Patient Blood Management**
“Three Pillars of PBM”

1. **Pre-operative Management of Anemia & Coagulation**
   PBM-ambulatory: Diagnosis and treatment of anemia in elective surgery (risk of transfusion >10%). Utilization of waiting time until surgery.

2. **Optimal Blood Use / Use of RBC**
   Adherence to implemented guidelines for transfusion

3. **Further Blood Saving Measures**
   Restrictive taking of blood samples, blood-less surgery, Cell-Saver, management of body temperature, point-of-care diagnostic, management of coagulation
Hemoglobin of patients in an intensive care unit after cardio-thoracic surgery

![Graph showing hemoglobin levels over time with initial Hb values and RBC transfusions indicated.](image)
Restrictive taking of blood samples

- **Restrictive**
  - Fewer blood samples taken.
  - Reduced blood usage.

- **Standard**
  - More frequent blood samples.
  - Increased blood usage.

Comparative diagram showing the number of blood samples taken over time, highlighting the difference in blood usage between restrictive and standard practices.
First multi-center, prospective study of PBM


**RESULTS:** A total of 129,719 patients discharged between July 2012 and June 2015 with different inclusion periods for pre-PBM (54,513 patients) and PBM (75,206 patients) were analyzed. … **The non-inferiority aim was achieved (P < 0.001).** Incidence of acute renal failure decreased in the PBM cohort (2.39% vs 1.67%; P < 0.001, regression model). The mean number of red blood cell transfused per patient was reduced from 1.210.05 to 1.000.05 (relative change by 17%, P < 0.001). *(But cave at: On average a comparable reduction was also observed in all other regions of Germany)*

**CONCLUSIONS:** The data presented show that implementation of PBM with a more conscious handling of transfusion practice can be achieved even in large hospitals without impairment of patient’s safety. Further studies should elucidate which PBM measures are most clinically and cost effective.
Development of RBC-Transfusion in Switzerland

*(Delivered! units to hospitals)*
Development of RBC-Transfusion per 1000 inhabitants in 9 European Countries

-15%
-31.5%
“Platelets on tour”

Circulation of the donor

Donation: extracorporeal circulation / centrifugation

Pathogen reduction, storage, ...

Transportation

Transfusion

Foreign / harmful (!?) circulation of the recipient

(Antibodies, drugs, toxins, …)
Platelet products in Switzerland

- Apheresis platelet concentrates (APC):
  Collection using blood cell separators
  → single-donor platelets

- Buffy coat / PRP platelet concentrates:
  Preparation of buffy coat or PRP from pooled ABO/Rh-identical whole blood donations (4 – 6)
  → multi-donor platelets
Pathogen Reduction by INTERCEPT: Mechanism of Action

- **Amotosalen**
- **Targeting**
- **Intercalation**
- **Crosslinking**
- **UVA Illumination**

Helical region of single- or double-stranded DNA or RNA.

Amotosalen

NH₂
The "new" Swiss PLT Unit*

*Starting in 2011 - reaching 80% in 2011 and 100% since 11/2011

- > 2.4x10^{11} / unit
- Pathogen reduced
- Intersol or SSP+
- 7 day storage
- Apheresis or pooled BC
Development of PC-Transfusion in Switzerland

(Delivered! units to hospitals)
Development of PLT-Transfusion per 1000 inhabitants in 8 European Countries

- CH: 81.7%
- MW: 21%

### Platelet transfusion: aims

<table>
<thead>
<tr>
<th>Treat active bleeding</th>
<th>Prevent bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic</strong></td>
<td><strong>Prophylactic</strong></td>
</tr>
<tr>
<td>Prove of effectiveness:</td>
<td>Prove of effectiveness:</td>
</tr>
<tr>
<td>Stop of bleeding</td>
<td>(?)</td>
</tr>
</tbody>
</table>
Why we transfuse PLT

Platelet transfusion: a systematic review of the clinical evidence


Key results

- ... **RCTs** (n=17) showed a **beneficial effect of prophylactic compared with therapeutic transfusion** for the prevention of significant bleeding in ... hematologic disorders undergoing chemotherapy or stem cell Tx.

- ...no difference in significant bleeding events related to the PLT count threshold for transfusion or the dose of PLTs transfused.

- Overall **methodologic quality of RCTs was moderate**.

- ... **observational studies** (n=55) ... no evidence that PLT transfusion prevented significant bleeding in patients undergoing central venous catheter insertions, lumbar puncture, or other surgical procedures.

- The methodologic **quality of observational studies was very low**.
Therapeutic vs prophylactic platelet transfusion

Crighton GL et al: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst Rev. 2015 Sep 30;(9):CD010981

Key results
- Giving platelet transfusions to prevent and treat bleeding in patients with low platelet counts due to blood cancers or their treatments may result in a reduction in bleeding when compared with giving platelet transfusions only to treat bleeding.
- There may not be an increased risk of death or adverse events if platelet transfusions are only given to treat bleeding versus giving platelet transfusions to prevent and treat bleeding, but there was not enough evidence to be certain about this.
- Giving platelet transfusions only when bleeding occurs probably reduces the number of platelets given.
- None of the six studies reported any quality-of-life outcomes.

**Recommendation 1:** (Grade: strong recommendation; moderate-quality evidence)

- PLT should be transfused prophylactically to reduce the risk for spontaneous bleeding in hospitalized adult patients with therapy induced hypo-proliferative thrombocytopenia with a platelet count of ≤ 10 G/L
- Transfusing up to a single apheresis unit or equivalent per episode … greater doses are not more effective

**Recommendation 2:** (Grade: weak recommendation; low-quality evidence)

- Prophylactic PLT transfusion for patients having elective central venous catheter placement with a platelet count less than 20 G/L.

**Recommendation 3:** (Grade: weak recommendation; very-low-quality evidence)

- Prophylactic PLT transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than 50 G/L.

Recommendation 4: (Grade: weak recommendation; very-low-quality evidence)
… prophylactic PLT transfusion for patients having major elective non-neuraxial surgery with a platelet count less than 50 G/L.

Recommendation 5: (Grade: weak recommendation; very-low-quality evidence)
… against routine prophylactic platelet transfusion for patients who are non-thrombocytopenic and have cardiac surgery with cardiopulmonary bypass. The AABB suggests PLT transfusion for patients having bypass who exhibit perioperative bleeding with thrombocytopenia and/or evidence of PLT dysfunction.

Recommendation 6: (Grade: uncertain recommendation; very-low-quality evidence)
… cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous).
"The art of platelet transfusion"

"He who feels confident that he has a thorough understanding of platelet transfusion is confused."


“PLT transfusion practices are being questioned more than ever before. As we develop better therapies & guidelines, the practice of PLT therapy can be expected to change in the near future."

Kyle Annena, and Jordan E. Olson; Curr Opinion Hematology 2015;22:559-564
Plasma Products for Transfusion

- Quarantine storage, second testing after ≥ 4 months (q-FFP)
- Solvent/Detergent treated (out of plasma-pools, e.g. Octaplas®)
- Amotosalen treated (single donor / small pools, 2014 CH-approval)
- Untreated and not quarantine stored (not available in CH)
- Methylene-blue treated (single donor plasma, not available in CH)
Development of Plasma-Transfusion in Switzerland

*(Delivered! units to hospitals)*

![Graph showing the development of plasma-transfusion in Switzerland from 2003 to 2015.](image)
Development of Plasma-Transfusion per 1000 inhabitants in 8 European Countries

-61.3%

-3%


1
2
3
4
5
6
7

CH
MW
When to Transfuse FFP

In case of an insufficient coagulation potential

Prophylactic

In bleedings
Plasma and Plasma Protein Product Transfusion: A Canadian Blood Services Centre for Innovation Symposium


Highlights

- Plasma is usually transfused to prevent or reduce bleeding, but evidence of benefit of plasma transfusion is scant.
- The use of plasma before invasive procedures, the clinical benefit of prothrombin complex concentrates & the optimal ratio of plasma to red blood cells during massive transfusion remain areas of controversy.
- In Canada, plasma use has declined more than 30% since 2004, whereas prothrombin complex concentrate utilization has climbed.
- Next-generation factor VIII or factor IX products may revolutionize care in hemophilia.
- Optimal plasma utilization remains a challenge in the interconnected worlds of transfusable plasma, plasma protein products & recombinants.
"The art of plasma transfusion"

"He who feels confident that he has a thorough understanding of platelet transfusion is confused."


"The sentiment could be equally applied to plasma transfusion therapy with a disturbing degree of accuracy."

Triulzi DJ. The art of plasma transfusion therapy. Transfusion 2006;46:1268-1270

"Optimal plasma utilization remains a challenge in the interconnected worlds of transfusable plasma, plasma protein products & recombinants."

## Plasma Protein Products I

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Conditions Treated</th>
<th>Treatment Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coagulation factors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential for blood clotting, used to treat genetic bleeding disorders and surgical bleeding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>➢ <em>Bleeding from trauma</em></td>
<td>Improves quality of life and life expectancy</td>
</tr>
<tr>
<td></td>
<td>➢ <em>Over dosage of anticoagulants</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>➢ <em>Liver disease</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>➢ <em>Bleeding Disorders</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>➢ <em>Hemophilia A and B</em> – Disorders that prohibit a person's blood from clotting.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>➢ <em>Von Willebrand disease</em> – The most common inherited bleeding disorder.</td>
<td></td>
</tr>
</tbody>
</table>

http://www.pptaglobal.org/plasma-protein-therapies/therapies
## Plasma Protein Products II

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Conditions Treated</th>
<th>Treatment Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulins:</td>
<td><strong>Immunodeficiencies:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Primary</em> - Life threatening genetic defect of immune system.</td>
<td>Improved quality of life and life expectancy</td>
</tr>
<tr>
<td></td>
<td><em>Secondary</em> - Caused by outside factors such as viruses, chemotherapy, etc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Autoimmune disorders:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Chronic Inflammatory Demyelinating Polyneuropathy</em> (CIDP) – *(Auto-)*immune disorder of the peripheral nerves.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Idiopathic Thrombocytopenic Purpura (ITP)</em> - *(Auto-)*immune bleeding disorder in which the immune system destroys platelets,</td>
<td></td>
</tr>
</tbody>
</table>

In primary and secondary immunodeficiencies and autoimmune disorders.

http://www.pptaglobal.org/plasma-protein-therapies/therapies
## Plasma Protein Products III

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Conditions Treated</th>
<th>Treatment Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperimmune Globulins:</strong></td>
<td>Rabies, tetanus and hepatitis</td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td>Rh negative pregnancy</td>
<td>Treatment</td>
</tr>
<tr>
<td></td>
<td>Liver transplant and surgery</td>
<td>Protection of fetus</td>
</tr>
<tr>
<td><strong>Alpha-1 Proteinase Inhibitors:</strong></td>
<td>Alpha-1 Antitrypsin Deficiency - Genetic deficiency which may result in life-threatening lung disease in adults and/or liver disease in people of any age.</td>
<td>Improved quality of life Halts progression</td>
</tr>
<tr>
<td></td>
<td>Protects tissues from enzymes of inflammatory cells.</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>Conditions Treated</td>
<td>Treatment Outcomes</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Albumin:** The major plasma protein, regulating blood volume and providing many essential functions. | **Cardiac surgery**  
**Liver disease**  
**Severe infections**  
**Emergency and Surgical Medicine** - Used to treat shock, severe burns and during surgery | Life-saving in severe situations  
Decreased morbidity and mortality |
| **C1-esterase inhibitor (C1-INH):** A blood protein controlling a protein called C1, which is part of the complement system. | **Hereditary angioedema** – Rare but potentially life-threatening condition characterized by acute attacks of usually non-itching edema (swelling) of the face, larynx (airway), abdomen and extremities. | Improved quality of life  
Increased life expectancy |

http://www.pptaglobal.org/plasma-protein-therapies/therapies
Many thanks to…
• Markus Müller, Frankfurt
• Markus Jutzi, Bern
• Balthasar Eberle, Bern
• Transfusion Committee, Insel Gruppe
• …

And to all of you for your attention
‘We’re still confused, but on a higher level.’

Enrico Fermi
* 29.09.1901 Rom, † 28.11.1954
1938 Nobelpreis für Physik
5 Key Questions

- What are the common kinds of blood donation and products?
- When do you transfuse RBC?
- When do you transfuse PLT?
- When do you transfuse plasma?
- What do you know about adverse events, safety and haemovigilance in blood transfusion?