EDQM Blood Conference
Innovation in Blood Establishment Processes

14-15 January 2025
Strasbourg, France

Session B1 (part 2):
Innovative & novel blood components
(15:30 – 17:00)

Moderators: **Peter O'Leary**, European Blood Alliance, Belgium
Richard Forde, CD-P-TS Secretary, EDQM

Speakers: **Torunn Oveland Apelseth**, Department of Immunology and Transfusion Medicine, Haukeland University Hospital & Faculty of Medicine, University of Bergen, Norway
Thibaut Bocquet, Établissement Français du Sang, France
Beatrice Hechler, University of Strasbourg, Établissement Français du Sang, France
Jens Altrichter, ARTCLINE GmbH, Germany

Please note:
- *Food and drink are not permitted in the conference rooms*
- *Photography & filming during the presentations are strictly forbidden*
- *Photos and videos may only be taken by Council of Europe staff members*
- *The session will be recorded for internal purposes only*

Implementation of a Whole Blood program for treatment of patients with massive haemorrhage – a practical guideline for blood providers

Torunn Oveland Apelseth, MD PhD

Norwegian Centre for Blood Preparedness, Department for Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway;

Faculty of Medicine, University of Bergen

Disclosures

I have no conflict of interest in relation to this congress or this presentation

Nokblod

The Norwegian Center for Blood Preparedness

Government funded center for national coordination of Civilian-Military blood preparedness in Norway
Established June 2022

Stakeholders represented:

- Civilian blood services
- Clinical hospital services
- Prehospital and community health services
- Military medical services

Work tasks:

- Coordination of civilian and military blood supply in crisis and war
- Training
- Counselling
- Logistics
- Research and innovation

Authors

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11. European Blood Alliance, Brussels, Belgium
12. NHS Blood and Transplant, Cambridge, UK
13. The Blood Bank, Landspitali University Hospital, Reykjavik, Iceland
14. Reykjavik University, Reykjavik, Iceland

EUROPEAN BLOOD ALLIANCE

INNOVATION AND NEW PRODUCTS WORKING GROUP

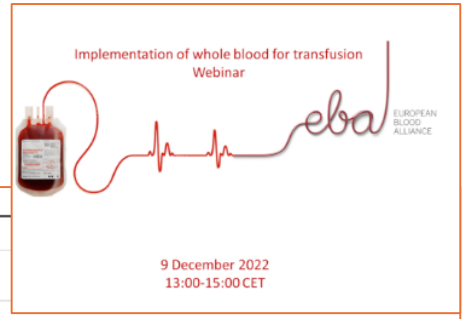
Overview of presentation

- Background and aim
- Definition
- Implementation of a Whole Blood Program:
  - Donor Selection
  - Collection and production
  - Storage and transport
  - Validation, quality control, post-implementation follow-up
  - Inventory management
  - Emergency preparedness.
- Conclusion

Whole Blood = Red Blood Cells, Plasma and Platelets in a physiological (1:1:1) ratio:

Background

- Shift in resuscitation strategy for patients with severe bleeding, moving from a clear fluid-based to a blood-based resuscitation strategy
- Civilian and military guidelines recommend early balanced transfusion to patients with major haemorrhage
- Whole Blood has been reintroduced as a logistically feasible alternative to blood components
- In a previous survey, the European Blood Alliance (EBA) Working Group on Innovation and New Blood Products have identified an interest from the European Blood Services in implementation of WB programs



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DOI: 10.1111/trf.17349

MAJOR HEMORRHAGE

TRANSFUSION

Current transfusion practice and need for new blood products to ensure blood supply for patients with major hemorrhage in Europe

Torunn Oveland Apelseth[1,2,3] | Barry Doyle[4] | Ryan Evans[5] | Chloe George[6] | Catherine Humbrecht[7] | Thomas Klei[8] | Tome Najdovski[9] | Ólafur Eysteinn Sigurjónsson[10,11] | Michael Wiltshire[12] | Dirk de Korte[8,13]

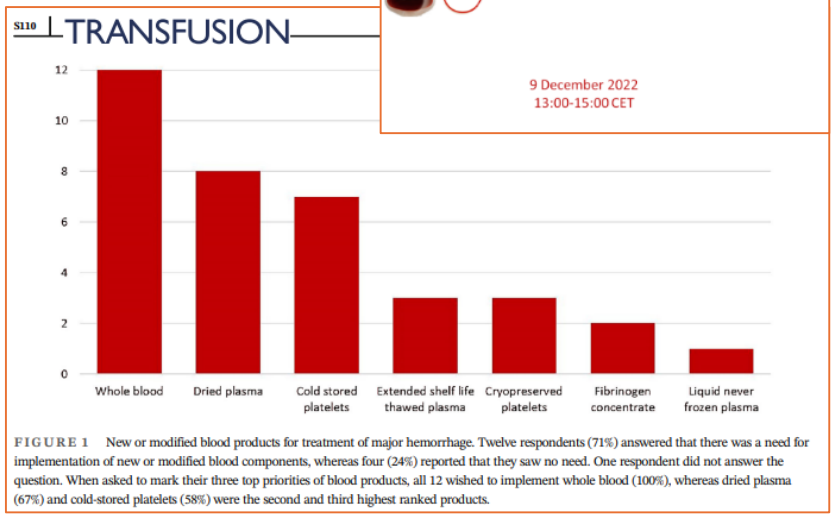


FIGURE 1 New or modified blood products for treatment of major hemorrhage. Twelve respondents (71%) answered that there was a need for implementation of new or modified blood components, whereas four (24%) reported that they saw no need. One respondent did not answer the question. When asked to mark their three top priorities of blood products, all 12 wished to implement whole blood (100%), whereas dried plasma (67%) and cold-stored platelets (58%) were the second and third highest ranked products.

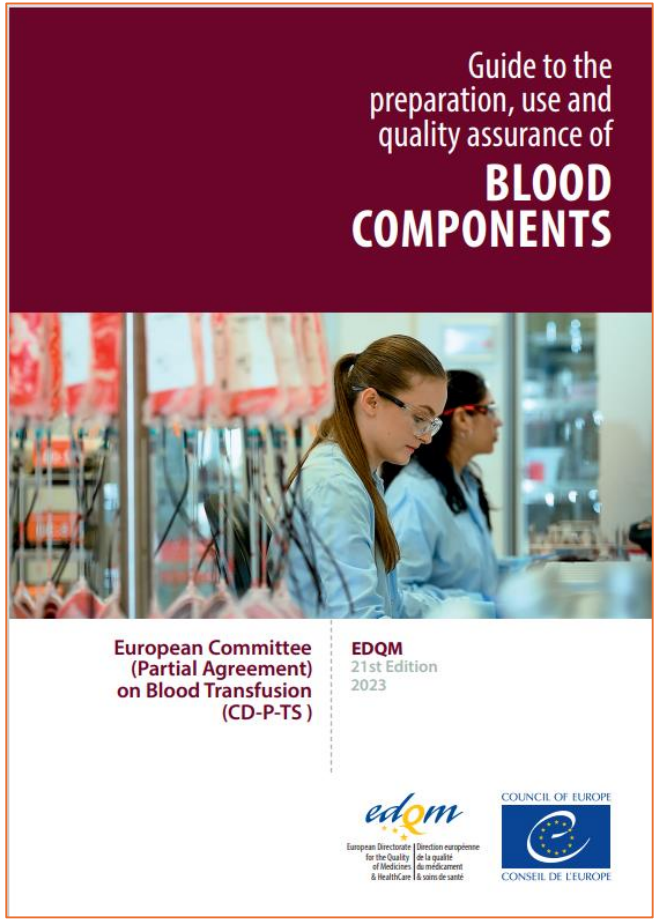
Aim

- To provide a practical guideline for Blood Providers who wish to implement a Whole Blood program.
- To summarize recommendations and practical implications identified from published literature, regulatory requirements and current WB programs in Europe.

EDQM Definition

"Whole Blood is blood taken from a suitable donor using a sterile and pyrogen-free anticoagulant and container. Whole Blood is a source material for Whole Blood, Leucocyte-Depleted and component preparation, which is its major use. Whole Blood for transfusion is used without further processing."

EDQM Blood Guide, 21 ed, Chapter 5, A-1 Whole Blood, page 215



EDQM Blood Guide 21st ed: Whole blood monograph, Chapter 5

Component monographs

Part A. **Whole Blood components**

A-1. WHOLE BLOOD

Definition and properties

Whole Blood is blood taken from a suitable donor using a sterile and pyrogen-free anticoagulant and container. *Whole Blood* is a source material for *Whole Blood, Leucocyte-Depleted* and component preparation, which is its major use. *Whole Blood* for transfusion is used without further processing.

Whole Blood for transfusion should not contain irregular antibodies of clinical significance.

Table 5A-1

Parameter to be checked	Requirements	Frequency of control
ABO, RhD	Grouping	All units
Anti-HIV 1 & 2	Negative by approved screening test	All units
HBsAg	Negative by approved screening test	All units
Anti-HCV	Negative by approved screening test	All units
Volume [a]	450 mL ± 50 mL volume (excluding anticoagulant) A non-standard donation should be labelled accordingly	as determined by SPC
Haemoglobin per final unit [a]	Minimum 45 g	as determined by SPC
Haemolysis at the end of storage [a]	< 0.8 % of red cell mass	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

A-2. WHOLE BLOOD, LEUCOCYTE-DEPLETED

Definition and properties

Whole Blood, Leucocyte-Depleted (LD) is a component for transfusion or a source material for component preparation derived from *Whole Blood* by removing the leucocytes to a minimal residual content.

Whole Blood, LD contains a minimum haemoglobin content of 43 g.

Whole Blood, LD contains less than 1×10^6 leucocytes.

Whole Blood, LD for transfusion should not contain irregular antibodies of clinical significance.

Preparation

Generally a filtration technique is used to produce *Whole Blood, LD.* Pre-storage leucocyte depletion within 48 hours after donation is the standard.

Requirements and quality control

Table 5A-2 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 – Screening for markers of transfusion-transmissible infection).

Table 5A-2

Parameter to be checked	Requirements	Frequency of control
ABO, RhD	Grouping	All units
Anti-HIV 1 & 2	Negative by approved screening test	All units
HBsAg	Negative by approved screening test	All units
Anti-HCV	Negative by approved screening test	All units
Volume [a]	450 ± 50 mL volume (excluding anticoagulant) A non-standard donation should be labelled accordingly	as determined by SPC
Haemoglobin per final unit [a]	Minimum 43 g	as determined by SPC
Residual leucocytes per final unit [a]	$< 1 \times 10^6$	as determined by SPC
Haemolysis at the end of storage [a]	< 0.8 % of red cell mass	as determined by SPC

a A minimum of 90 % of units tested should meet the required value.

Implementation of a Whole Blood Program

- Donor Selection
- Collection and production
- Storage and transport
- Validation, quality control, post-implementation follow-up
- Inventory management
- Emergency preparedness.

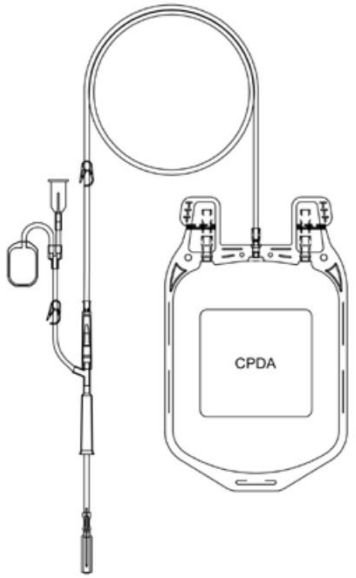
Donor selection

- ABO type-specific or Low titer group O whole blood (LTOWB)
- Anti-A and anti-B titer for group O whole blood donors
  - Titer donor not blood product
  - Titer treshold (<256)
  - Frequency of titering donors
- No irregular antibodies of clinical significance.
- RhD
- TRALI mitigation strategies
- Medication that influences on platelet function

Collection and production

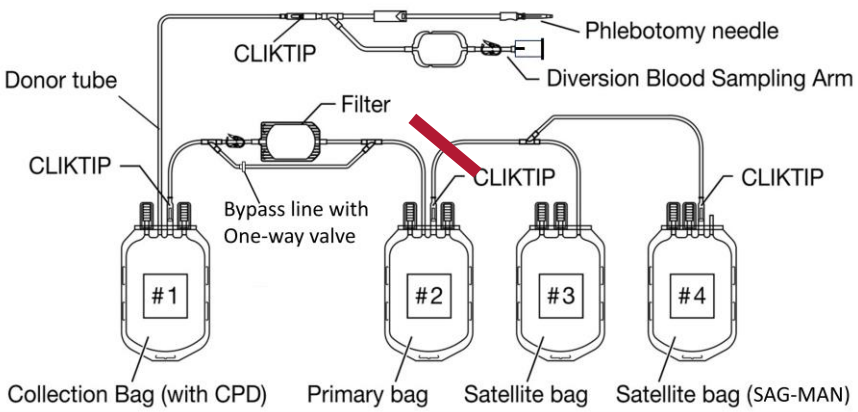
Non-leucocyte depleted:

- CPDA (citrate-phosphate-dextrose-adenine)



Leucocyte-depleted with a platelet-sparing filter:

- CPD (citrate-phosphate-dextrose)



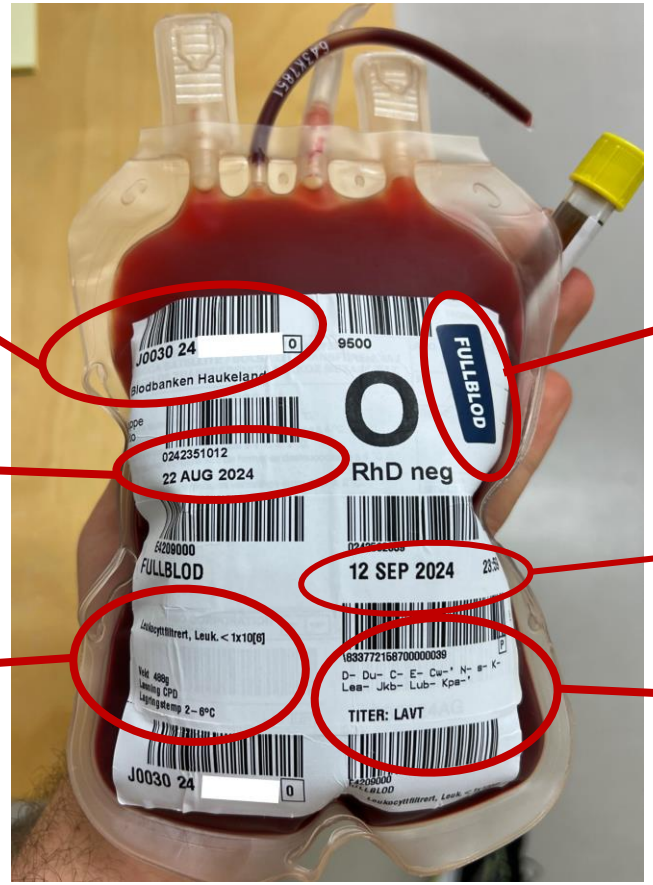
Labelling

- ISBT standards for labelling are recommended to favour interoperability between countries in emergencies.

Unique donation identification number

Donation date

Product info



Whole blood sticker

Expery date

Info on titer of anti- A and B and other phenotypes

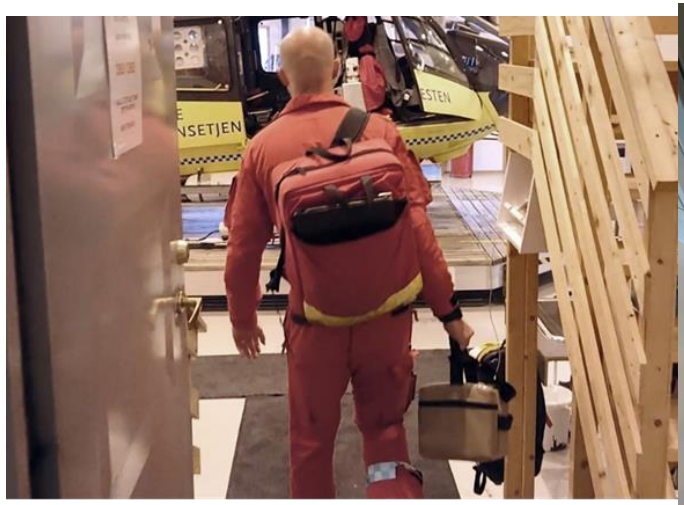
Storage and transport

- Storage and transport Whole Blood for transfusion must be kept at a controlled temperature, i.e. between + 2 °C and + 6 °C (Directive 2004/33/EC, Annex IV).
- Validated transport systems should ensure that the temperature does not go below + 1 °C or exceed + 10 °C over a maximum transit time of 24 hours. Transport times may exceed 24 hours if temperature conditions are maintained between + 2 °C and + 6 °C.

EDQM Blood Guide, 21 ed, Chapter 5, A-1 Whole Blood, page 216

In hospital storage

Prehospital storage



Validation and Quality Control

- The storage time depends on the anticoagulant/preservative solution used and should be validated.
- Specifications for WB are described within the monographs of the EDQM *Guide* to the *preparation*, *use* and *quality assurance* of *blood components* (Blood *Guide*).

Minimum requirements defined in the EDQM Blood Guide 21 ed.		
Volume	450 ml +/- 10%	At collection and/or production (d0, d1)
Haemoglobin	45 g/unit (non-leukodepleted) 43 g/dl (leukodepleted)	At collection and/or production (d0, d1)
Haemolysis	< 0.8%	At end of storage
Leukocyte count (if leukodepleted)	< 1×10^6	At collection and/or production (d0, d1)

EDQM Blood Guide, 21 ed, Chapter 5, A-1 and A-2

- Markers of red cells, platelet and plasma quality should be included in the validation of the whole blood product.
- Platelet function declines during storage, however impact on clotting time and strength preserved (TEG).
- Validation study find similar results when comparing whole blood stored in hospital and prehospitally

Transfusion Medicine Reviews 34 (2020) 234–241

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journal homepage: https://www.journals.elsevier.com/transfusion-medicine-reviews/

Quality of Platelets in Stored Whole Blood

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ARTICLE INFO

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Keywords:
Whole blood
Transfusion
Massive transfusion
Blood components
Platelets
Pathogen inactivation
Recovery
Survival

ABSTRACT

Transfusion of whole blood rather than blood components is gaining popularity. It is easy to use, with one transfusion product to administer rather than 3, and is held at one storage temperature. It only contains anticoagulant-preservative solution, while components contain various storage solutions, which in theory may induce dilution coagulopathy.
In this review, the quality of platelets in stored whole blood is summarized. In cold-stored whole blood, the platelet count declines by 1% to 2% per day. The responsiveness to various agonists declines during the storage time, but this appears to have a limited impact on clotting time or on clot strength as measured with thromboelastography. Animal studies have confirmed that platelets from stored whole blood participate equally well in clot formation. The recovery of platelets in stored whole blood is acceptable during at least 15 days of storage. The survival of platelets after transfusion is only 1 day, but this is likely to be sufficient for the intended patient group requiring massive transfusions, as the platelets are rapidly consumed in the wound area.
In addition to the logistic benefits, there are drawbacks, most importantly having a sufficiently large inventory with an acceptable outdating rate, particularly since massive transfusions are rare, while requiring a lot of whole blood. The positive experience of the United States military with whole blood transfusion is often brought forward for introduction in the civilian blood bank, but patients with trauma are only a small fraction of the civilian population requiring massive transfusions. It needs to be determined whether in the resourceful environment of the hospital, these patients benefit from whole blood transfusions. Optimization of whole blood storage, with focus on platelet quality, needs to be performed to allow extension of the storage time beyond 15 days to a point where the number of units in inventory and outdating can be balanced.

Cold-stored whole blood in a Norwegian emergency helicopter service: an observational study on storage conditions and product quality

Christopher Bjerkvig [1,2,3], Joar Sivertsen [4], Hanne Braathen [4], Turid Helen Felli Lunde [4], Geir Strandenes [4,5], Jörg Assmus [6], Tor Hervig [3,4], Andrew Cap [7], Einar K. Kristoffersen [3,4], Theodor Fosse [1,2,3] and Torunn Oveland Apelseth [4,8]

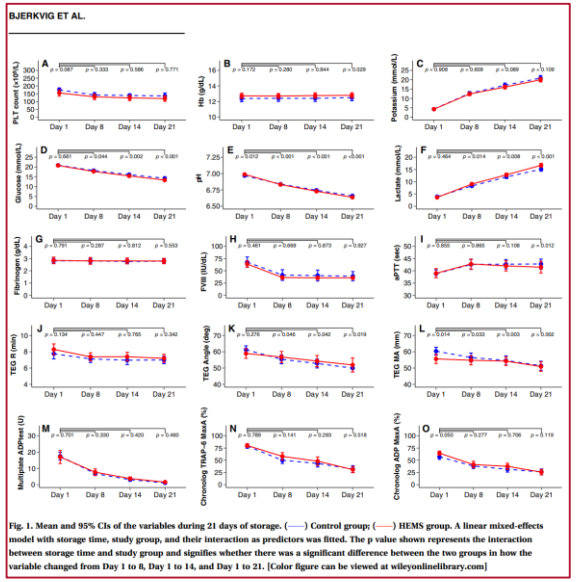

Fig. 1. Mean and 95% CIs of the variables during 21 days of storage. (——) Control group; (——) HEMS group. A linear mixed-effects model with storage time, study group, and their interaction as predictors was fitted. The p value shown represents the interaction between storage time and study group and signifies whether there was a significant difference between the two groups in how the variable changed from Day 1 to 8, Day 1 to 14, and Day 1 to 21. [Color figure can be viewed at wileyonlinelibrary.com]

Post implementation follow up

- Post-implementation follow-up of the program includes hemovigilance and quality surveillance of the use and clinical effectiveness of the product.
- End users of the product should be involved in the development and evaluation of the program and training of clinical personnel must be performed.

Supplementary Table 1. Survey of user experience.

	Blood Bank Laboratory Staff (n=21)	Physicians (n=40)	Nurses (n=25)
Have you ever handed out whole blood?			
Yes	21 (100%)	-	-
No	0	-	-
Have you ever transfused whole blood to a patient?			
Yes	-	38 (95%)	20 (80%)
No	-	2 (5%)	5 (20%)
Did you get sufficient information and training before whole blood was introduced in the massive transfusion protocol?			
Yes	21 (100%)	30 (75%)	16 (64%)
No	0	10 (25%)	7 (28%)
Which blood product would you choose for a massively bleeding patient?			
Balanced transfusion with components	0	0	0
Whole blood	21 (100%)	36 (90%)	24 (96%)
Both options are equal	0	4 (10%)	0
Which of the following were deciding factors for your choice in the previous question			
Easier handling	10 (48%)	28 (70%)	14 (56%)
Faster handling	20 (95%)	33 (83%)	20 (80%)
Less labor intensive	12 (57%)	24 (60%)	17 (68%)
Better physiological option	12 (57%)	36 (90%)	15 (60%)
Economic benefit	1 (5%)	0	0

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DOI: 10.1111/trf.16490
SUPPLEMENT ARTICLE
TRANSFUSION

A whole blood based resuscitation strategy in civilian medical services: Experience from a Norwegian hospital in the period 2017–2020

Kristin Gjerde Hagen[1] | Geir Strandenes[1,2] | Einar Klæboe Kristoffersen[1,3] | Hanne Braathen[1,4] | Joar Sivertsen[1,4] | Christopher Kalhagen Bjerkvig[3,5] | Nina Sommerfelt-Pettersen[3] | Irmelin Beathe Aasheim[1] | Turid Helen Felli Lunde[1] | Tor Hervig[1,3,6] | Torunn Oveland Apelseth[1,2]

Inventory management

Strategies to reduce outdating:

1. Rotation between prehospital and inhospital use

2. Use whole blood for treatment of patients with bleeding of all etiologies, not only traumas (in MTPs)

3. Re-manufacturing of RBC from stored whole blood

Transfusion Medicine and Hemotherapy

Research Article

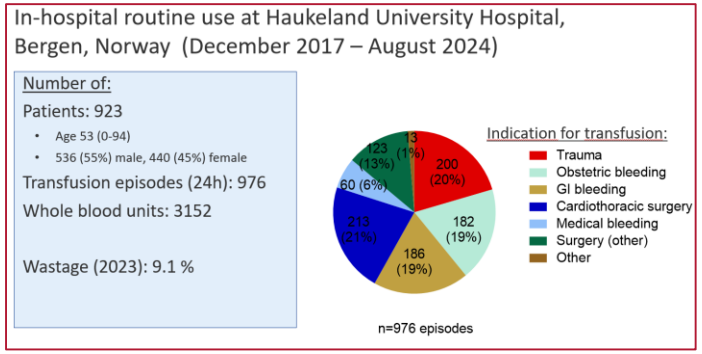
Transfus Med Hemother 2021;48:324–330
DOI: 10.1159/000519676

Prehospital Whole Blood Transfusion Programs in Norway

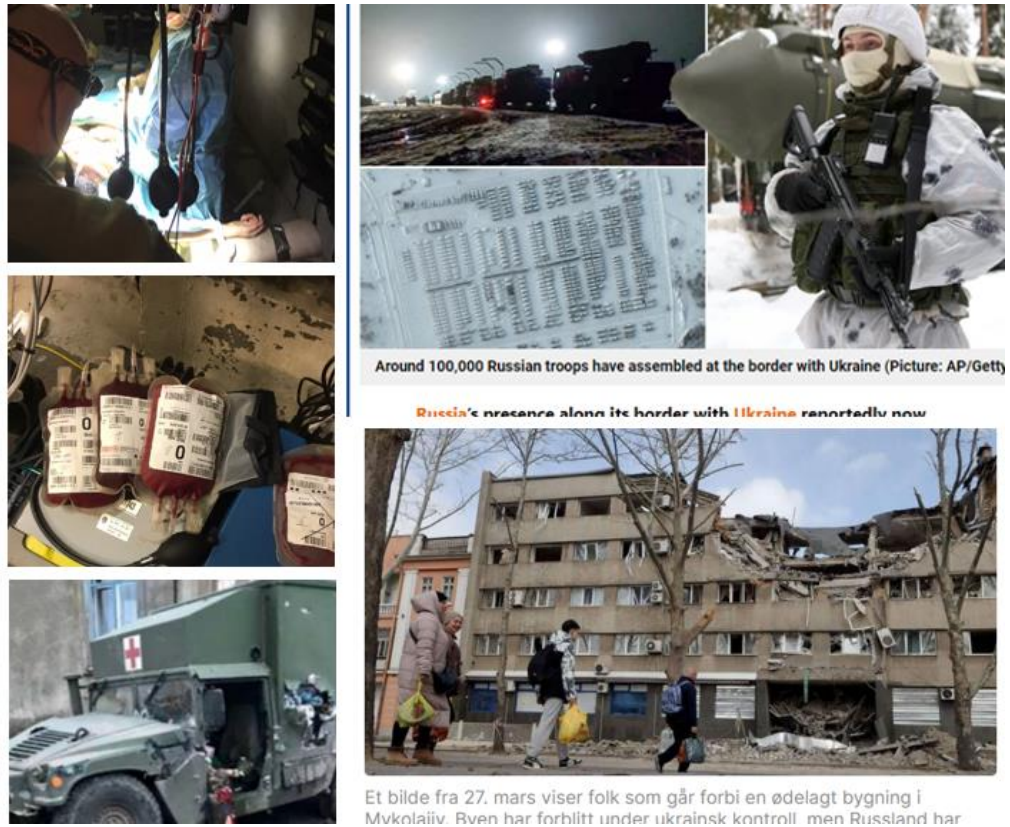
Christopher Kalhagen Bjerkvig[a, b, c, d] Geir Strandenes[e, f] Tor Hervig[e, g]
Geir Arne Sunde[a, d] Torunn Oveland Apelseth[c, e, f]

[a]Department of Anesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway; [b]Norwegian Naval Special Operations Commando, Norwegian Armed Forces, Bergen, Norway; [c]Institute of Clinical Science, University of Bergen, Bergen, Norway; [d]Helicopter Emergency Medical Services, HEMS Bergen, Bergen, Norway; [e]Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway; [f]Department of War Surgery and Emergency Medicine, Norwegian Armed Forces, Medical Services, Oslo, Norway; [g]Laboratory of Immunology and Transfusion Medicine, Haugesund Hospital, Haugesund, Norway

LTOWB that is not transfused during the predefined storage time at the HEMS base is returned to the blood bank. Two blood banks utilize LTOWB that is not used at HEMS for in-hospital patients, whereas for the other two blood banks, the units are outdated and discarded. The waste rates were 79.6%, 73.2%, 77.0%, and 26.4% for the four different blood banks, with the lowest waste rate observed at the blood bank that regularly utilizes whole blood for in-hospital massive transfusion packages.



Whole blood in contingency planning and emergency preparedness



The COVID 19 pandemic: New (old) blood products were introduced

- Extended shelf-life RBCs and platelets
- Reduced platelet dose
- Cold stored and frozen platelets
- Liquid plasma
- Whole blood

Effects of the COVID-19 pandemic on supply and use of blood for transfusion

Simon J Stanworth, Helen V New, Torunn O Apelseth, Susan Brunskill, Rebecca Cardigan, Carolyn Doree, Marc Germain, Mindy Goldman, Edwin Massey, Daniele Prati, Nadine Shehata, Cynthia So-Osman, Jecko Thachil

The COVID-19 pandemic has major implications for blood transfusion. There are uncertain patterns of demand, and transfusion institutions need to plan for reductions in donations and loss of crucial staff because of sickness and public health restrictions. We systematically searched for relevant studies addressing the transfusion chain—from donor, through collection and processing, to patients—to provide a synthesis of the published literature and guidance during times of potential or actual shortage. A reduction in donor numbers has largely been matched by reductions in demand for transfusion. Contingency planning includes prioritisation policies for patients in the event of predicted shortage. A range of strategies maintain ongoing equitable access to blood for transfusion during the pandemic, in addition to providing new therapies such as convalescent plasma. Sharing experience and developing expert consensus on the basis of evolving publications will help transfusion services and hospitals in countries at different stages in the pandemic.

Lancet Haematol 2020
Published Online
July 3, 2020
https://doi.org/10.1016/S2352-3026(20)30186-1

Transfusion Medicine (Prof S J Stanworth FRCP) and Systematic Review Initiative (S Brunskill Msc, C Doree PhD), NHS Blood and Transplant, Oxford, UK; Department of Haematology, Oxford

***Panel*: Strategies to modify production, specification, and storage of blood components to help prevent blood shortage**

Red blood cells

Extend shelf life if validated and within regulations

Review manufacturing process.[64,65]

Platelets

Extend shelf life from 5 days to 7 days with appropriate bacterial testing or pathogen inactivation

Recovery and survival of platelets, as well as count increments following transfusion, decline with increasing storage duration.[66,67] Bacterial risk depends on the timing of sampling, sample volume, and the length of culture; delayed culture methods with 7 day storage have been shown to be effective.[68] Depending on screening methodology, a further test at day 4 or at the end of storage might be required.

Extend shelf life to 8 days after review of internal laboratory data to guide feasibility

Review internal laboratory data to guide feasibility, and review data on bacterial risk. There is scant clinical data beyond day 7. At day 8, the recovery of fresh platelets manufactured from buffy-coats is nearly 70% and platelet survival is 45%.[69,70] Improved recovery and survival of platelets with prolonged storage has been observed with some types of additive solution.[69,70]

Reduce dose for prophylactic transfusion (split products)

Some countries already issue split products for neonatal transfusion. Consider half doses, or methods to produce two-thirds to three-quarter doses, such as pooling fewer so-called buffy coats or splitting aphaeresis collections into more doses.[71]

Consider use of cold-stored platelets with 7–14-day shelf life for patients with bleeding only

Studies in healthy volunteers suggest that the survival of platelets from whole blood or platelet concentrates refrigerated for 10–15 days might maintain acceptable viability. Laboratory data suggest that platelets remain functional for 14–21 days without the need for agitation.[72,73,76]

Consider frozen platelets for bleeding patients only[77,78]

Plasma

Remove requirements to freeze plasma

Consider use of liquid (never frozen) plasma if freezer capacity or staff to freeze plasma are in short supply.[79]

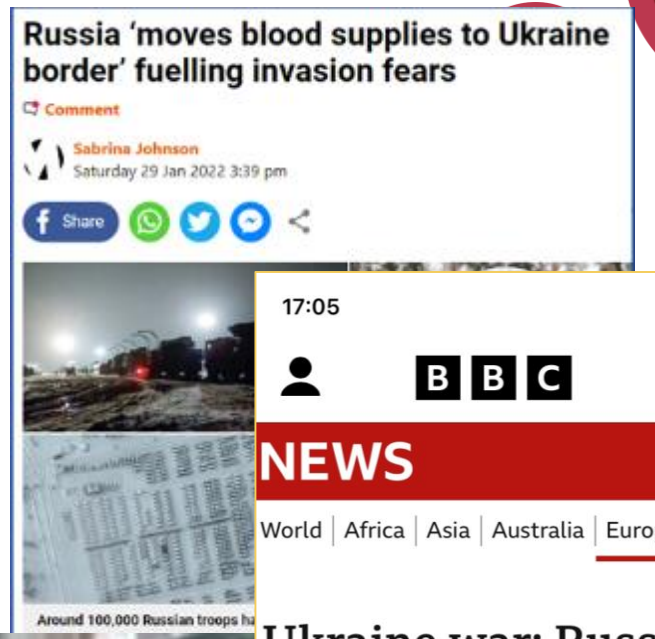
Whole Blood

Use of whole blood

Consider if staff to manufacture components are in short supply or for massive transfusion.[80–84]

Blood services being pushed to the extremes in crisis and war

- No electricity, no water, no IT
- Bombed hospitals and blood services
- Medical evacuation under attack
- Large number of wounded soldiers and civilians



Emergency Collection of Whole Blood - implemented as a preparedness measure on all levels of health care

- Level 1 trauma center
- Small rural hospitals
- Primary health care services (civilian walking blood banks)

Emergency whole blood collection and transfusion

SUPPLEMENT ARTICLE

How do I get an emergency civilian walking blood bank running?

Silje Helland Kaada,[1] Torunn Oveland Apelseth,[1,2] Kristin Gjerde Hagen,[1] Einar Klæboe Kristoffersen,[1,3] Stig Gjerde,[4] Kristian Sønstabø,[4] Henrik Halvorsen,[5] Tor Hervig,[1,3] Geir Arne Sunde,[4] Geir Olav Dahle,[4] Mari Christine Johnsen,[4] and Geir Strandenes[1,6]

DOI: 10.1111/trf.16057

HOW DO I?

TRANSFUSION

How do I implement a whole blood–based blood preparedness program in a small rural hospital?

Torunn O. Apelseth[1,2] | Geir Strandenes[1,2] | Einar K. Kristoffersen[1,3] | Kristin G. Hagen[1] | Hanne Braathen[1,3] | Tor Hervig[1,3,4]

Received: 15 February 2022 | Revised: 2 May 2022 | Accepted: 2 May 2022

DOI: 10.1111/trf.16968

DISASTER PREPAREDNESS

TRANSFUSION

The Norwegian blood preparedness project: A whole blood program including civilian walking blood banks for early treatment of patients with life-threatening bleeding in municipal health care services, ambulance services, and rural hospitals

Torunn Oveland Apelseth[1,2,3] | Mirjana Arsenovic[4] | Geir Strandenes[1]

Conclusions

- We conclude that subject to successful validation, hemovigilance surveillance and authorization by competent authorities, implementation of a whole blood program for routine and emergency management of patients with severe bleeding can be performed in a structured and sustainable way.
- We recommend that whole blood continue to be included as a blood product in the EDQM Blood Guide Monograph section

NEW METHOD FOR CRYOPRESERVED PLATELETS (CPP) WITH MINIMAL POST-THAW PROCESSING.

The French experience

Thibaut Bocquet

Disclosures

- **EFS employee**
- **No disclosure**

Summary

1. Why ?
    1. Why do we use CPP ?
    2. Why do we changed ?
2. Results
    1. During regulatory validation
    2. During implementation
    3. In routine use
3. Conclusion

1

WHY ?

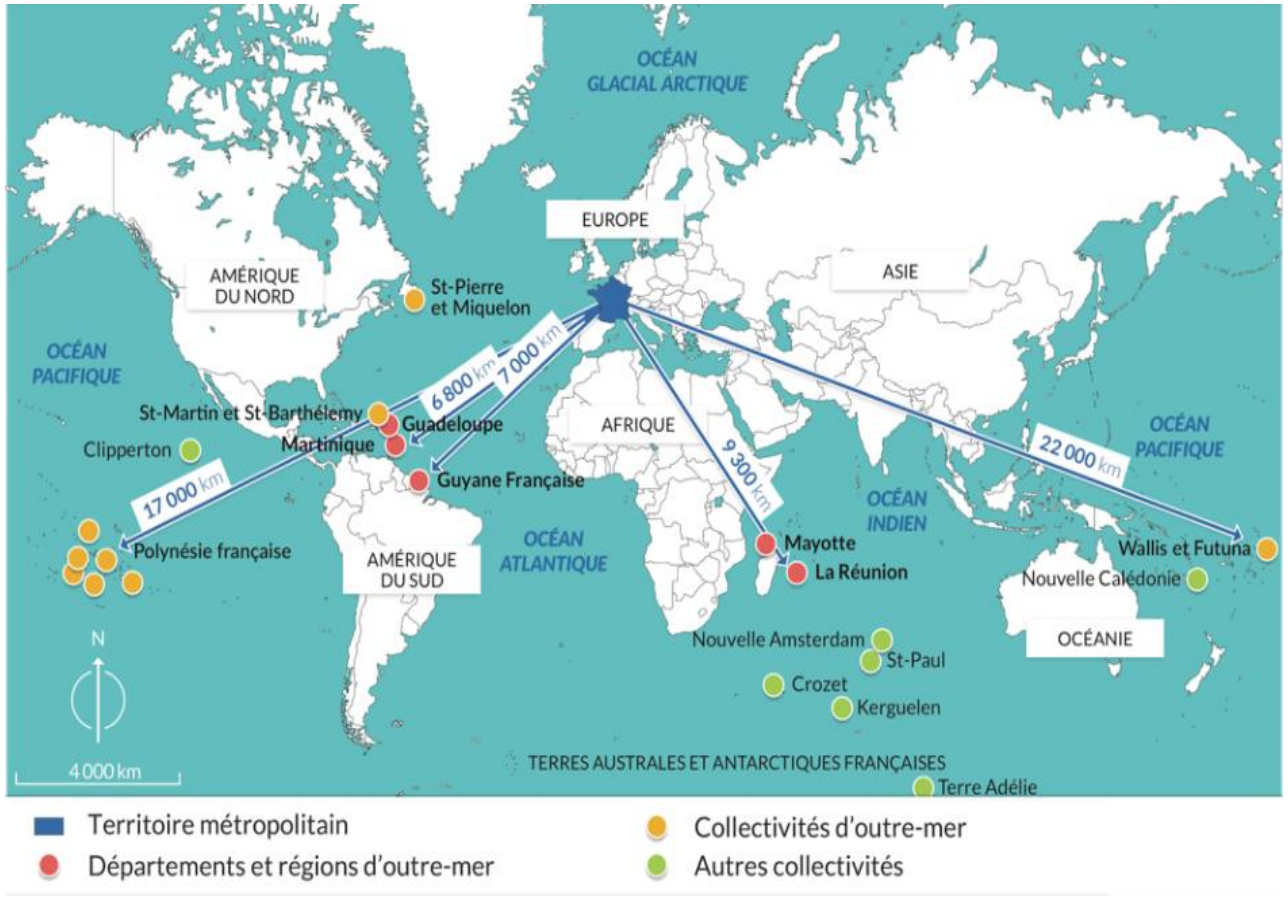
WHY DO WE USE CPP ?

EFS : the only Blood Donation stakeholder in France

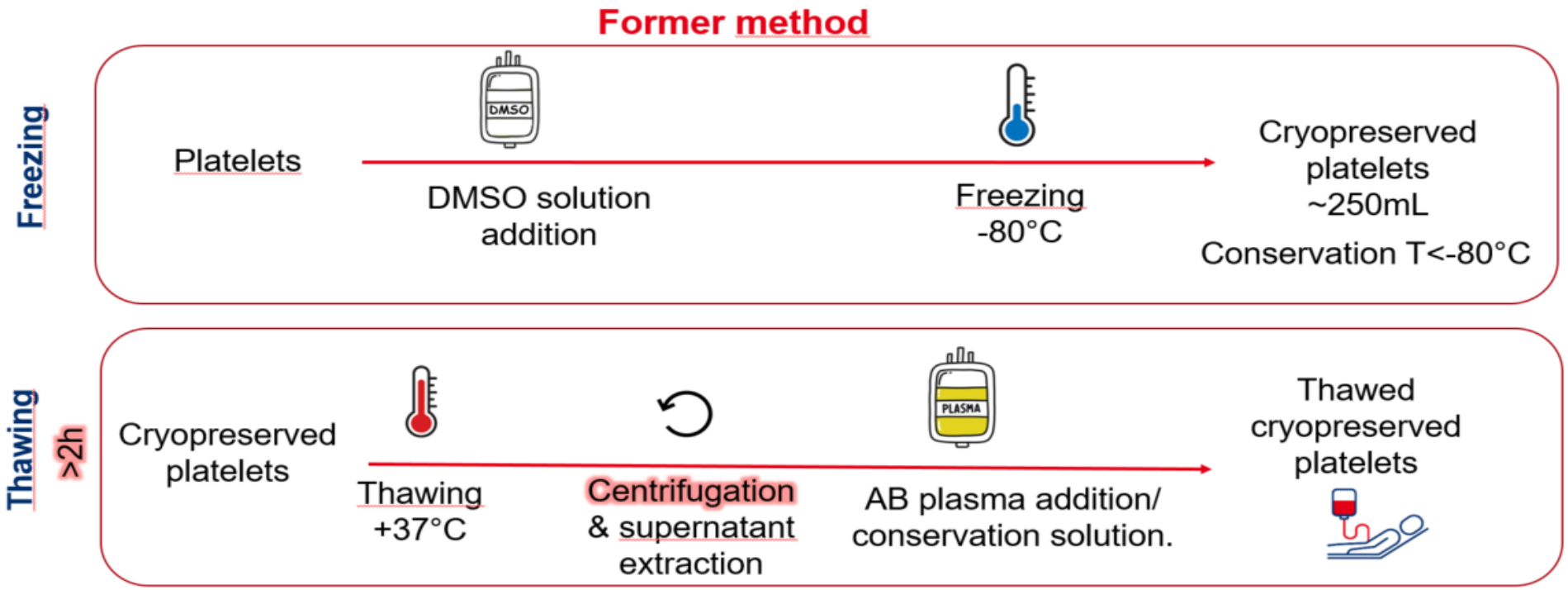
We collect, prepare and distribute blood products to our healthcare establishments across the country

CPP for :

- **Routine : special HLA/HPA units** (stock in the National Rare blood bank)
- **Back up : fresh platelets shortage** (Overseas islands due to supply issues)



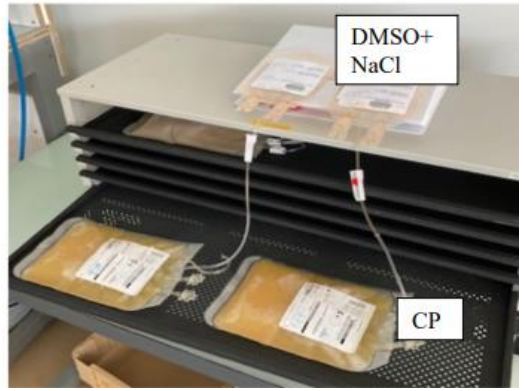
WHY DO WE CHANGED?



- **Post thaw manipulation : ☹**
  - > 2h
  - Centrifuge needed
  - **Losses and quality issues**.

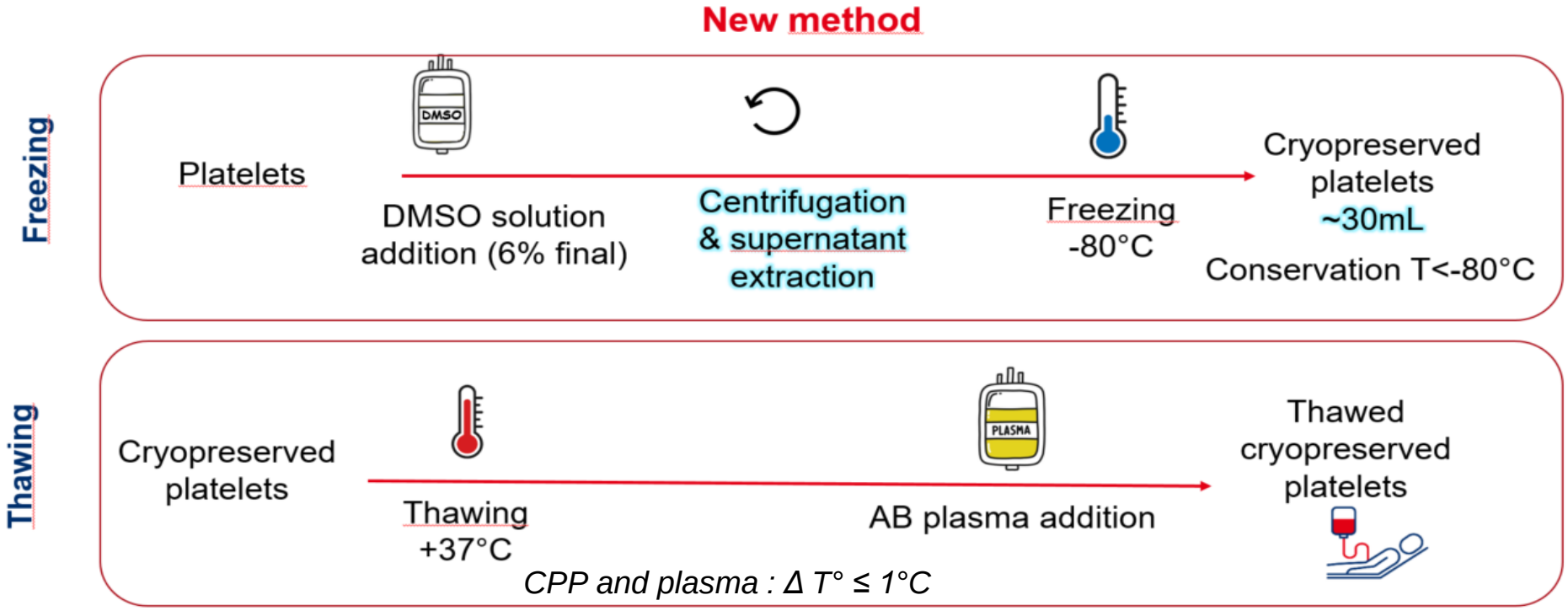
→ New method : currently used in civilian or military applications

NEW METHOD *



Platelets specifications :

- **Platelets in PAS (not PI)**
- **<24h for Apherisis or <48h for Mixed Pooled Buffy coat Platelets**
- **Content >3*10^{11}**



Valeri et al. Transfusion 2005; 45:1890–1898

02

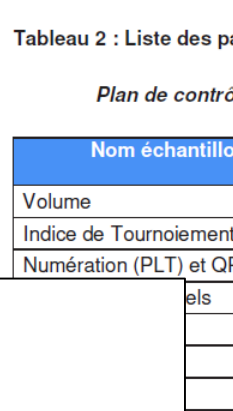
RESULTS

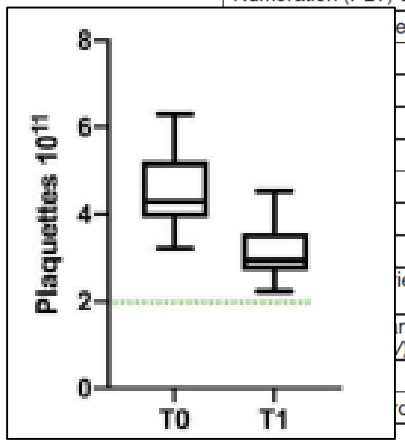
1. During regulatory validation
2. During implementation
3. In routine use

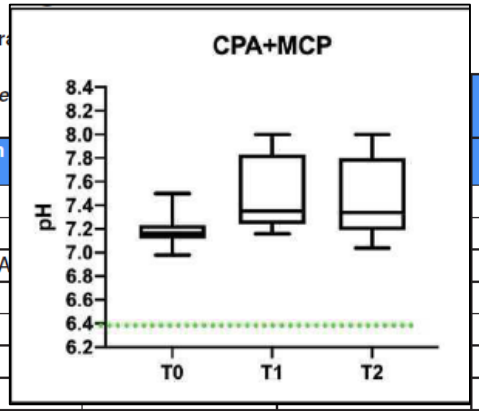
1- REGULATORY VALIDATION

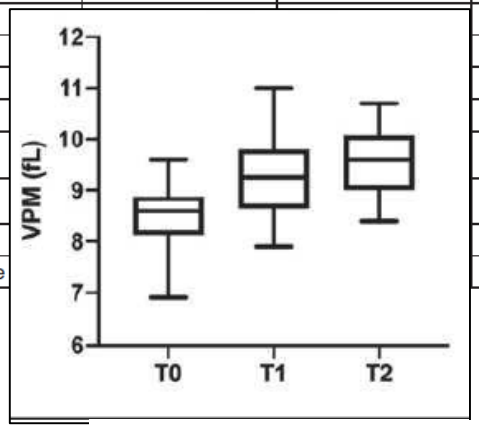
- Codevelopment with **French Blood Army Services**

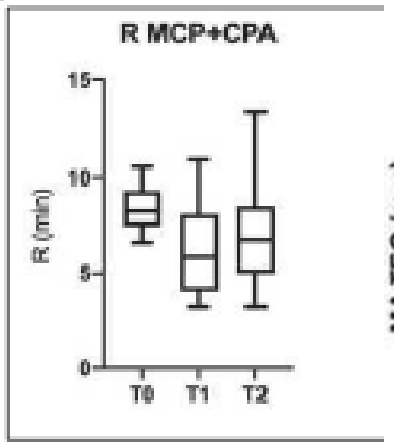
→ resuspended in **AB plasma or Lyophylized plasm**

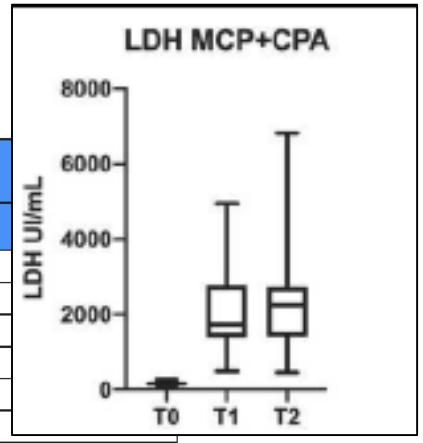


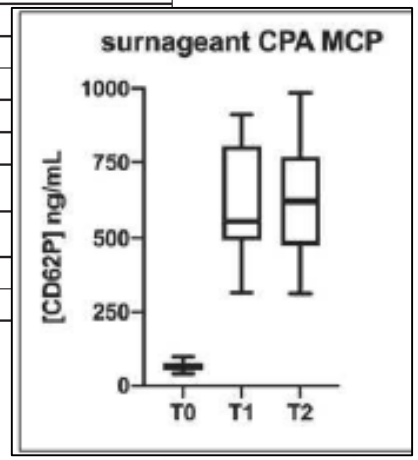


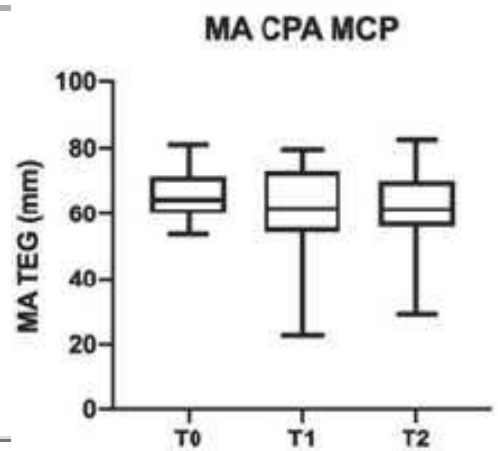












<u>Results</u> (n= 32)

- **DMSO = 2.5** (+/-1.4) **g/CPP**
- **Freezing/thawing = stress**
  - Platelets loss : recovery 78% (+/-14)
  - Partially activated
  - **<u>But</u>** still fonctional → clot initiation / formation / strength

CPP met French regulatory requirements

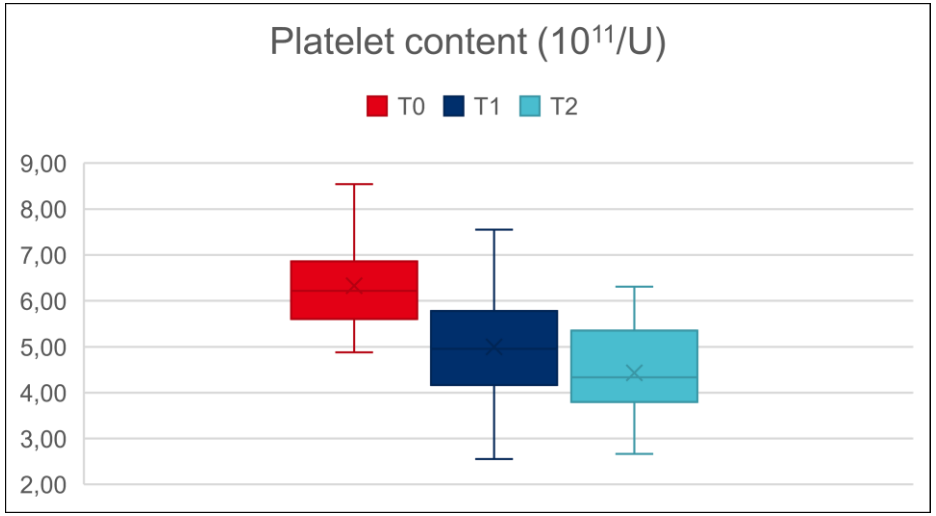
→ ANSM authorization 26/01/21 :

- **2 years at -80°C**
- **6 h**

2- DURING IMPLEMENTATION

4 production sites (n=40)

- **T0 V_{mean}= 29.5 mL** (±14.3) → **T1 V_{mean}= 303 mL** (±23)
- **Residual DMSO/CPP = 0.9** ± 0.3 **g** (n=20)
- **T1 : Recovery = 79 %** (±15)
- **T0 / T1 : MPV** (p<0.05)* **; pH** (p>0.05)*



n = 40	Before freezing (T0)	Immediately after thawing (T1)	6h after thawing (T2)
Platelet content per unit	6.3 ± 0.8x 10^{11}	5.0 ± 1.0 x 10^{11}	4.4 ± 0.9
Mean Platelet Volume (μm^3)	9.1 ± 1.1	9,9 ± 1.8	10.2 ± 2.0
pH	7.11 ± 0.20	7.09 ± 0.15	7.0 ± 0.1

- **Platelet Swirling Index (SI) : T1 < T0 but T2 > T1.**
- **Thawing CPP < 5min and Plasma ≈ 12 min → CPP ready to use <1h**

** Wilcoxon test*

3- ROUTINE USE

1 year in 2 EFS Overseas region

- **110 CPP units were thawed** → 97 issued (41 were controlled) and 13 discarded
- **Mean platelets recovery : 68 - 78**%
- **Visual aspect :**
  - conform and homogeneous.
  - Occasionally **small platelets aggregate**
  - SI present but **weak**
- ☺ 45 to 75min // simplicity (no wastage)
- ☹ Time to T° balance CPP/plasma

	EFS Guadeloupe-Guyane (n=12)		EFS Martinique (n=29)	
	Before freezing (T0)	**Immediately after thawing (T1)**	**Before freezing (T0)**	**Immediately after thawing (T1)**
Platelet content per unit (x 10^{11})	5.4 ±0.9x 10^{11}	3.6 ±0.6x 10^{11}	4.6 ± 0.7x 10^{11}	3.6± 0.6x 10^{11}
Recovery (%)	68.3 ±13.9%		78.1 ±8.7%	

CPP used :

- **Majority for hemorrhagic indications**
- **Some for oncohematology indications during unexpected high demand.**

3

CONCLUSION

CONCLUSION

New method for CPP

- **Successfully implemented** (+ pediatric availability)
- **Benefits are confirmed :**
  - “Universal” for transfusion (AB plasma used)
  - Simplicity + Quickly available (≈1h) = staff serenity
  - Thawed in anticipation → preserve fresh platelet for hematology prescriptions and give time to supply.
- **CPP seem to successful fulfill their purpose**
  - In vitro quality (procoagulant activity)
  - Suggestions : safe and effective

The best alternative to fresh platelets in remote location in case of supply chain failure !

- **EFS strategic decision :**
  - Minimal safety stock nationwide (Overseas department and contingency plan)

THANKS TO ALL EFS TEAM :

Processing team

-Siège : C.Davaine
-Rennes : S. Bois, S. Requiem
-Marseille : N. Marais, L. Boissy, R. Iapicco
-Lille : S. Luc, F. Bruwaert, S. Boivin
-Créteil BNSPR : G. Di Liberto-Vandemeulebrouck
-Staff who thawed CPP
-S.Begue and **French Blood Army Services**

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Cold-storage of amotosalen-UVA pathogen-reduced buffy-coat platelet concentrates for up to 21 days: biochemical and functional characterization, and identification of emerging platelet subpopulations

Beatrice Hechler, PhD

Inserm UMR_S1255 Biologie et pharmacologie des plaquettes sanguines : hémostase, thrombose, transfusion – Établissement Français du Sang, Strasbourg, France

Tuesday, January 14th, 2025 / Innovative & novel blood components (part 2)

Disclosures for Beatrice HECHLER

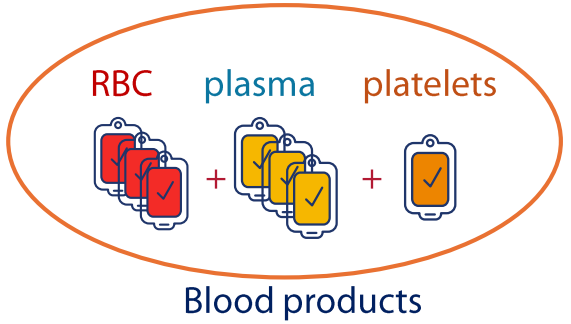
Research Support/P.I.	No relevant conflicts of interest to declare
Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	No relevant conflicts of interest to declare

Interest in cold-stored platelet concentrates

- **Main use of PC:** Prophylactic transfusion
  ➔ time of platelet recirculation must be as long as possible

  Therapeutic transfusion for minimal bleeding

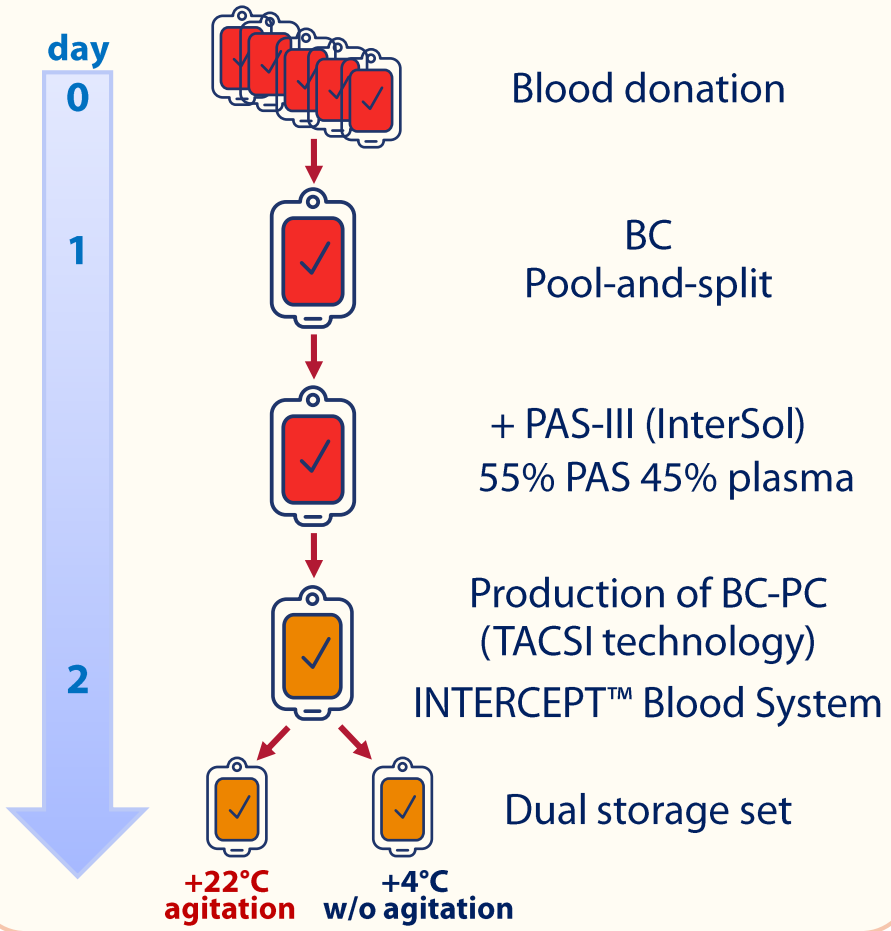
- **Increased therapeutic platelet transfusions in patients with massive bleeding:**
  - Transfusion as early as possible: RBCs / FFPs / PCs
  - Rapid hemostatic activity of platelets prevails over recirculation time
  - Medical challenge in providing the right product
  - Logistical challenge in reducing transfusion delay: PCs are inaccessible in pre-hospital care



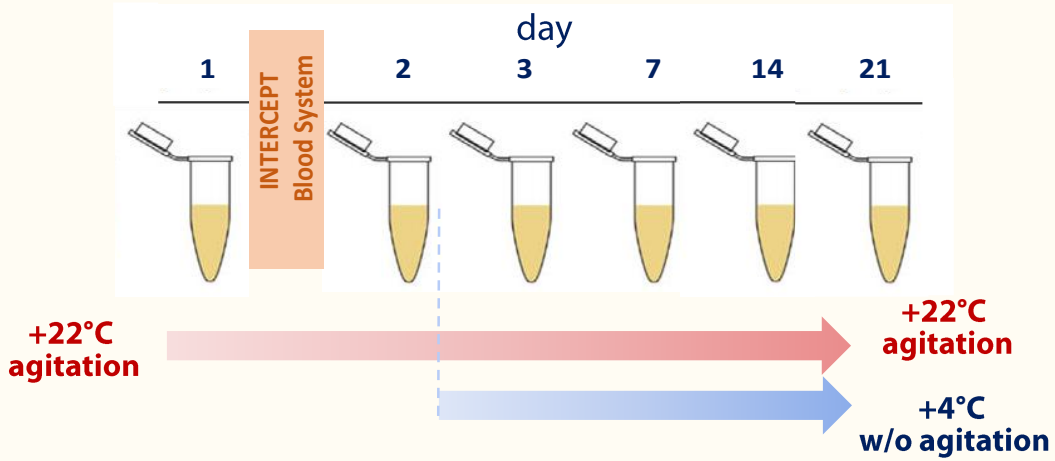
Blood products

- **Recent interest in cold-stored platelets:**
  - Potentially more effective hemostatically
  - Potentially longer shelf life
  - But reduced recovery and survival

Quality assessment of BC-PC stored at +4°C for 21 days



- Amotosalen and UVA treatment (IBS, Cerus, Concord, CA)
- Sampling:

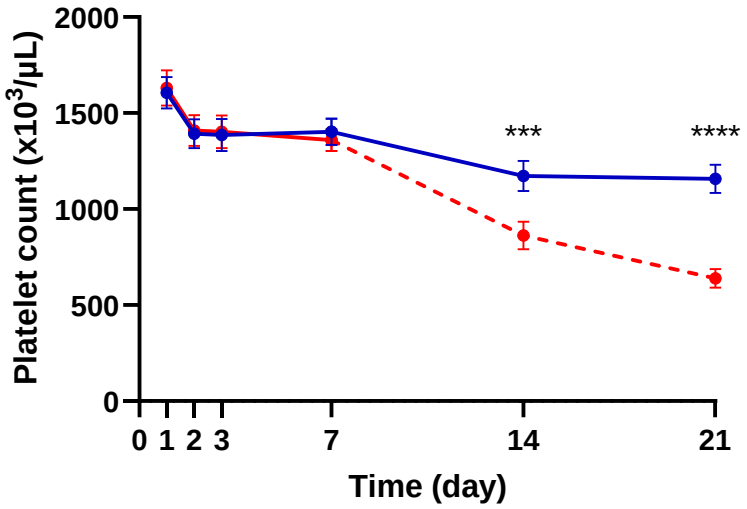


➔ **Evaluation of platelet storage lesions up to day 21**

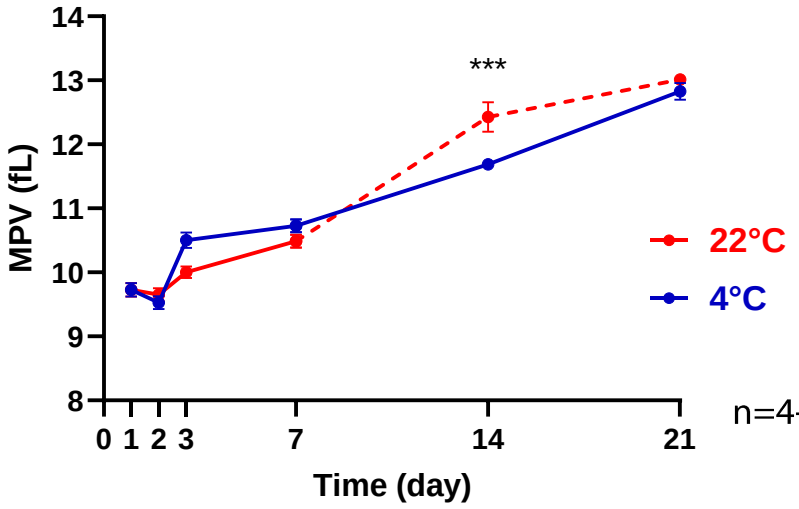
➔ **n=4-7 different campaigns**

Platelet count and mean platelet volume

Platelet count

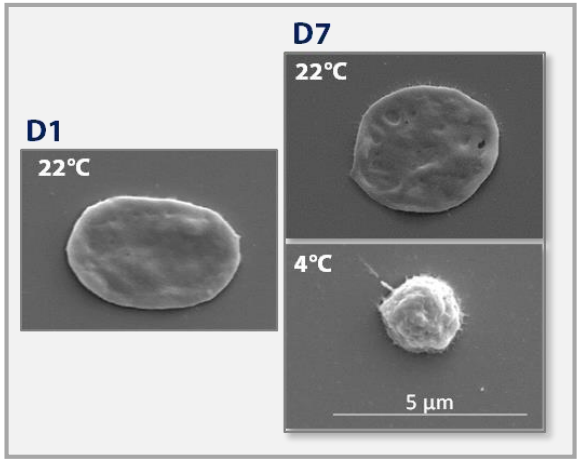


Mean platelet volume



n=4-7

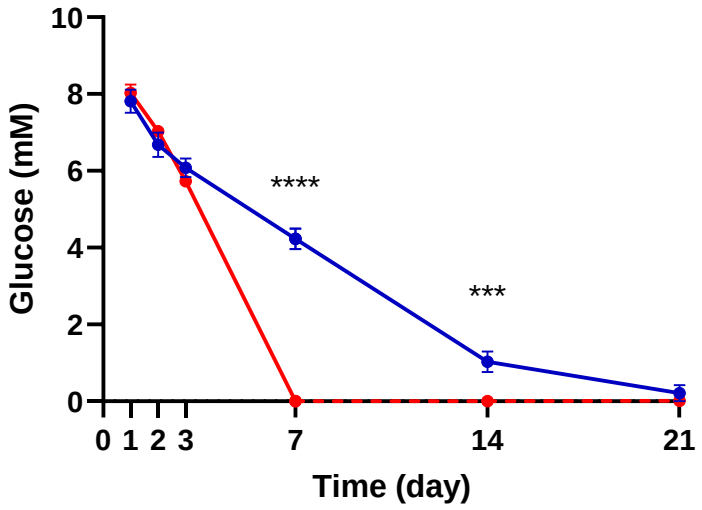
Swirling index	D1	D2	D3	D7	D14	D21
+ 22°C	+++	+++	+++	+++	++	0
+ 4°C			0	0	0	0



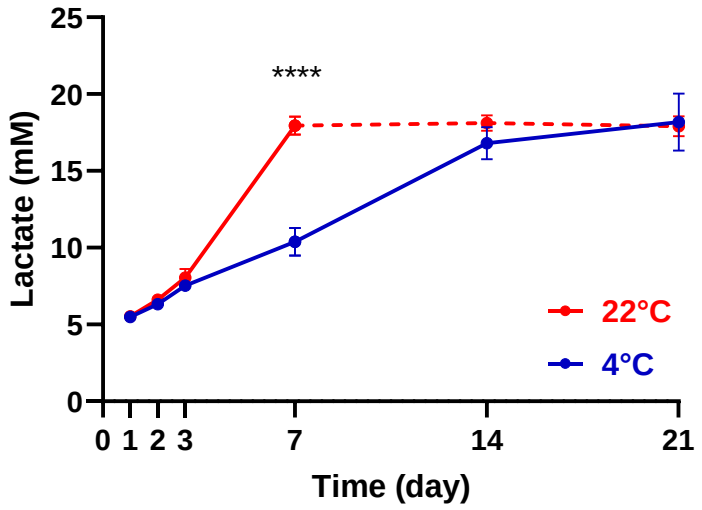
- Loss of swirling index at +4°C
- Absence of aggregates

Metabolic parameters and pH

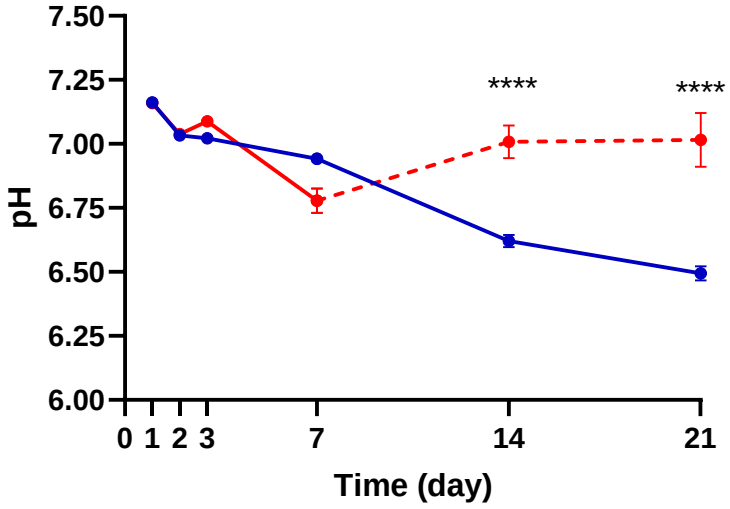
Glucose



Lactate



pH

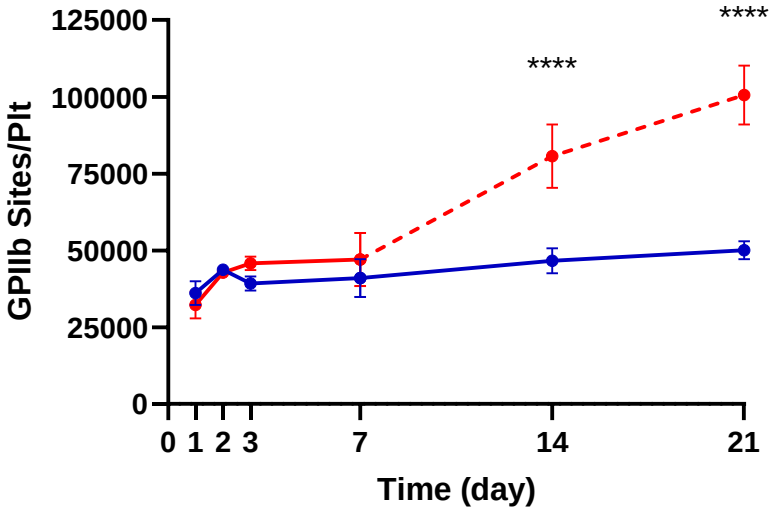


n=4-7

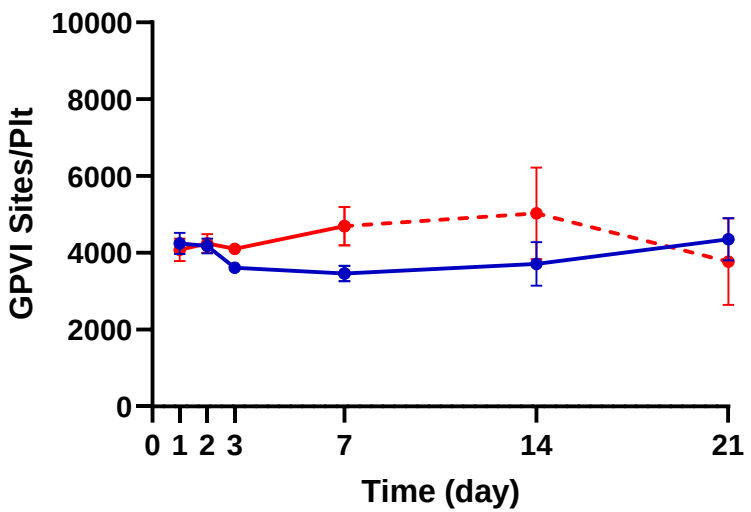
Metabolic activity is reduced at +4°C

Expression of major platelet glycoproteins

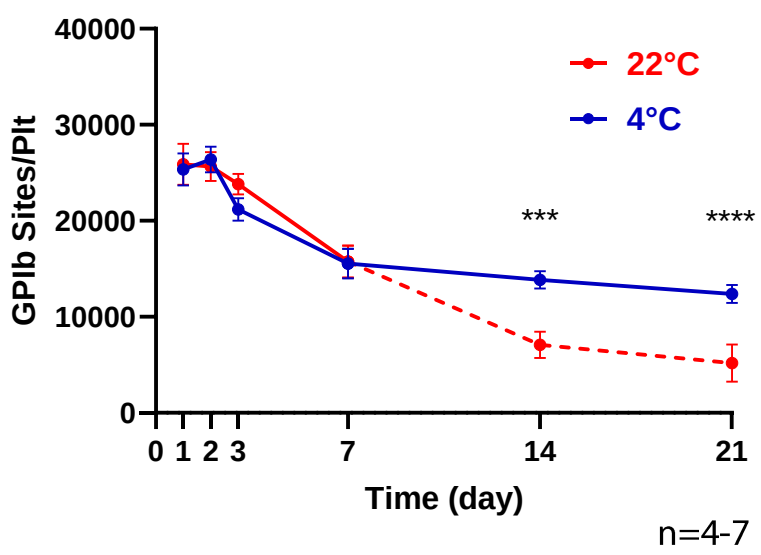
GPIIb



GPVI



GPIbα

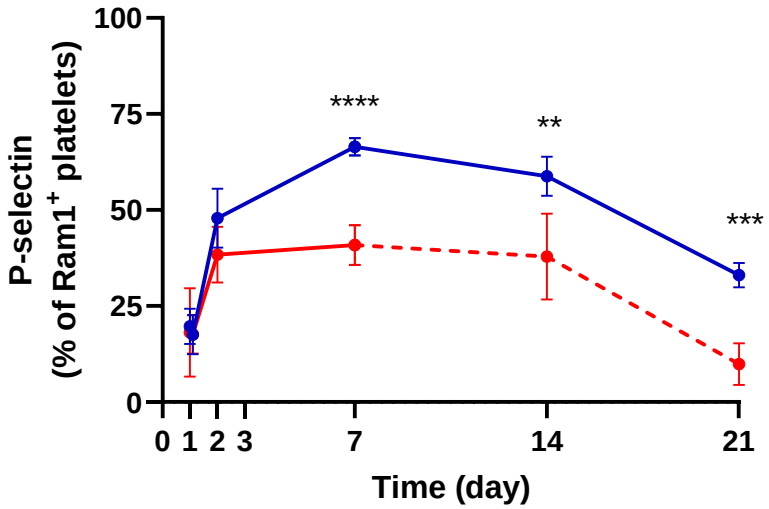


n=4-7

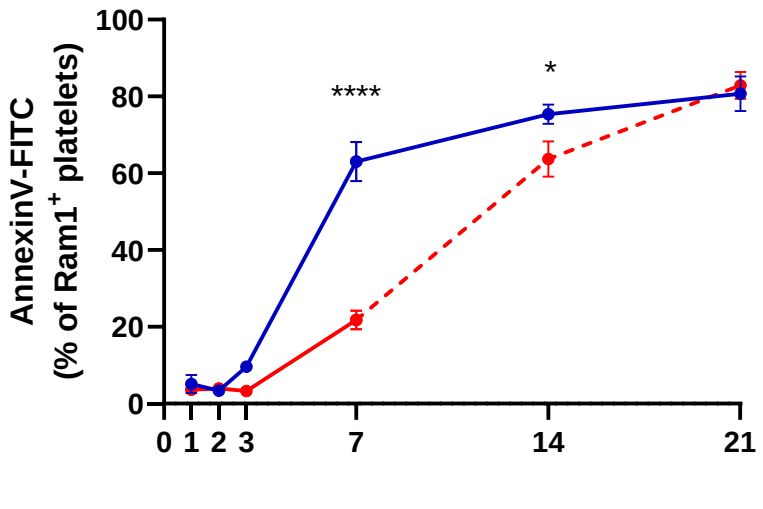
At +4°C, stable expression of GPIIb and GPVI but decrease in GPIbα

Activation state of stored platelets

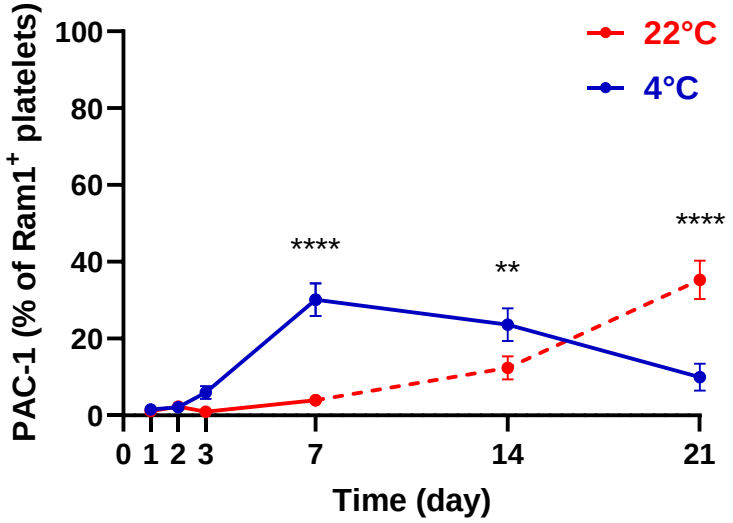
α-granule secretion
(P-selectin exposure)



Phosphatidylserine externalization



Activated GPIIbIIIa

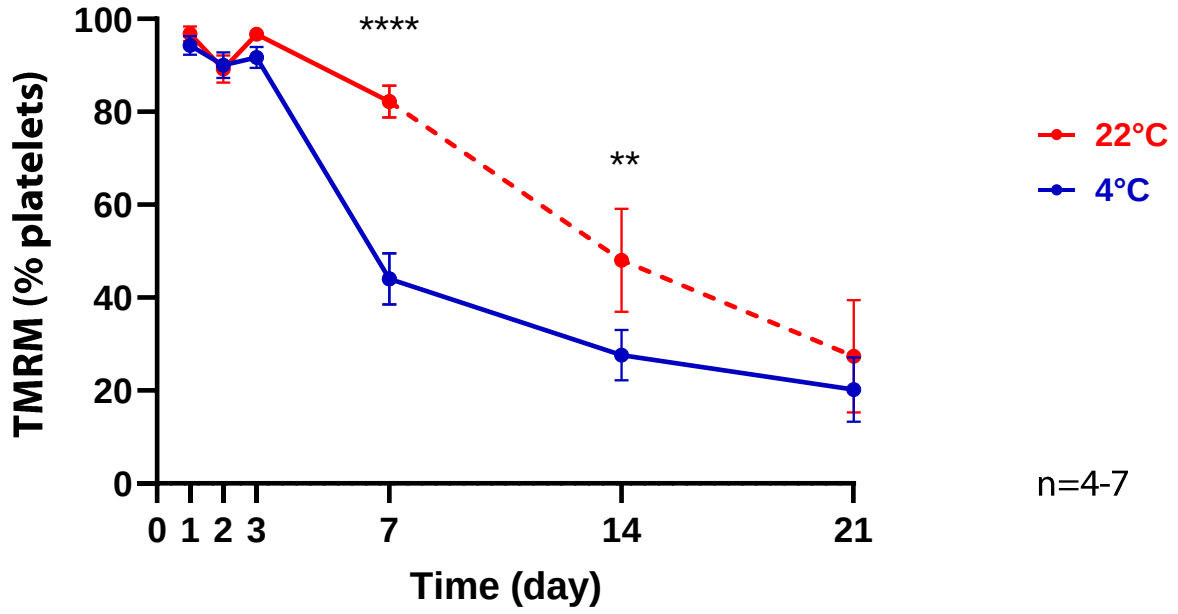


n=4-7

Platelets exhibit strong spontaneous activation at +4°C

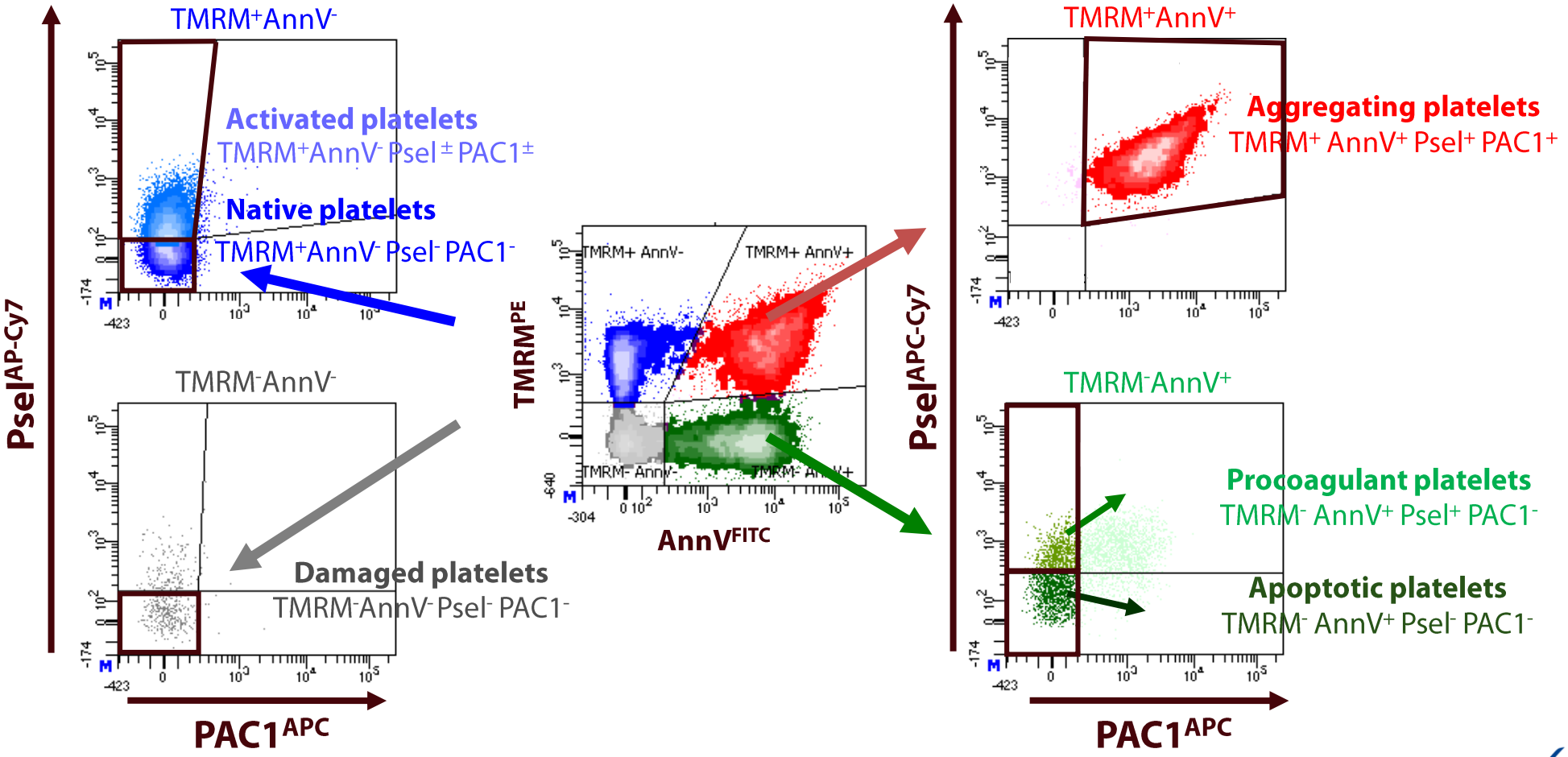
Mitochondrial integrity

- Evaluated using the fluorescent probe TMRM, retained in intact mitochondria



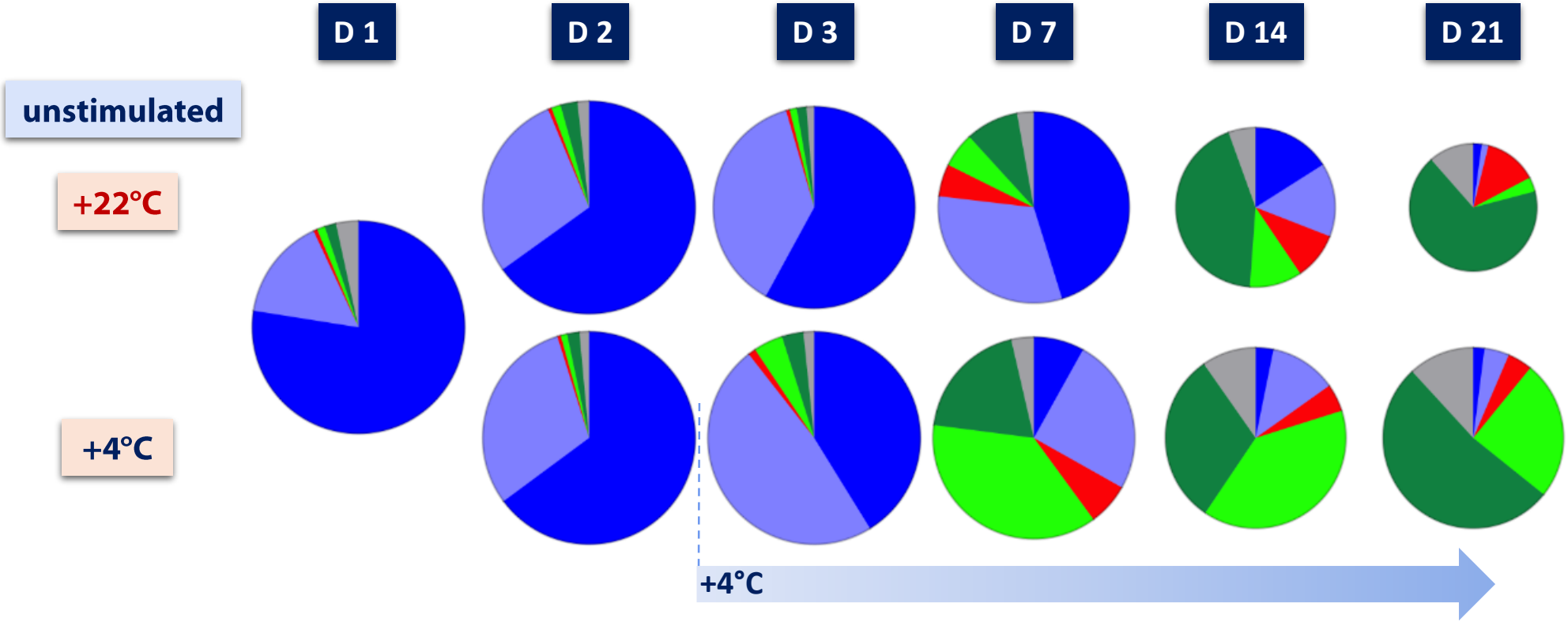
Mitochondrial integrity declines more rapidly at +4°C

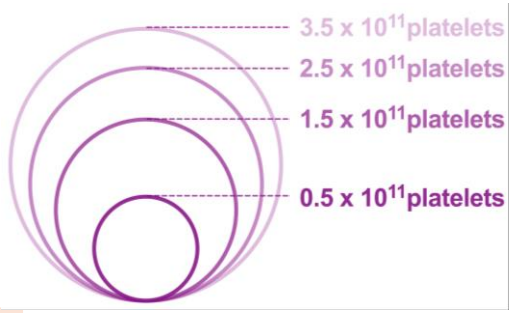
Emergence of various platelet subpopulations



Communication from the SSC of the ISTH (J Thromb Haemost 2023)

Evolution of platelet subpopulations during storage



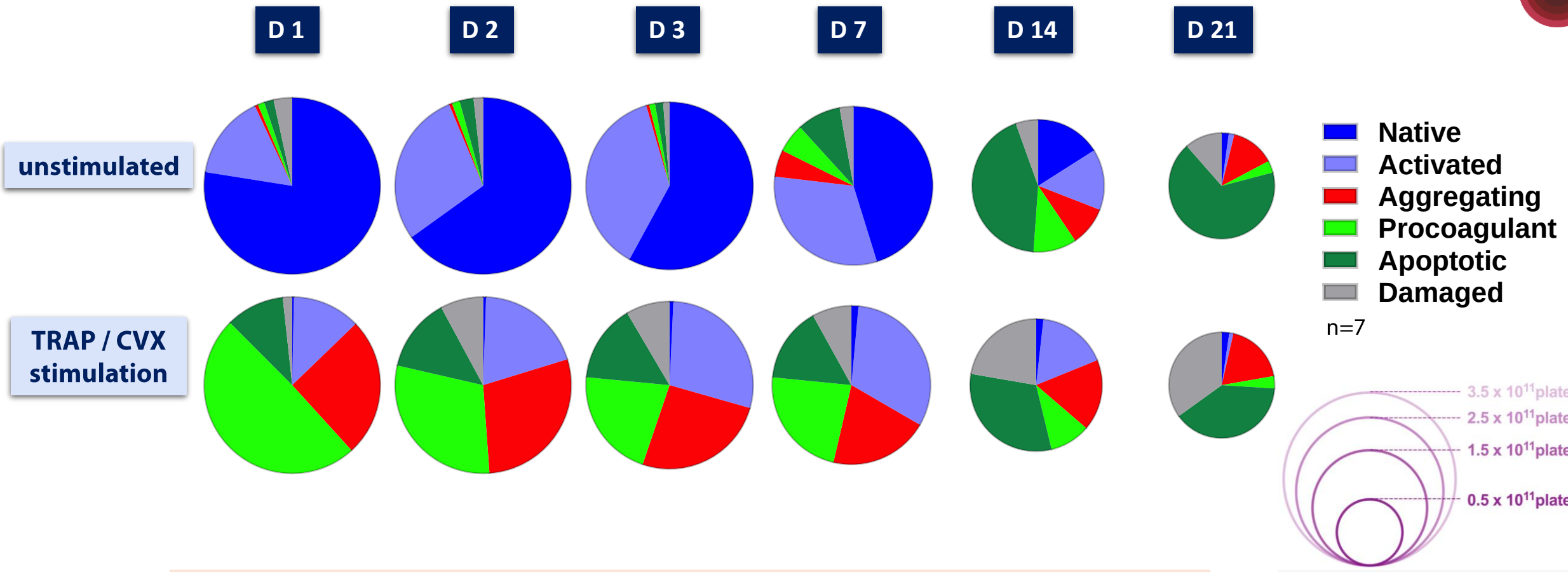


At +4°C, procoagulant and apoptotic platelets dominate and supplant native platelets

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

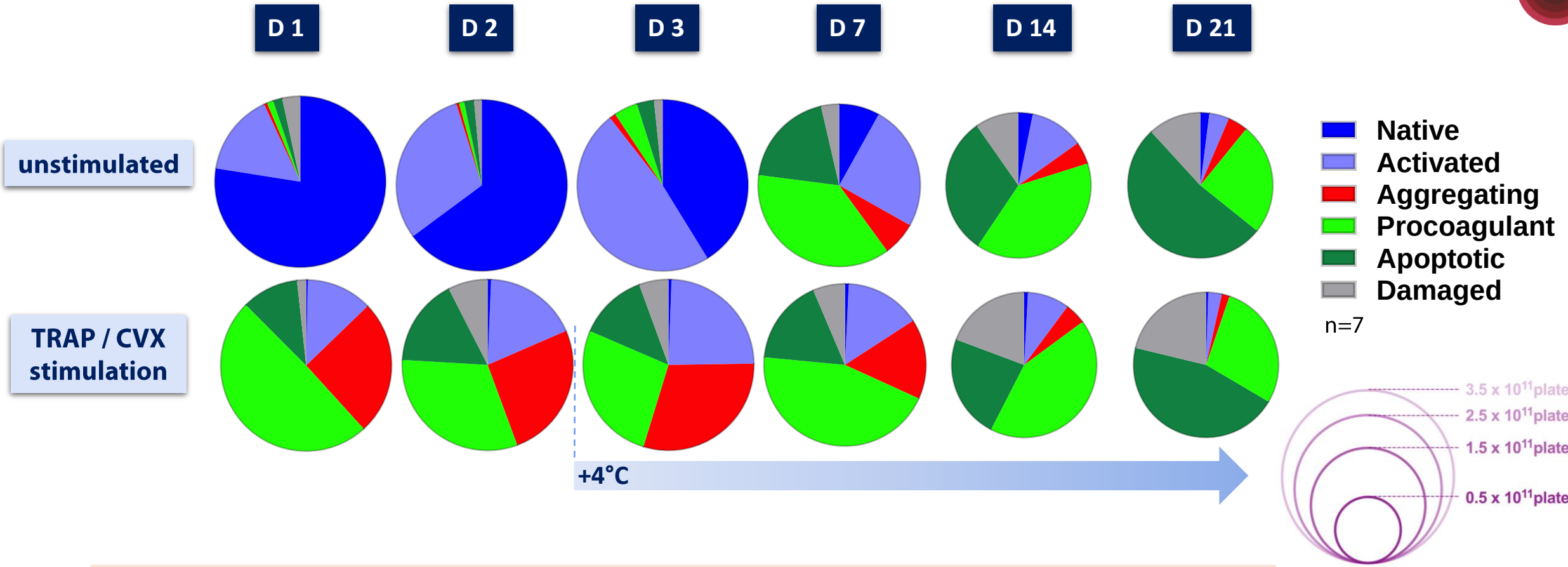
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Residual activability of platelets at +22°C



At +22°C, platelets retain a reserve of activation

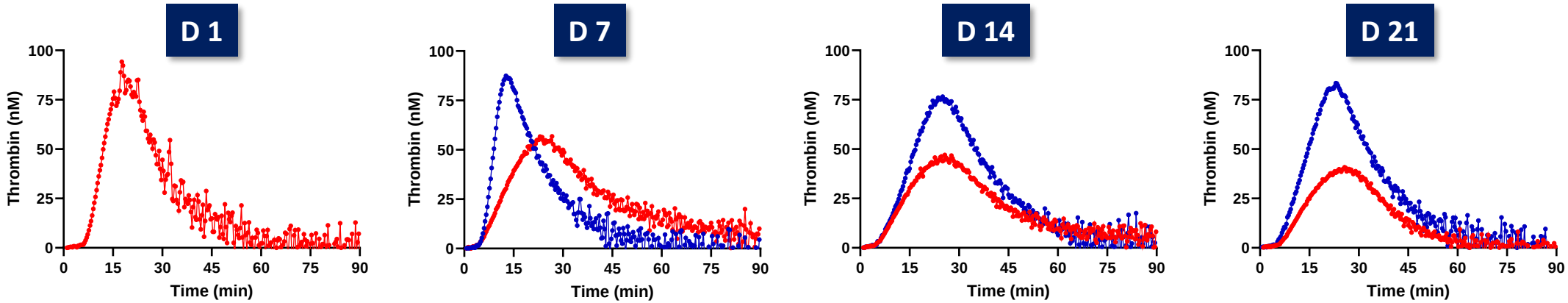
Residual activability of platelets at +4°C

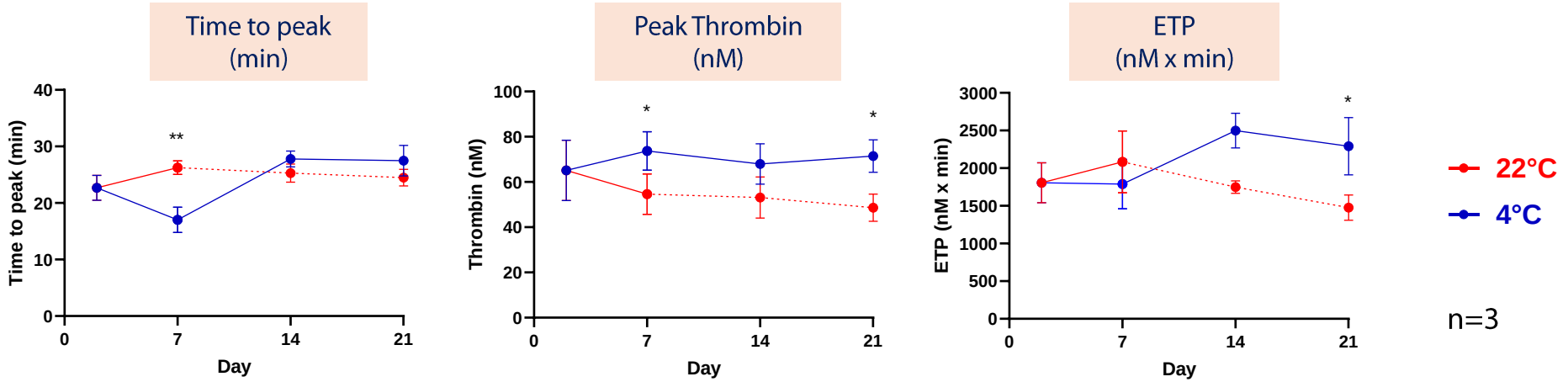


At +4°C, platelets are highly activated and display little reserve of activation

Thrombin generation capacity

- Evaluated by Calibrated automated thrombography (CAT)

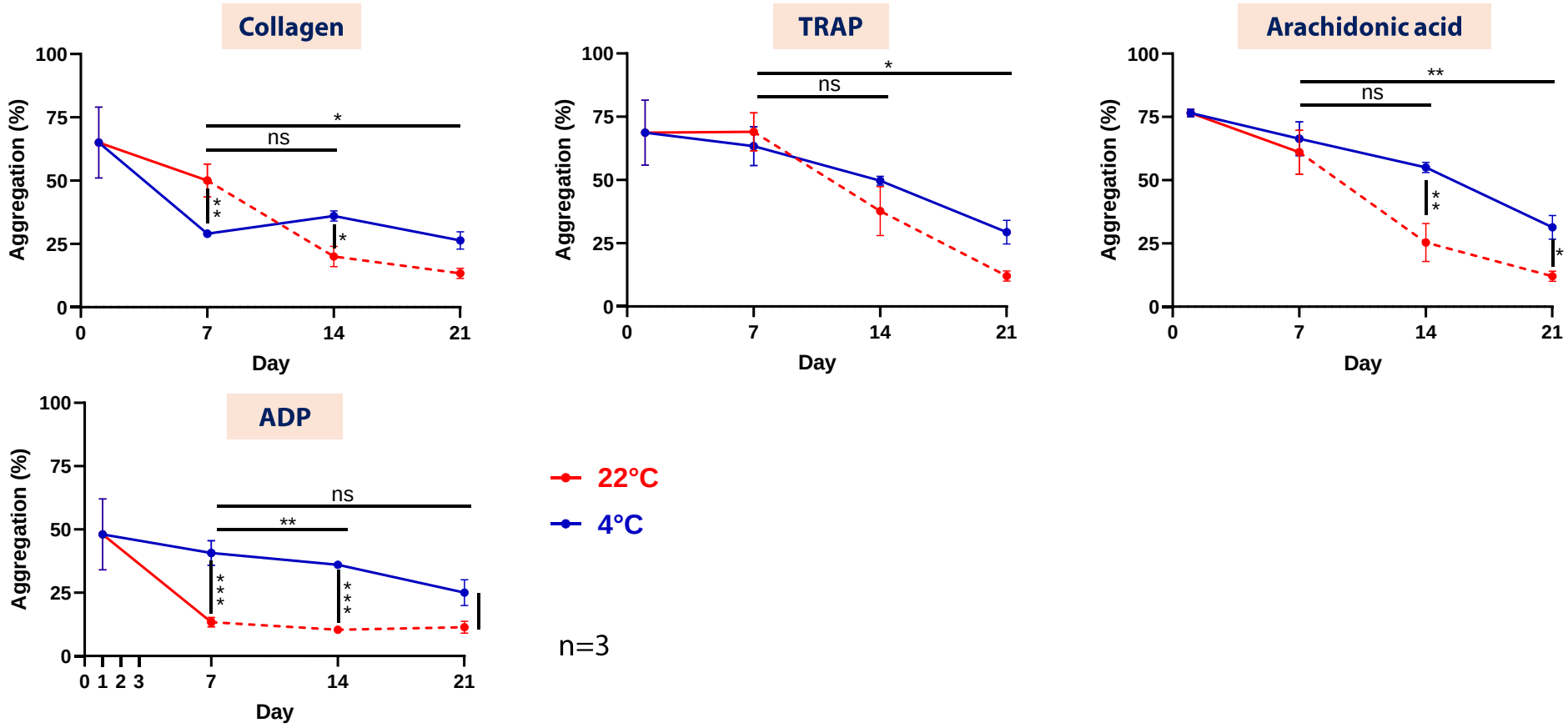




At +4°C, platelets have enhanced thrombin generation capacity

Aggregation responses

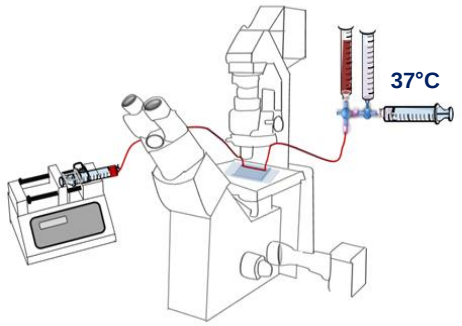
- Evaluated by light-transmission aggregometry



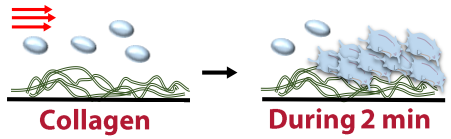
- Better retention of aggregation at +4°C than +22°C when comparing same-day (D14 or D21)
- Reduced aggregation at +4°C (D14 and D21) if compared with D7 +22°C (except ADP)

Thrombus formation under flow conditions

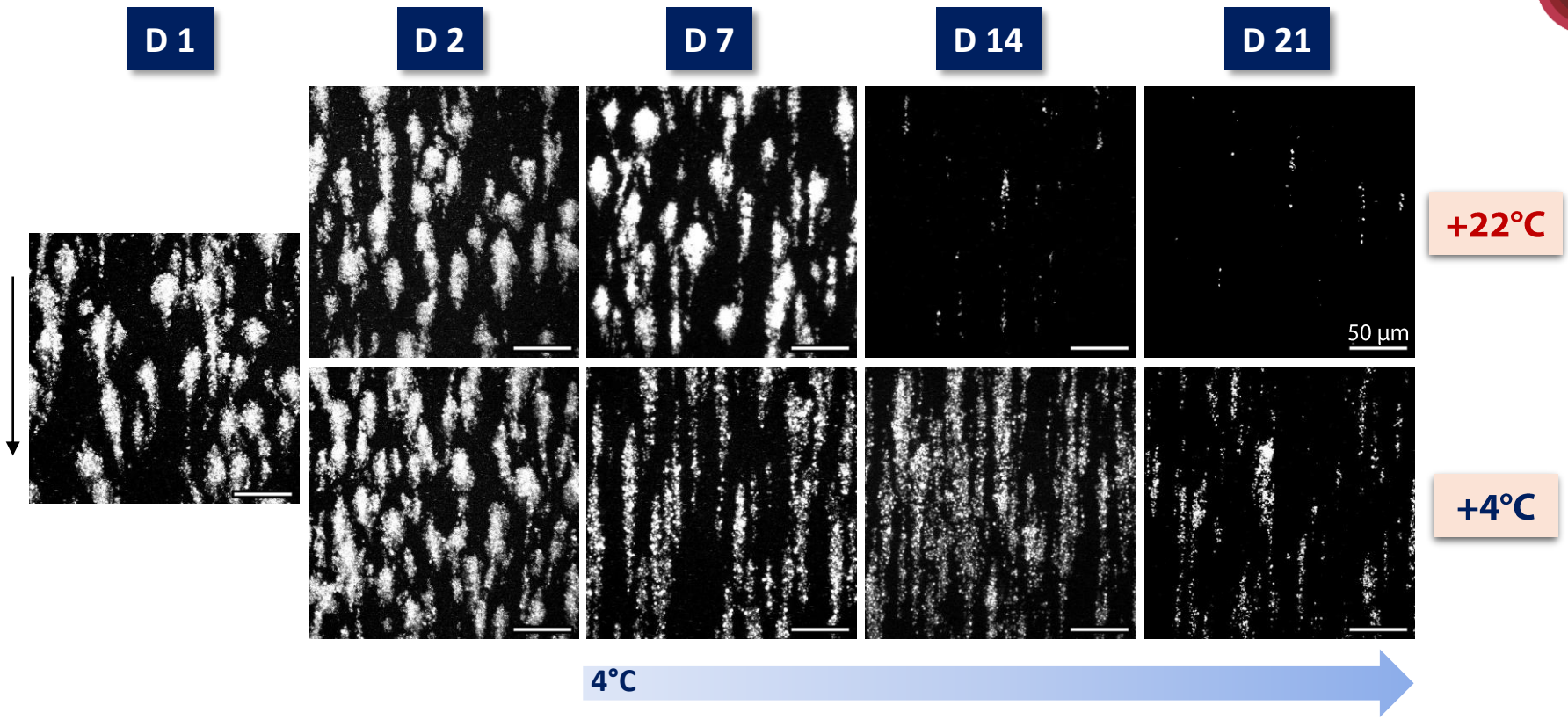
Perfusion system



Shear rate: 1500 s^{-1}



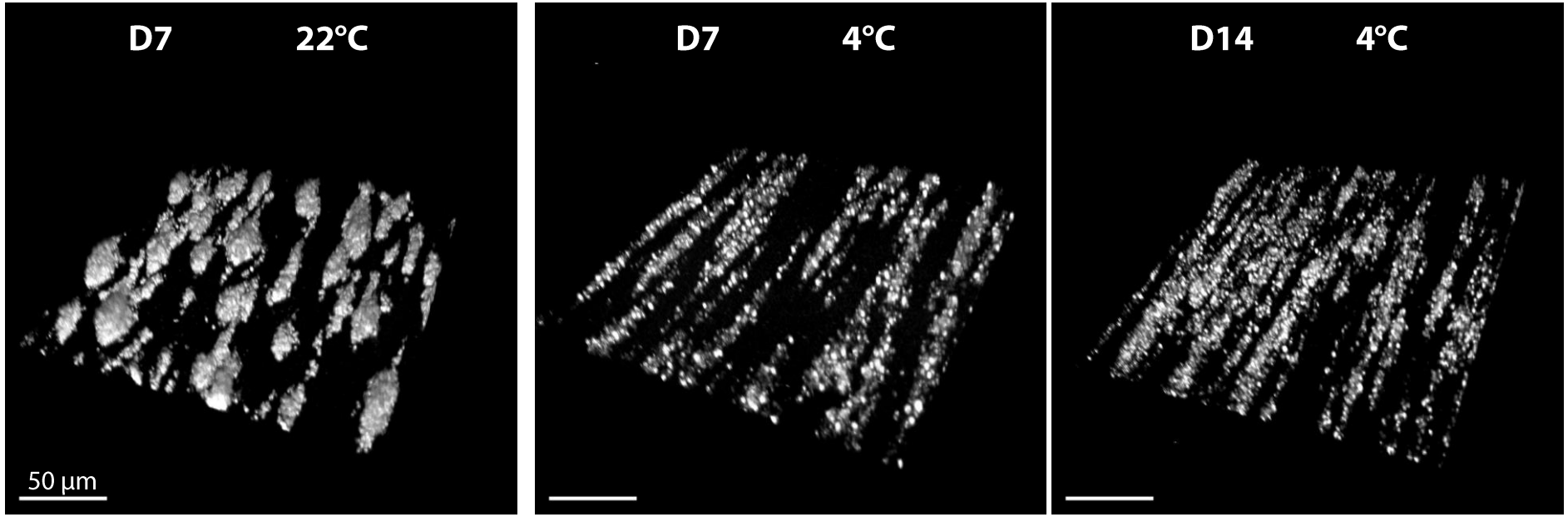
PCs reconstituted
with RBCs + hirudin
➔ no contribution of thrombin



At 4°C, platelets retain the ability to adhere and form thrombi on collagen under flow conditions for a prolonged period (D14)

Thrombus formation under flow conditions

Volume of thrombi after 2 min perfusion



At 4°C, platelets retain the ability to adhere and form thrombi on collagen under flow conditions for a prolonged period (D14)

Clinical studies on the efficacy of cold-stored PCs

- **Healthy volunteers:**
  - Recovery and survival of cold-stored platelets reduced to 2-3 days (Murphy S et al 1969; Becker GA et al 1973; Stolla M et al 2018)
- **FDA approval (USA), june 2023:**

> • Exceptions to 21 CFR 606.65(e) and 21 CFR 610.53(b) to manufacture apheresis platelets, platelet additive solution (PAS-C) added, leukocytes reduced, stored at 1-6 degrees Celsius for up to 14 days without agitation, and apheresis platelets, leukocytes reduced, psoralen-treated, stored at 1-6 degrees Celsius for up to 14 days without agitation. Both of the cold-stored platelet products are intended to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.

- **In Europe:**
  - Norway: storage up to 14 days; for actively bleeding patients (Braathen H et al, Transfusion 2022)
  - France: no approval

Clinical trials underway

- **Cardiac surgery:**
  - CHASE: *Extended Cold Stored Apheresis Platelets in Cardiac Surgery Patients*

    Phase 1/2 RCT in 30 patients; Apheresis-PC (100% plasma) 4°C (10-14 days) *vs* 22°C (up to 7 days)
  - CHIPS: *Chilled Platelet Study*

    Phase 3 RCT in 1000 patients; PC 4°C (up to 21 days) *vs* 22°C (up to 7 days)
  - PLTS-1: *Delayed Cold-Stored Platelets*

    Phase 2 RCT in 150 patients; IBS-BC-PC (PASIII) 4°C (5-14 days) *vs* 22°C (up to 7 days)
- **Trauma patients:**
  - CriSP-HS: *Cold-Stored Platelet in Hemorrhagic Shock*

    Phase 2 RCT in 200 patients; prehospital apheresis-PC 4°C (1-14 days) *vs* standard of care (Sperry JL et al, Ann Surg 2024)
    - 24h mortality: 6/102 vs 10/98 *p*=0,30; no side effect
    - Among treated patients: PC 4°C (8-14 days) *vs* (up to 7 days) improved TEG parameters (ns)
  - CriSP-TBI: *Cold-stored Platelet Early Intervention in Traumatic Brain Injury*

    Phase 2 RCT in 100 patients without shock; prehospital 2 apheresis-PC 4°C (1-14 days) *vs* standard care
- **Hematology:**
  - CoVeRTS-HM: *Cold versus Room Temperature-Stored platelets for bleeding in Hematologic Malignancy*

    Phase 2 RCT in 50 patients, bleeding; IBS-PC (PASIII) 4°C (up to14 days) *vs* 22°C (up to 7 days)

Conclusions

Preserved platelet count (D14)

Reduced metabolic activity

Modifications of surface glycoproteins

Increased P-selectin, phosphatidylserine and activated GPIIbIIIa

Procoagulant and apoptotic platelets predominate

Enhanced thrombin generation capacity

Alteration in the mitochondrial function

Prolonged ability to form thrombi in-vitro (D14)

- **Cold-stored platelets have an "activated" profile**
- **Healthy platelets are progressively replaced by procoagulant and apoptotic platelets during storage.**
- **Platelets have enhanced thrombin generation capacity (up to D21)**
- **Platelets retain the ability to adhere and form thrombi on collagen under flow conditions for a prolonged period (D14)**

Getz TM et al, Transfusion 2016; Johnson L et al, Transfusion 2016, 2021; Braathen H et al, Transfusion 2019; Six KR et al, Transfusion 2019; Zhao HW et al, J Proteome Res 2021; Shea SM et al, J Thromb Haemost 2023.

Conclusions

- **Cold-stored platelets**
  - Potentially more effective hemostatically
  - Risk of infection: INTERCEPT^{TM} Blood System for pathogen reduction
  - But: reduced circulation time and viability
- **Clinical benefit**
  - Clinical evaluation underway: are cold-stored PCs effective for the management of hemorrhage?
  - What about prophylaxis?
- **Operational benefit**
  - Longer shelf life (14 Days); no need to agitate
  - Remote area: rural and military settings
- **Progress in knowledge**
  - To be applied to cold-stored whole blood

Acknowledgments

- **Établissement Français du Sang-Grand Est, Strasbourg, France**
  Director: D. Kientz
- **Inserm UMR_S1255: Biology and pharmacology of blood platelets: hemostasis, thrombosis, transfusion**
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Adeline Galvanin

Hervé Isola

Xavier Delabranche

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BIO-THERAPIES

Prolonged storage of purified granulocyte concentrates from pooled buffy coats

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Torsten Schulze, MD[2], Jessica Rach, MD[2]

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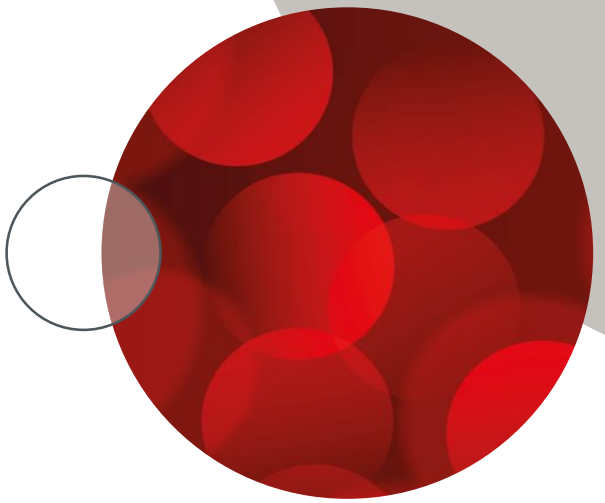
[2] German Red Cross NSTOB, Springe, Germany and University Medicine Oldenburg, Germany



STRASBOURG| 14.01.2025

Disclaimer

Jens Altrichter is founder, inventor and Managing Director at ARTCLINE GmbH

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BIO-THERAPIES

Agenda

1 Granulocyte concentrates - background

2 Purified GCs from apheresis

3 Purified GCs from buffy coats using HES

4 Purified GCs from buffy coats using gelatin

5 Clinical Use of granulocytes in non-neutropenic sepsis patients in an extracorporeal dialysis-like therapy

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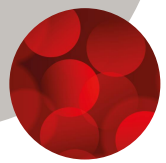


1

Granulocyte concentrates - background

Granulocyte concentrates (GC) - background

- **GCs are used for more than 60 years for transfusion, rarely used (500 p.a. in Germany)**
- **Main indication for transfusion:**
  - Chronic Granulomatosis (hereditary granulocyte malfunction in oxidative burst)
  - Severe infections in neutropenic patients
- **Recently, GCs are used in non-neutropenic sepsis patients in an extracorporeal treatment**
- **Two different manufacturing methods according to EDQM Guide for blood components**

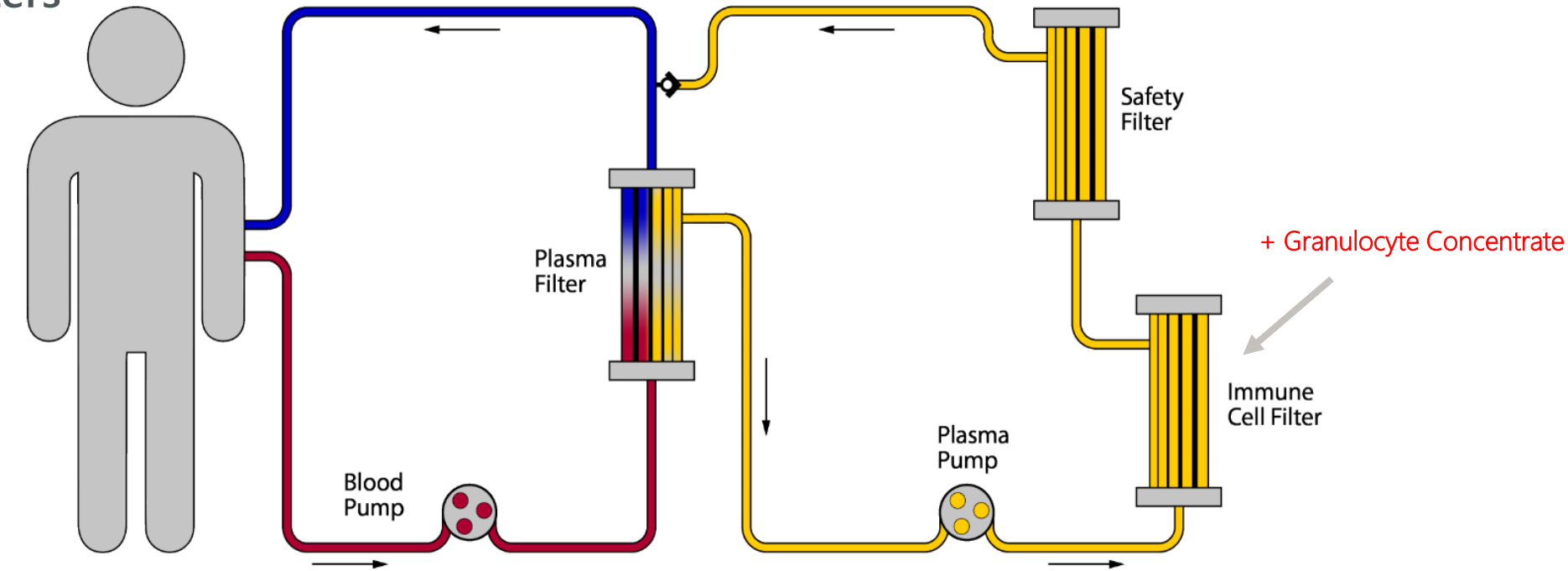
  Granulocytes, Apheresis: Single donor after stimulation with G-CSF und Glucocorticoid using sedimentation agents like HES or gelatin (main method in e.g. Germany) with >1E10 granulocytes

  Granulocytes, Pooled from buffy coats (used e.g. in UK, NL, FR) with >5E9 granulocytes
- **GCs contain mainly RBC (>90%) and PLT, but only 2-10% WBC**
- **Transfusion within 24h due to production of lactate by RBC, resulting in pH of <6.3 in 24h**

HES: hydroxy ethyl starch

Use of GCs in extracorporeal immune cell therapy ARTICE

Patients with septic shock are treated with GCs by separating the immune cells of patient and donor to minimize potential side effects (local endothelium damage by enzymes, ROS; GvHD) using plasma filters



Target: Re-activation of the patients immune system from immunoparalysis in later stage sepsis in order to overcome primary and prevent secondary infections.

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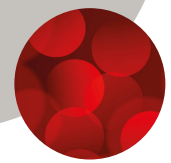
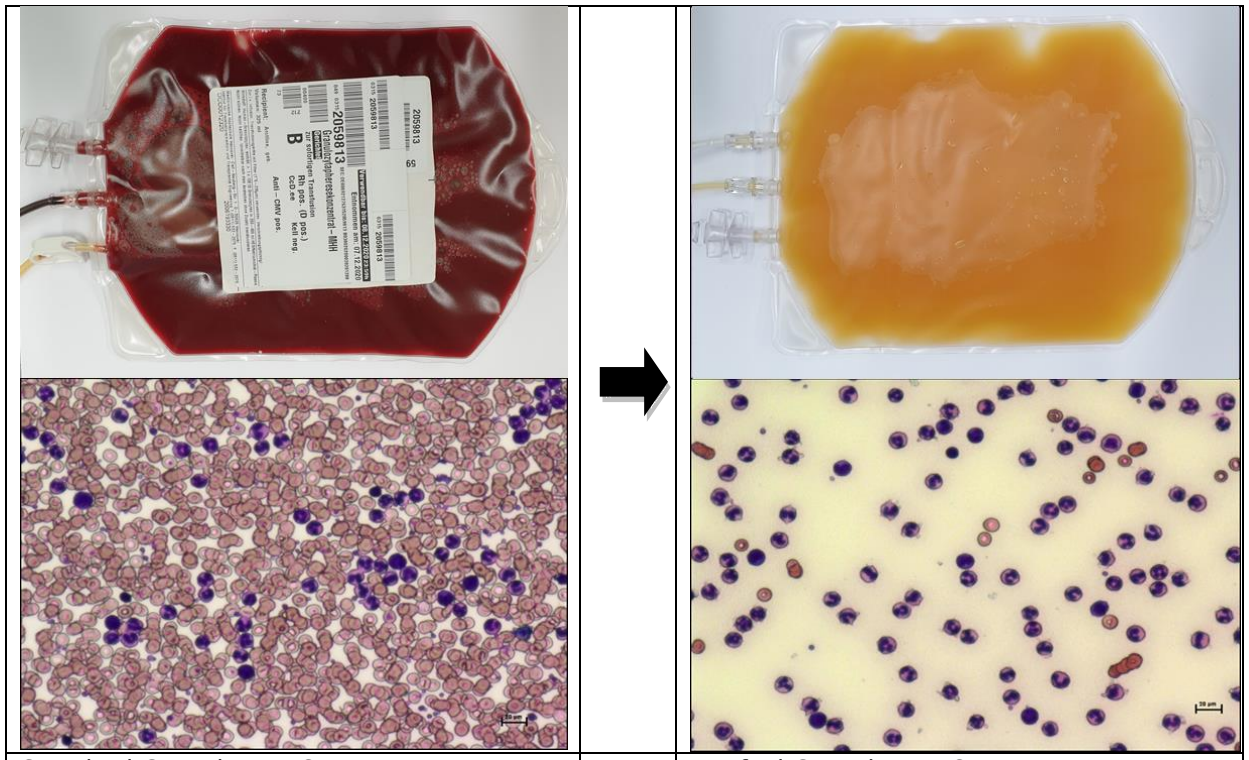


2

Purified GCs from apheresis

Purified granulocyte concentrates from Apheresis GC



Standard Granulocyte Concentrate		Purified Granulocyte Concentrate

ORIGINAL RESEARCH

TRANSFUSION

Prolonged storage of purified granulocyte concentrates: Introduction of a new purification method

The standard GCs are sedimented and the leukocyte rich supernatant is washed twice and the resulting washed cells are resuspended in donor plasma.

Purified GC contain approx. 98% less red blood cells (RBC) and 95% less platelets (PLT) than standard concentrates.

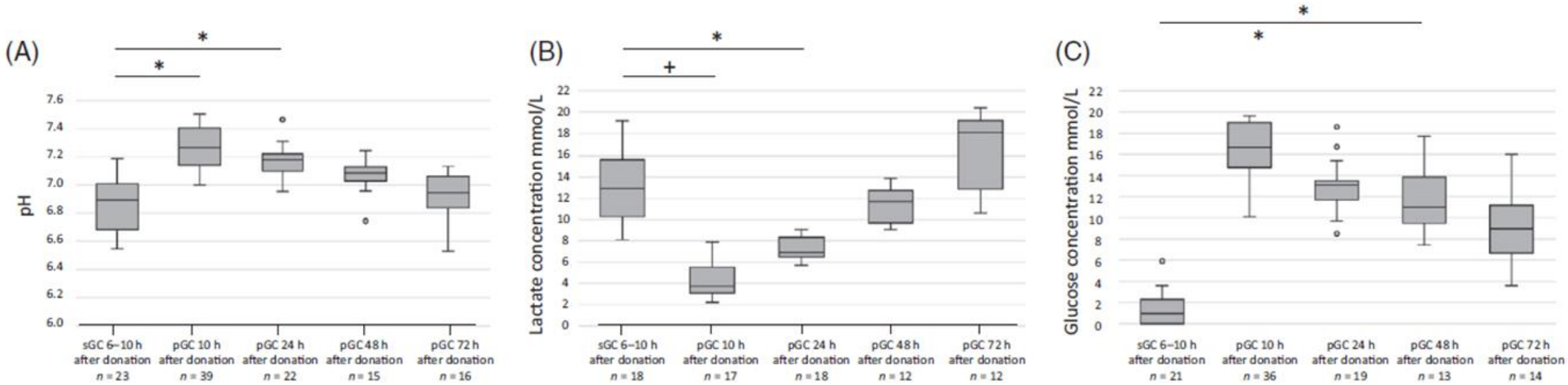
Klinkmann et al. Transfusion. 2022; 62:194–204

Comparison of standard GCs with purified GCs from Apheresis

pH

Lactate

Glucose

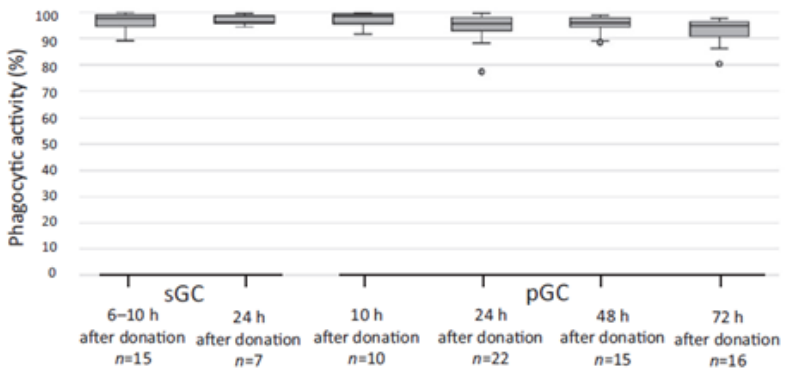


pH and lactate in purified GC are equal or better after 3 days than in standard GC within 6-10 hours. Glucose in purified GC is sufficient for at least four days.

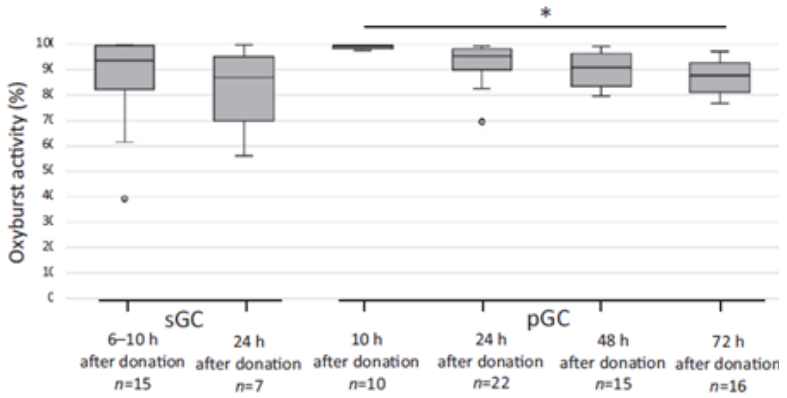
Klinkmann et al. Transfusion. 2022; 62:194–204

Comparison of standard GCs with purified GCs from Apheresis (II)

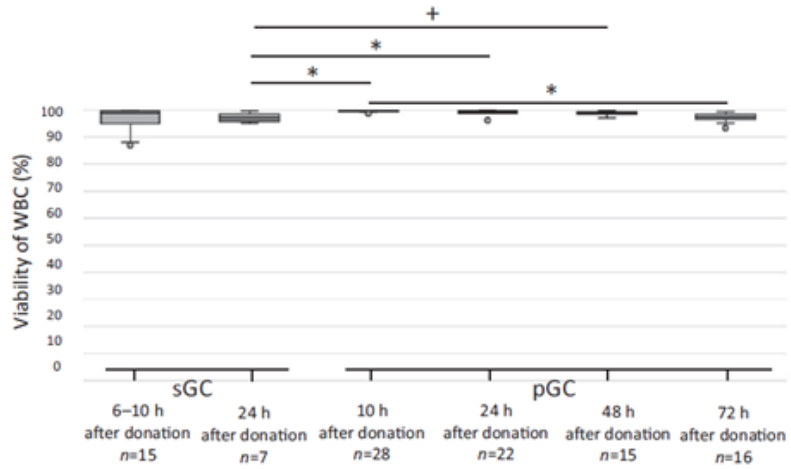
Phagocytosis



Oxydative burst



Viability



Oxidative burst, phagocytosis and viability in purified GC are equal or better after 3 days than in standard GC within 24 hours.

Klinkmann et al. Transfusion. 2022; 62:194–204

Comparison of standard GCs with purified GCs from Apheresis (III)

	Standard-GC from Apheresis	Purified GC from Apheresis
Granulocytes	> 1 x E10	1 bis 2,5 x E10
RBC	> 1 x E11	< 1 x E10
PLT	> 5 x E10	< 1 x E10
From 1 Donation	1 -2 preparations	2 - 4 preparations
Maximal storage time	1 day	At least 3 days
ABO compatibility	mandatory	ABO independent use possible
residual amount of sedimentation accelerator (HES / gelatin)	15-30 ml	Removed during washing steps

Comparison of standard GCs and purified GCs from Apheresis - Summary

- **Purified GC can be stored for 3-4 days, standard GC only 1 day**
- **From one apheresis usually 3 -4 purified GC ca be produces with 1 - 2.5 E10 granulocytes that can be used on three subsequent days**
- **More homogenous dosing possible with purified GCs**
- **Purified GCs contain less than 2 ml RBC, potentially allowing ABO independent use**
- **In purified GC the sedimentation agent is washed away**

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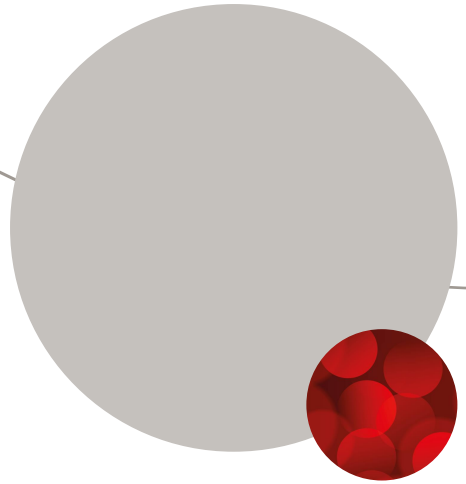
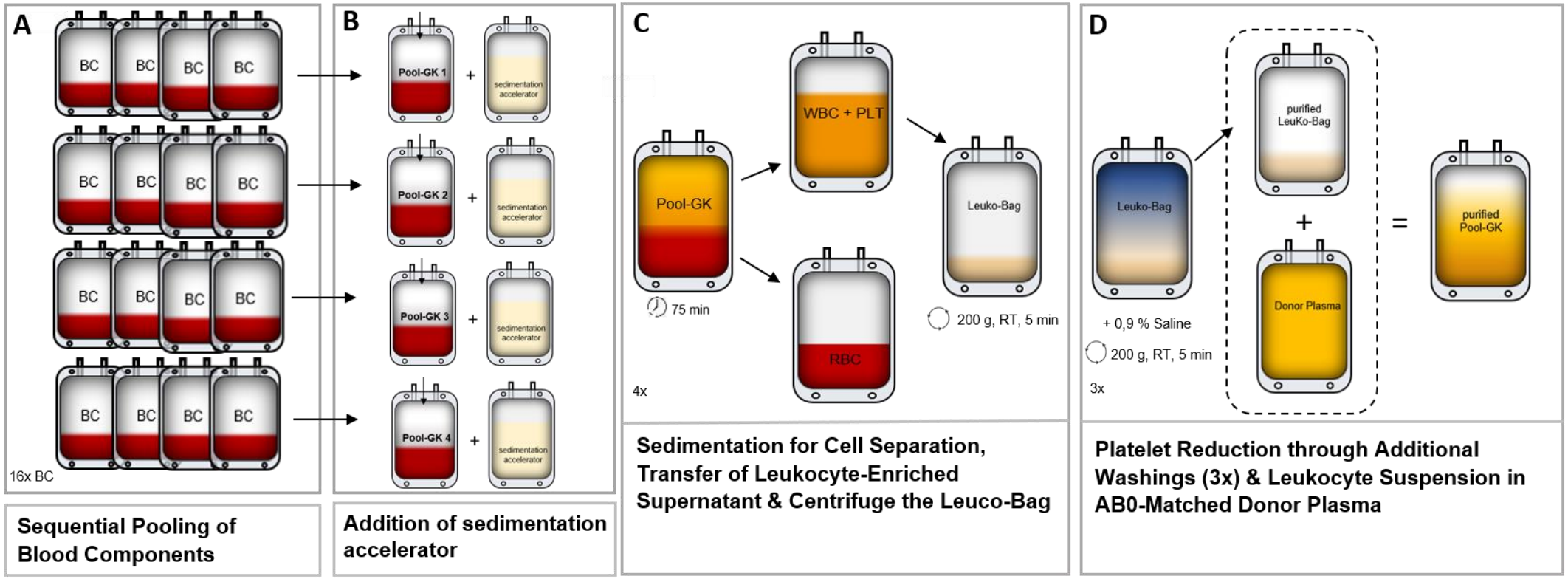


3

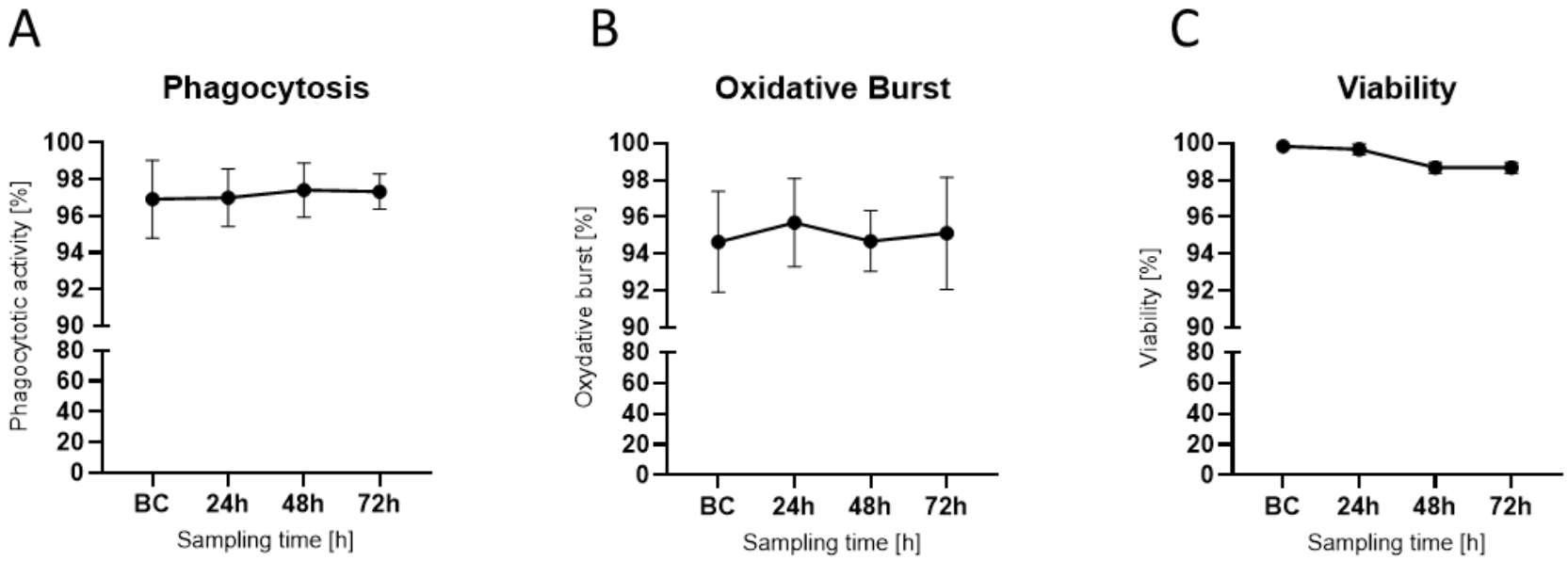
Purified GCs from buffy coats using HES

Purified GCs from pooled buffy coats

The buffy coats are pooled, a sedimentation accelerator is added, after sedimentation the leukocyte rich supernatant is washed and the resulting cell pellet is resuspended in donor plasma.



Purified GCs from pooled buffy coats using hydroxy ethyl starch (HES)



Transfusion Medicine and Hemotherapy

Research Article

Transfus Med Hemother 2024;51:383–392
DOI: 10.1159/000537698

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Purified Granulocyte Concentrates from Buffy Coats with Extended Storage Time

Gerd Klinkmann[a, b] Fanny Doss[c] Sandra Doss[b, c] Antje Schwarz[d, e]
Susanne Reichert[d] Daniel A. Reuter[a] Kathleen Selleng[f] Thomas Thiele[g]
Steffen Mitzner[d, b] Jens Altrichter[c]

Oxidative burst, phagocytosis and viability in purified GC are stable for at least 3 days.

Both HES with molecular weight of 200.000 (pentastarch) and 450.000 (hetastarch) can be used.

Klinkmann et al Transfusion Medicine and Hemotherapy 2024;51:383–392

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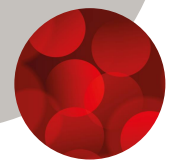
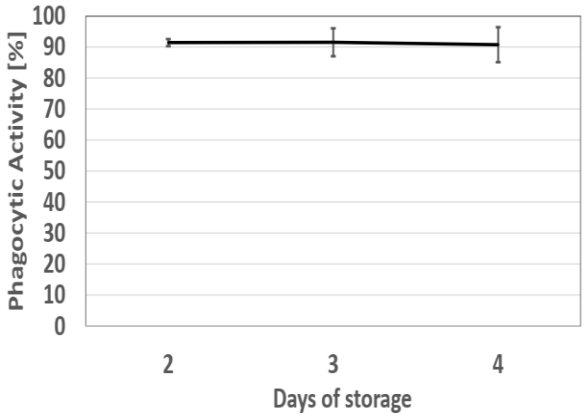


4

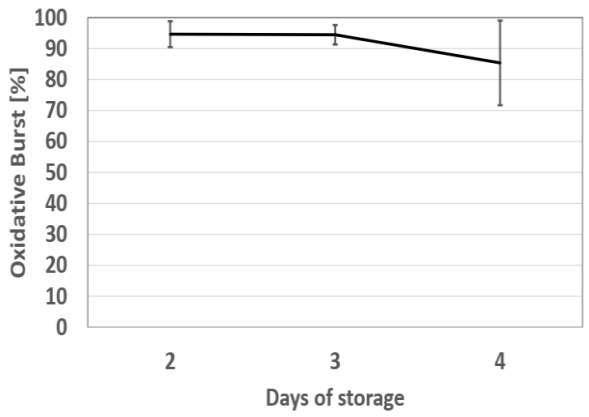
Purified GCs from buffy coats using gelatin

Purified GCs from pooled buffy coats using gelatin

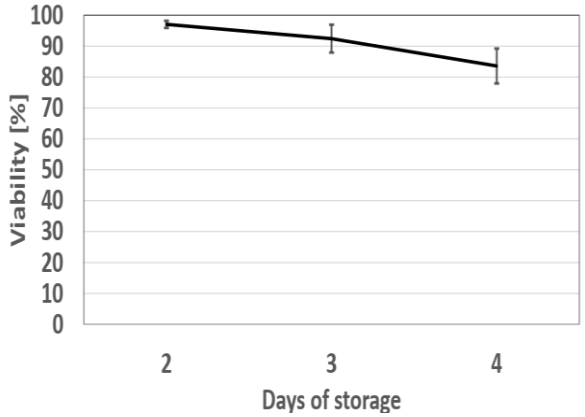
Phagocytosis



Oxydative burst



Viability



Oxidative burst, phagocytosis and viability in purified GC are stable for 3 - 4 days and comparable to standard granulocyte concentrates within 24 hours.

Altrichter et al Poster at DGTI congress 2024, Düsseldorf

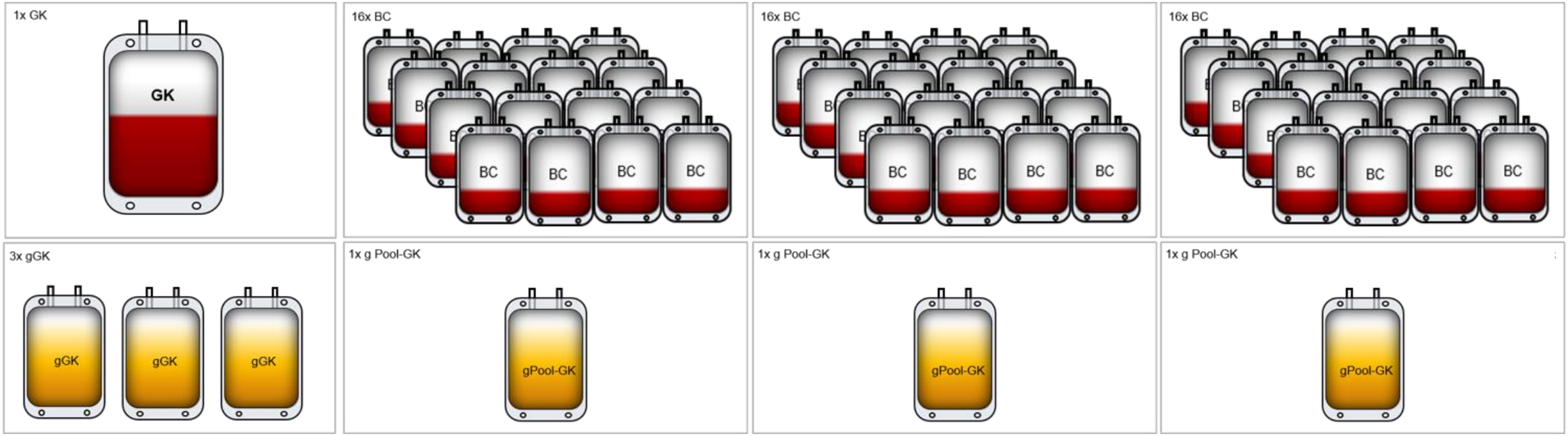
Comparison of purified GCs from apheresis and pooled buffy coats

Characteristic	Purified apheresis-GC	Purified pooled GC	Comment
Number of donors in 1 purified GC	1	in Germany max. 16	Higher potential infectious risk in pool
Number products from 1 manufacturing	2 to 4 products	1 product	
Donor impairment	High due to stimulation with G-CSF und glucocorticoids, apheresis procedure and sedimentation agent	Low	Higher Risk by apheresis
Availability of donors	Low	High	
Time till allocation	Low	Non-directed manufacturing possible	
Dose acc. to EDQM guide	>1E10	>5E9	Use of 2 Pooled GCs if needed
Composition	NEUT↑, PLT↓, RBC↓	NEUT↑, LYM↑, PLT↑, RBC↓	More PLT and LYM in Pooled GC

Comparison of purified GCs from apheresis and pooled buffy coats

Apheresis

Pooled buffy coats



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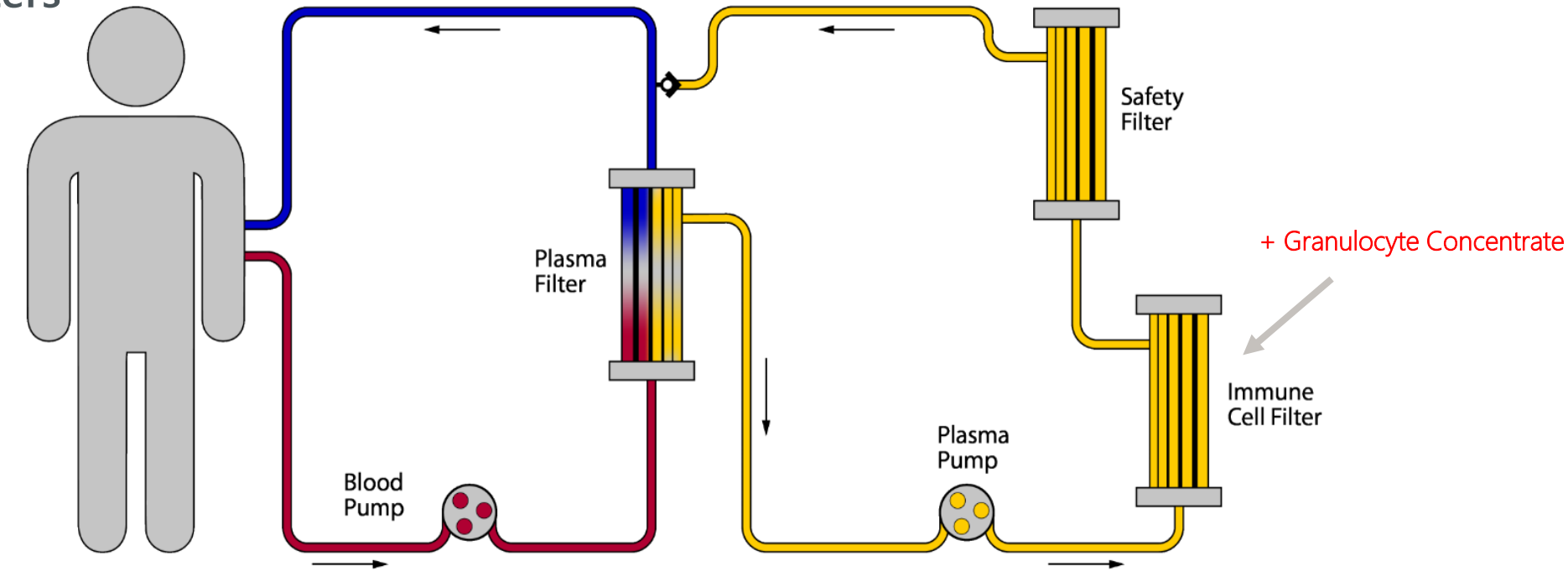
5

Clinical Use of granulocytes in non-neutropenic sepsis patients in an extracorporeal dialysis-like therapy

Use of GCs in extracorporeal immune cell therapy ARTICE

Patients with septic shock are treated with GCs by separating the immune cells of patient and donor to minimize potential side effects (local endothelium damage by enzymes, ROS; GvHD) using plasma filters



Target: Re-activation of the patients immune system from immunoparalysis in later stage sepsis in order to overcome primary and prevent secondary infections.

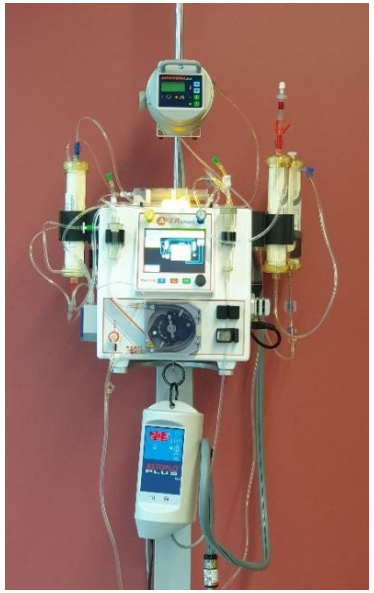
Elements of immune cell therapy platform ARTICE

Granulocyte concentrate

Produced acc. to GMP manufacturing authorisation

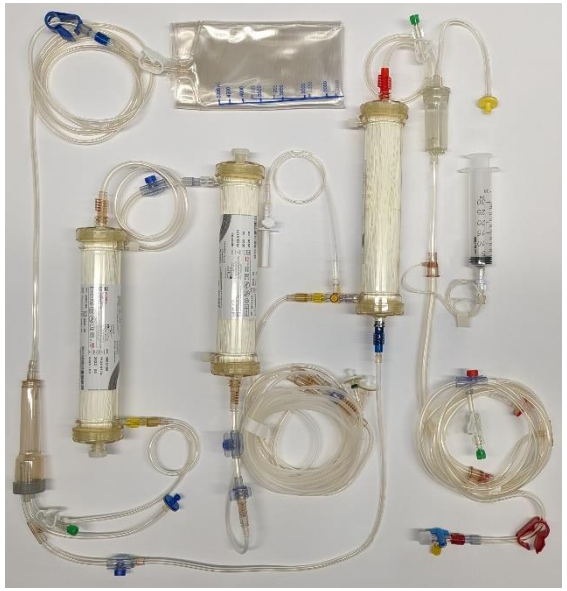
Machine

CE marked in EU.



Procedure Pack

All disposables (filters, tubing, etc.) are CE marked in EU.



Previous Clinical Trials


Altrichter et al. Critical Care 2011, 15:R82
http://ccforum.com/content/15/2/R82

CRITICAL CARE

RESEARCH Open Access

Extracorporeal cell therapy of septic shock patients with donor granulocytes: a pilot study

Jens Altrichter[1], Martin Sauer[2], Katharina Kaftan[1], Thomas Birken[2], Doris Gloger[3], Martin Gloger[4], Jörg Henschel[4], Heiko Hickstein[1], Ernst Klar[5], Sebastian Koball[1], Annette Pertschy[3], Gabriele Nöldge-Schomburg[2], Dierk A Vagts[2] and Steffen R Mitzner[2*]


Clinical Study

Bioartificial Therapy of Sepsis: Changes of Norepinephrine-Dosage in Patients and Influence on Dynamic and Cell Based Liver Tests during Extracorporeal Treatments

Martin Sauer,[1] Jens Altrichter,[2] Cristof Haubner,[1] Annette Pertschy,[3] Thomas Wild,[4] Fanny Doß,[4] Thomas Mencke,[1] Maren Thomsen,[1] Johannes Ehler,[1] Jörg Henschel,[2] Sandra Doß,[4] Stephanie Koch,[4] Georg Richter,[1] Gabriele Nöldge-Schomburg,[1] and Steffen R. Mitzner[2,4]

Safety & efficacy

#1 clinical trial

- 10 patients with septic shock
- demonstrated shock reduction, immune reactivation
- better survival than expected

↓

#2 clinical trial

- 10 patients with septic shock
- higher dose of immune cells
- confirms positive results from first clinical trial

Summary of study results

Primary objective of study **(safety):**

- Treatments **well tolerated**
- **No technical problems**

Secondary objective of study **(efficacy):**

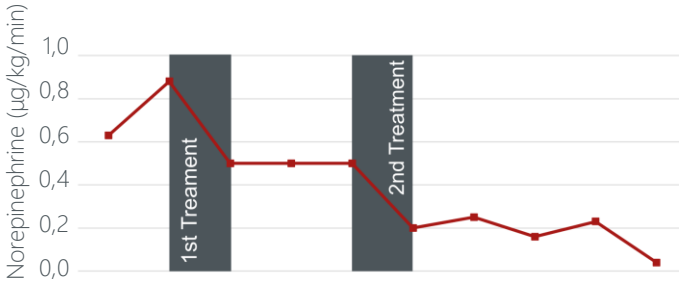
- **Improvement of shock** (reduction of norepinephrine dose)
- **Positive impact on immune competence** (cytokines, leukocytes, HLA-DR)
- **Significant decrease of infection** (endotoxins, PCT)

→ **Better survival** than expected from severity scores

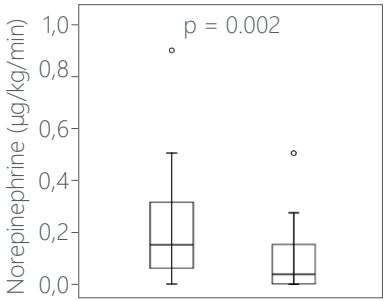
28-day survival:	13/20	(**65%**)
In-hospital survival:	11/20	(**55%**)
vs. predicted survival:		**30%**

(in-hospital survival according to APACHE II Score)

Reduction of shock symptoms (patient example):
During each treatment, pressure agents (norepinephrine) could be reduced.



Significant reduction of shock symptoms for total patient population in clinical trial



Norepinephrine dosage of (µg/kg/min) could be reduced significantly during extracorporeal granulocyte treatments (Mann-Whitney U test; n=10; median/0.25–0.75 quartile).

Altrichter et al. Crit Care 2011
Sauer et al. BMRI 2016
Sauer et al. TAD 2018

Previous Clinical Trials: Cytokines

	Patient				Extracorporeal circuit during treatment			
Mediator	Before extracorporeal treatment	After 6h extracorporeal treatment	%	p	Directly before cell compartment	Directly behind cell compartment	%	p
IL-2	3.67	11.92	325	n.s.	0.78	1.42	182	<0.05
IL-4	0.87	2.29	263	n.s.	0.09	0.24	268	<0.001
IL-6	102.22	313.15	306	n.s.	226.06	299.38	132	n.s.
IL-8	20.39	41.31	203	<0.05	31.79	165.15	520	<0.001
IL-10	2.57	6.54	254	<0.01	3.86	6.02	156	<0.05
IL-1 beta	1.21	2.12	175	<0.05	0.74	1.11	150	<0.05
IL-5	0.42	1.33	315	n.s.	0.39	0.52	135	n.s.
IL-7	3.19	5.19	163	n.s.	2.64	4.14	157	n.s.
IL-12(p70)	2.46	9.65	392	n.s.	0.09	0.45	498	<0.001
IL-13	1.68	3.34	199	n.s.	0.85	1.05	124	n.s.
IL-17	0.05	0.59	1185	n.s.	0.04	0.10	274	n.s.
IL-1ra	106.96	208.03	194	n.s.	113.40	134.53	119	n.s.
IL-15	4.19	6.35	151	n.s.	3.20	4.37	136	n.s.
IL-9	1.11	8.15	737	n.s.	0.29	0.78	265	n.s.
IP-10	240.16	561.57	234	n.s.	508.51	749.08	147	<0.05
G-CSF	30.84	43.73	142	n.s.	50.87	53.44	105	n.s.
GM-CSF	10.81	50.79	470	n.s.	1.52	3.41	224	n.s.
IFN gamma	50.29	79.07	157	n.s.	14.83	25.26	170	<0.05
TNF alpha	0.00	0.00	100	n.s.	0.81	0.19	24	n.s.
MCP-1(MCAF)	130.72	224.46	172	n.s.	299.52	225.67	75	n.s.
MIP-1b	55.93	98.89	177	n.s.	76.92	103.23	134	n.s.
Eotaxin	85.64	216.82	253	<0.05	80.23	130.72	163	<0.01
FGF basic	1.51	9.47	629	n.s.	0.61	0.00	0	n.s.
PDGF bb	652.01	1145.02	176	n.s.	10.28	62.25	606	<0.001
RANTES	137.70	298.64	217	<0.05	22.91	141.43	617	<0.001
VEGF	168.92	198.68	118	n.s.	1.12	2.45	219	n.s.
MIP-1 alpha	0.39	1.00	253	n.s.	0.34	0.51	148	n.s.

Altrichter *et al. Critical Care* 2011, **15**:R82
http://ccforum.com/content/15/2/R82

CRITICAL CARE

RESEARCH Open Access

Extracorporeal cell therapy of septic shock patients with donor granulocytes: a pilot study

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Significant immunomodulation not only in the extracorporeal circuit (shown in right table colored), but also in the patient (shown in left table, green).

Altrichter et al. Crit Care 2011

ReActIF-ICE Trial Currently Recruiting

Recovery from Acute Immune Failure in Septic Shock by Immune Cell Extracorporeal Therapy[1]

- Prospective, multicenter, randomized controlled parallel-group study ReActIF-ICE study, n = 142 patients
- **Experimental group**: Subjects with septic shock treated with immune cell extracorporeal therapy on top of standard of care (SoC)
- **Protocol:** Day 2-Day 9 up to 6 ARTICE® therapies for 6h each, Day 28 primary evaluation, Day 90 follow-up visit

Primary outcome measure

To investigate the safety and tolerability of ARTICE® therapy

Secondary outcome measure

To identify any clinical benefit of the ARTICE® immune cells when used in an extracorporeal treatment in a septic shock population

Additional endpoints

- Immunological parameters
  - immune dysfunction of patients after septic shock
  - influence of the ARTICE® therapy on these parameters
- Pre-specified interim analysis focusing on safety will be conducted after 50 treated and completed subjects (follow up through D28 already completed)

Trial conducted in ~20 leading intensive care centers in Germany, e.g.

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Trial objective: collection of post market data regarding performance, safety and usability of ARTICE® therapy

1 Clinicaltrial.gov: NCT05442710

Summary

- Purified GCs can be produced both from apheresis and pooled buffy coats
- Both can be stored for at least 3 days with high functionality and viability
- Each working day >10,000 buffy coats are discarded in Germany, allowing the daily production of purified GC from buffy coats
- Purified GCs contain less than 2 ml RBC, potentially allowing ABO independent use
- Beside transfusion GCs may also be used in non-neutropenic sepsis patients using an extracorporeal application
- Sepsis is a major threat in EU with almost 1,000 deaths every day
- Therefore, if demand is increasing a potential ABO independent of the shelf purified GC is possible

Collaborators

- Purified GCs from Apheresis: L. Goudeva, R. Blasczyk, L. Arseniev, K. Aleksandrova
- Purified GCs from buffy coats using HES: K. Selleng, T. Thiele
- Purified GCs from buffy coats using gelatin: T.J. Schulze, J. Rach
- Development of extracorporeal therapy: S. Mitzner
- Clinical trials: M. Sauer, G. Klinkmann, D. Reuter and many others

Thank You

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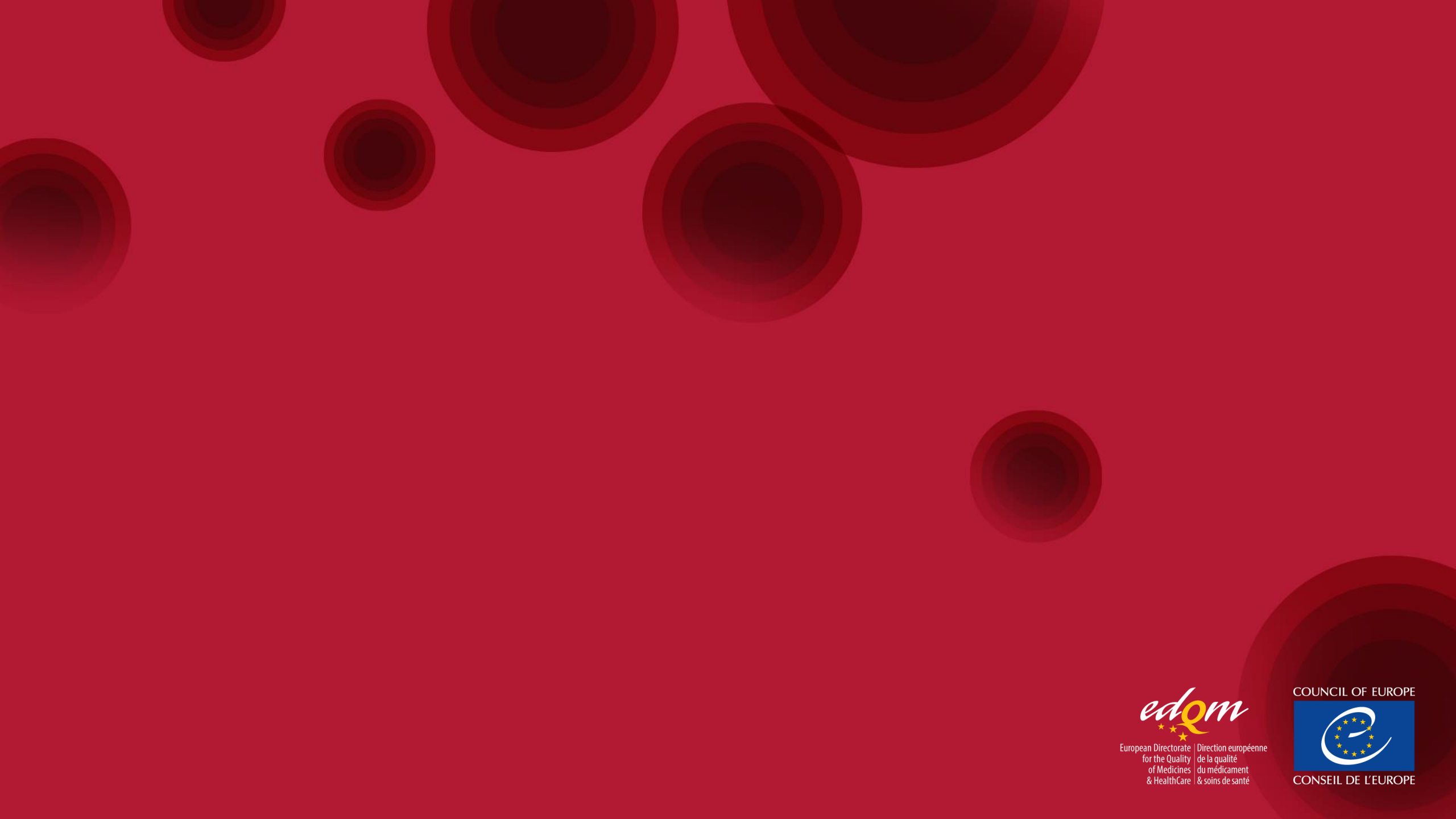
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