The future of blood transfusion in austere setting

[redacted]

PARIS SOF-CMC conference Fall 2022

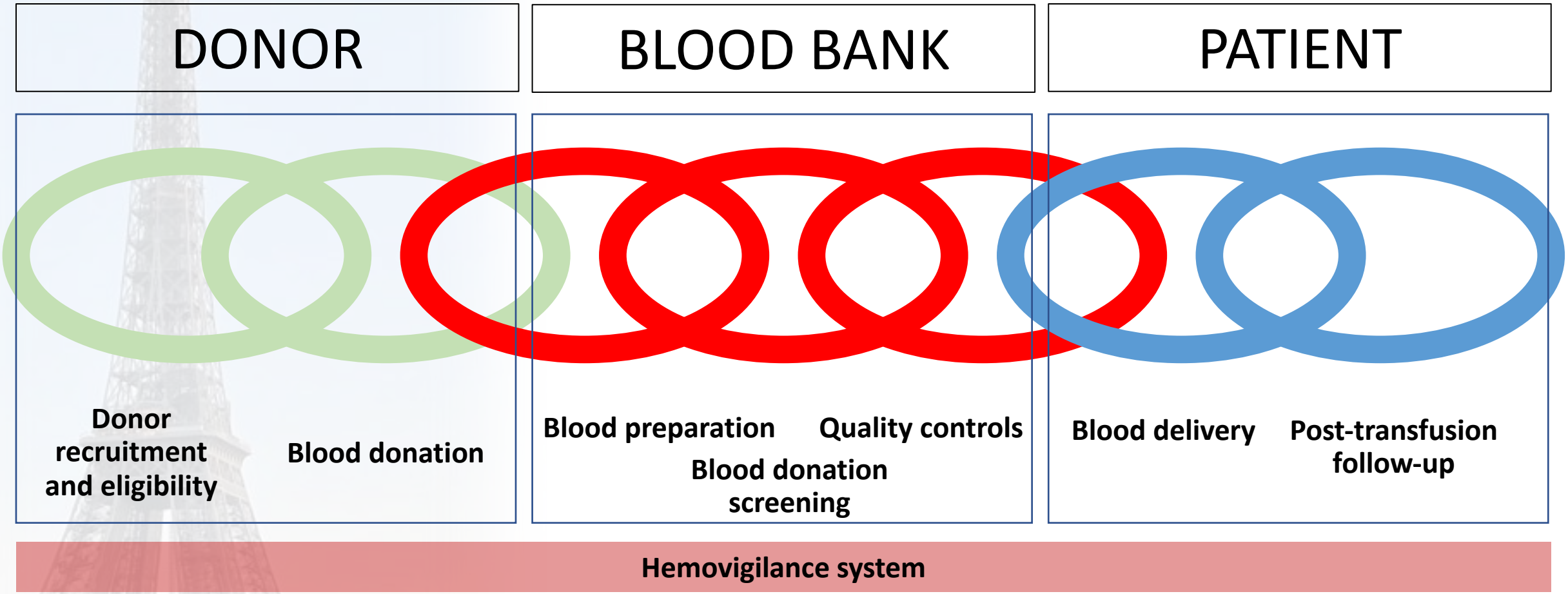
Disclaimer & disclosures

- The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the French « ministère des armées »

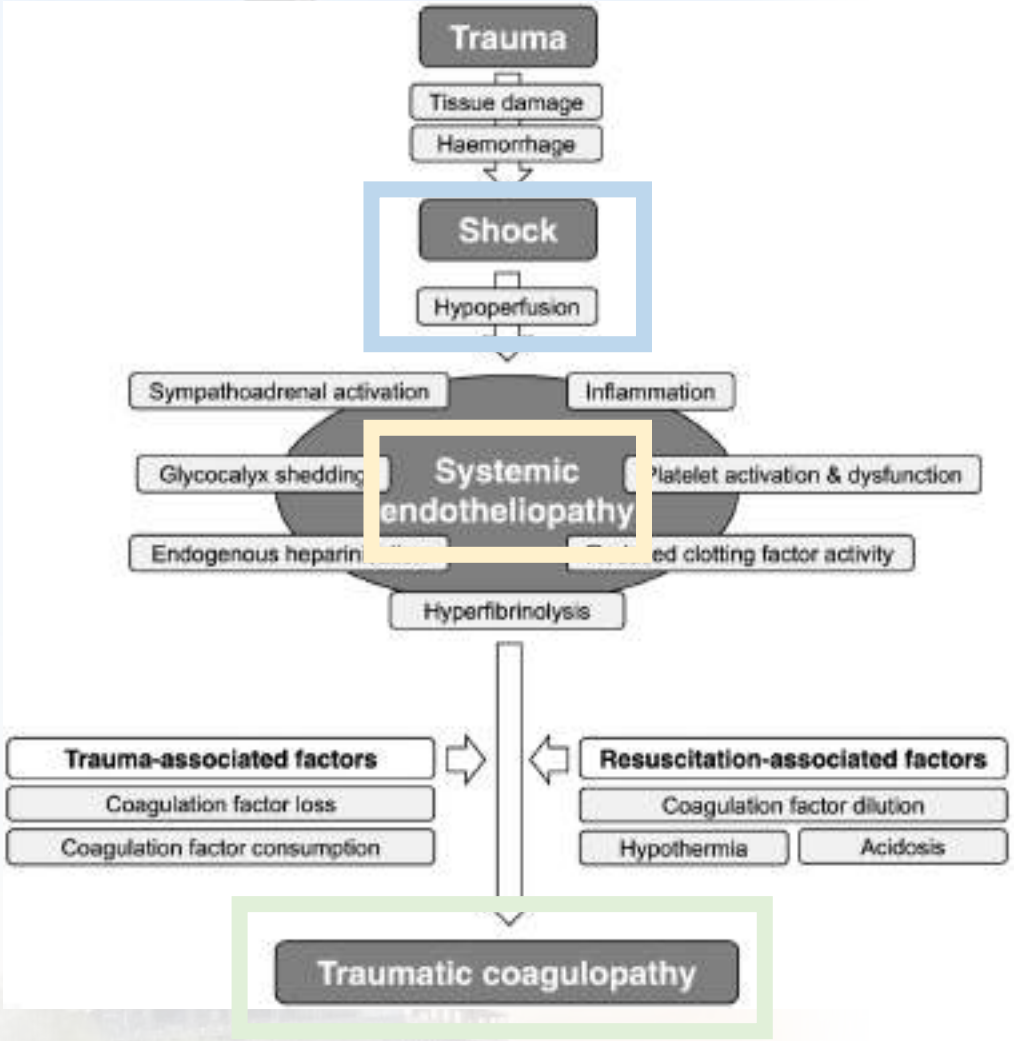
- I am retired officer of the French Military Medical Service
- Cepheid: employee
- Quotient: honoraria, regulatory studies

- **No conflict related to this presentation**

The transfusion chain



Pathophysiology of trauma-related hemorrhagic shock



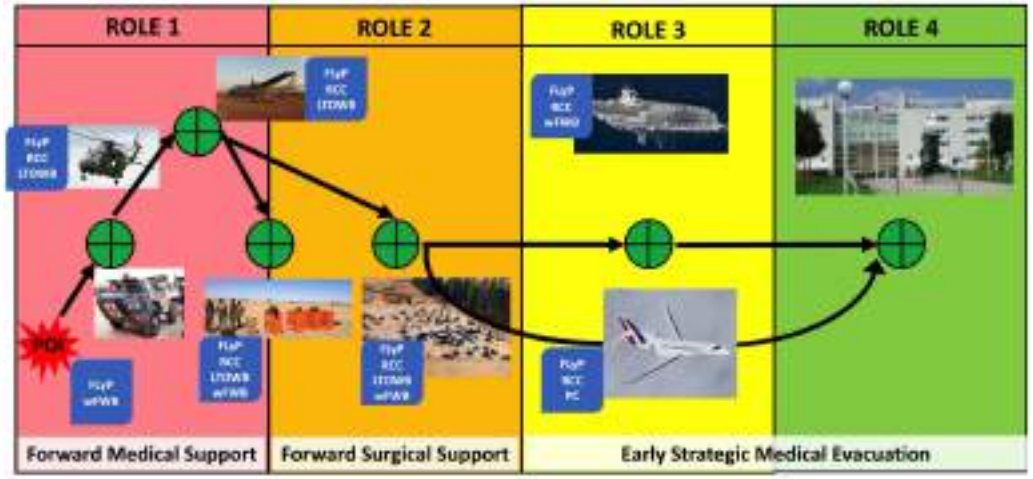
Blood Product	pRBC	Plasma	Platelets	Fibrinogen – cryo	Whole Blood
Oxygen debt (oxygen content and delivery)					
Endotheliopathy (glycocalyx, leukocytes adhesion, barrier)					
Coagulopathy (fibrinolysis, factors, clot formation)					

1. **Transfuse as soon as possible** ↘ 20 – 30% of mortality
2. **Transfuse plasma and not crystalloids** ↘ 20 – 30% of mortality
3. **Each minutes count** ↑ 5% of mortality / min
4. **Transfuse platelets** ↘ 20% of mortality
5. **Obtain a RCC: plasma: platelets ratio close to 1:1:1** ↘ 50 of mortality

Donat et al. J Crit Care 2019
Meyer et al. J Trauma 2017
Cardenas et al. Blood Adv 2018
Holcomb, et al. JAMA 2015
Shackelford et al. JAMA 2017
Sperry et al. NEJM 2018

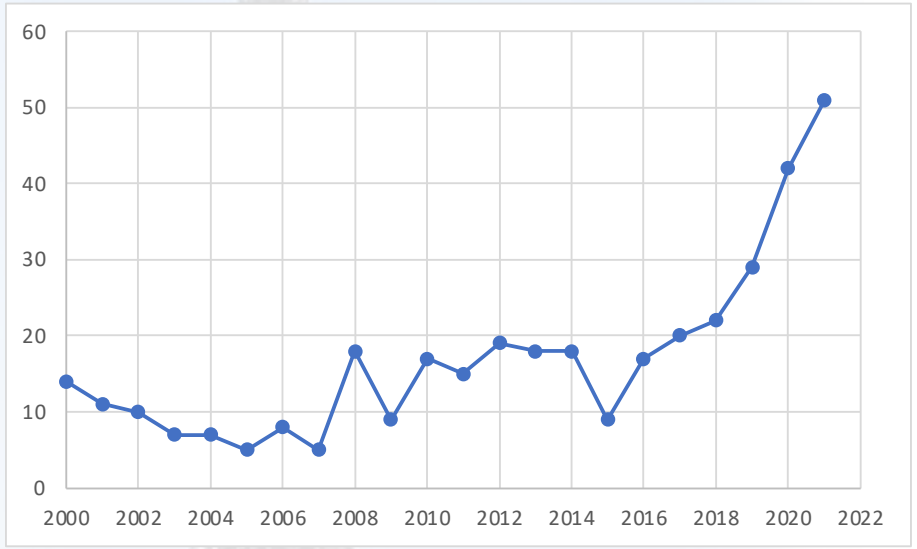
Current organization of remote blood transfusion

- ▷ Short time to transfusion
- ▷ End of surgery within 10h
- ▷ 11 blood products transfused
- ▷ Strategic evacuation within 24h



Aloird et al. Transfusion 2022
Martinaud et al. Transfusion 2019

The road to winning: Low Titer group O Whole Blood



ansm

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Monsieur le MCS Jean-Jacques LATAILLADE
Directeur du CTSA
1 rue Lieutenant Raoul Batany
92140 CLAMART

Saint-Denis, le 12/04/2021

Objet : DM 2021.004 / déleucocyté
sur le DMU Imuflex® WB-SP (Ref. LQG456E6) de Terumo-BCT.

Monsieur le Directeur,

En date du 01/03/2021, le CTSA a sollicité concernant la préparation de WB-SP (Ref. LQG456E6) de Terumo-BCT (Ref courrier CTSA : N°1-51/ARM/CTSA/DIR).

Après évaluation des données fournies, le CSP PSL-DS du 18 mars 2021 :

Avis Favorable

pour la préparation et de la conservation du sang total déleucocyté sur le DMU Imuflex® WB-SP de Terumo-BCT, à condition que la filtration soit réalisée le jour du prélèvement (filtration précoce) et que la durée de conservation à 4±2°C du sang total déleucocyté ne dépasse pas 21 jours à compter de la date de prélèvement.

Si le CTSA sang total filtré

être fourni.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

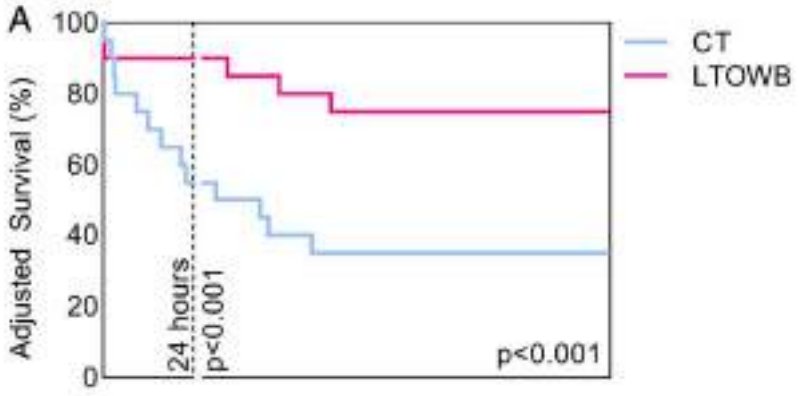
Copies :
- *Monsieur C. Martinaud - Centre de transfusion sanguine des armées (CTSA) - 1 rue Lieutenant Raoul Batany - 92140 Clamart*
- *Monsieur S. Bégué - Etablissement Français du Sang (EFS) - 20, avenue du stade de France - 93218 La Plaine Saint-Denis Cedex*

143/147 boulevard Anatole France - F-93285 Saint-Denis Cedex - Tél. : +33 (0)1 55 87 30 00 - **www.ansm.sante.fr**

7 January, 2018

Trauma Hemostasis and Oxygenation Research (THOR) Network Press Release:

EMERGENCY RELEASE LOW TITER GROUP O WHOLE BLOOD IS NOW PERMITTED BY THE AABB STANDARDS



Shea et al Transfusion 2020

Future needs: identify and fill the gaps

1. No harm, no worsening
2. Rapid reconstitution/availability
3. Small carry weight
4. Ease of portability without requiring cold storage and special conditions
5. Universally applicable no type matching.
6. Easy delivery

Blood substitutes? Existing products?

Red Blood Cells Substitutes

No shortage
No need of typing/matching
Long lifetime
Sterile

1. **O_2 transportation**

⇒ Hemoglobin <=> metHb

2. **CO_2 transportation**

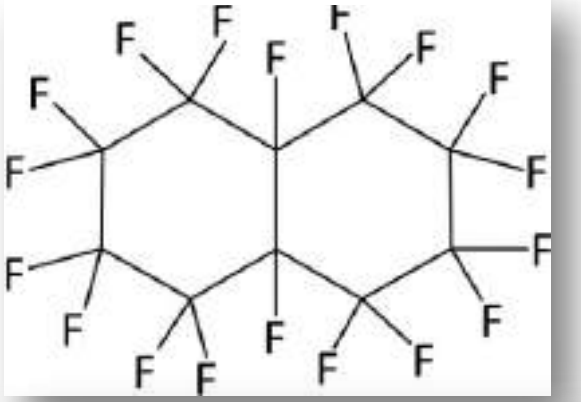
⇒ Erythrocyte carbonic anhydrase

3. **Free radical scavenging**

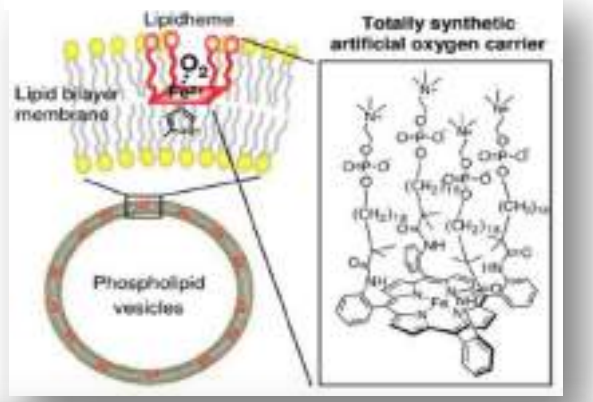
⇒ SOD and CAT

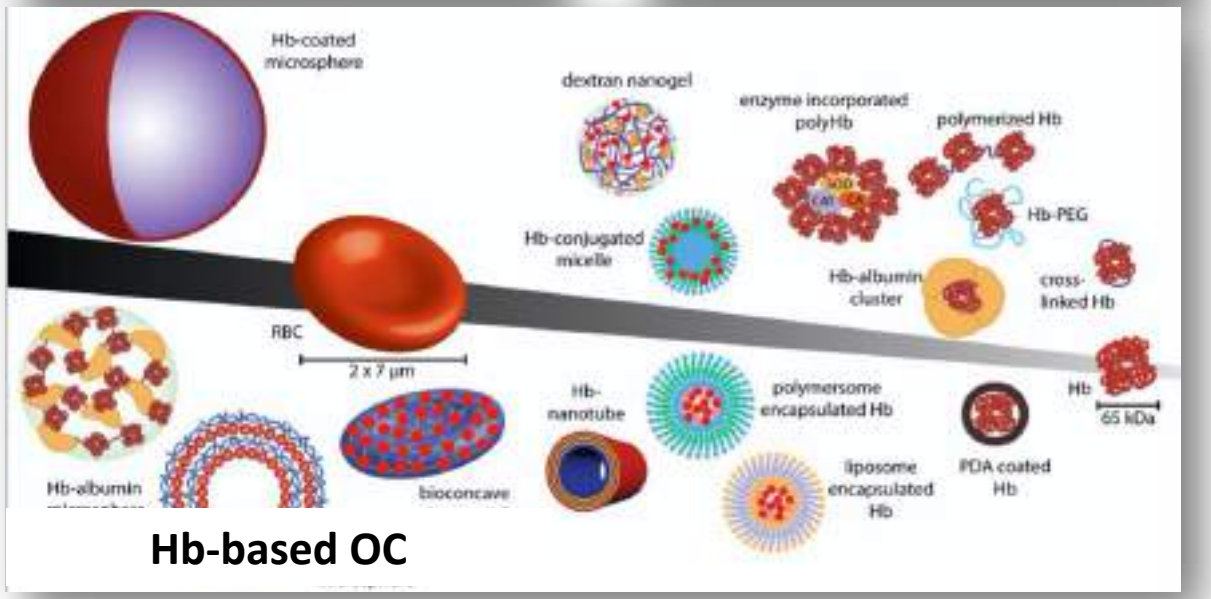
Jansman et al. Adv Coll Interf Sci 2018
Mohanto et al. J Pharm Invest 2022

Perfluorocarbons



Porphyrin-based aOC





Hb-based OC

Enhanced oxygen carriers: Perfluorocarbons

O_2 transportation

Immiscibility => require emulsification

Size << red cells: microcirculation

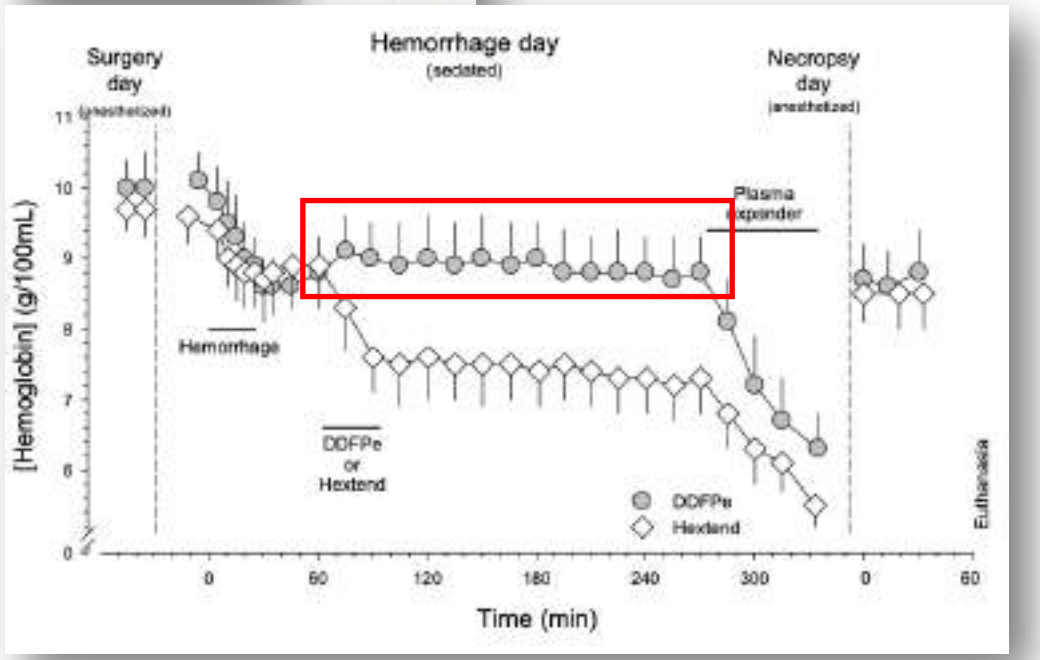
Fluosol-DA 20%
Oxygent™ (Alliance Pharmaceutical Corporation,San Diego, CA)
$NanO_2$® (NuvOx, Tucson, AR)

Limits

Dose limitation
Duration of required therapy
Impact of extreme hemodilution
Requirement for maintenance of high O_2 concentrations

Perspectives

Limit tissue damages
Limit organ dysfunctions
During a **reversible period of hypoxia**

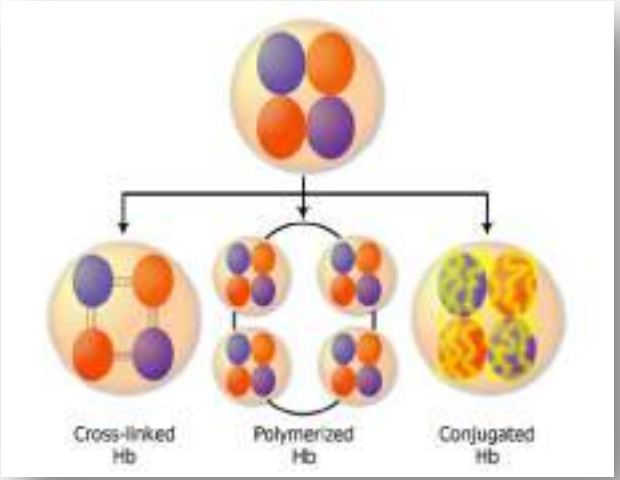


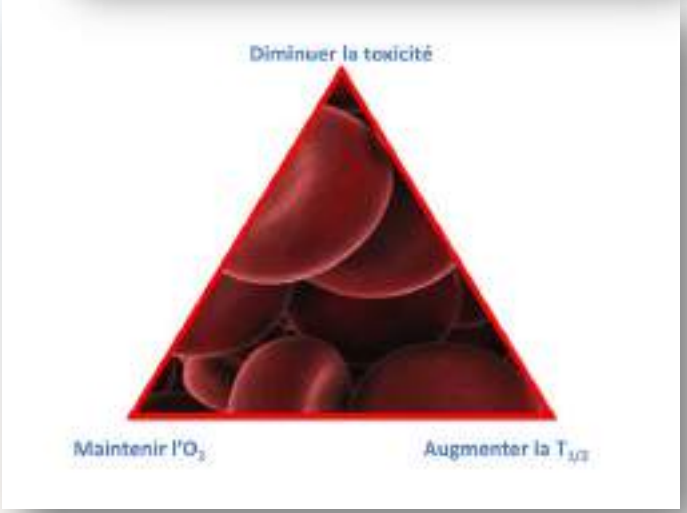
Lundgren et al. https://apps.dtic.mil/sti/pdfs/ADA511852.pdf 2009

Red Blood Cells Substitutes: Hemoglobin-Based Oxygen Carriers (HBOCs)

Double hemisynthetic systems

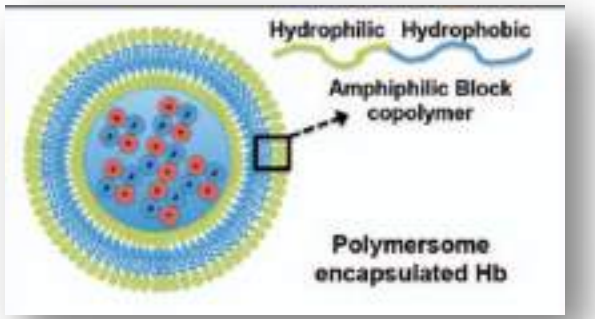
1. **Heme for O_2transport**
   - Human
   - Bovin
   - Recombined
2. **« Carrier »**
   - Chemical
   - Polymers
   - Microparticule





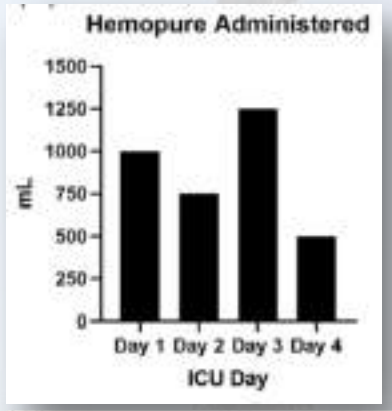
HBOCs formely/currently investigated

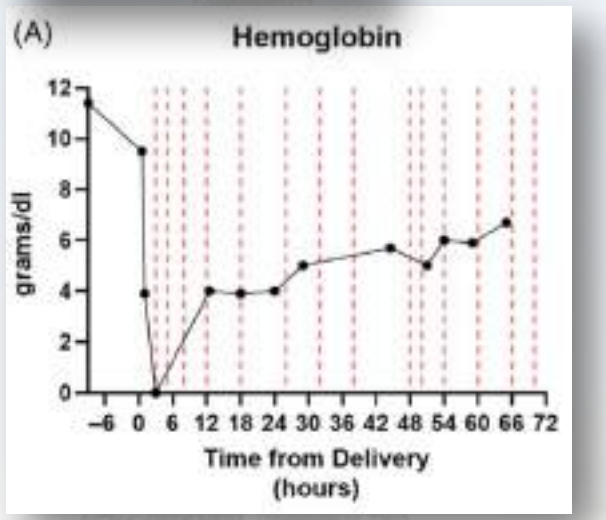
- **HemoPure®**
- **HemAssist®**
  - ✓ Stopped late 90's
  - ✓ Mortality 72% during clinical trial
- **PolyHeme®**
  - ✓ No approval (FDA, 2009)
  - ✓ Compagny gave up (2009)
- **HemoSpan®**
  - ✓ Toxicity led to end of the phase III trial



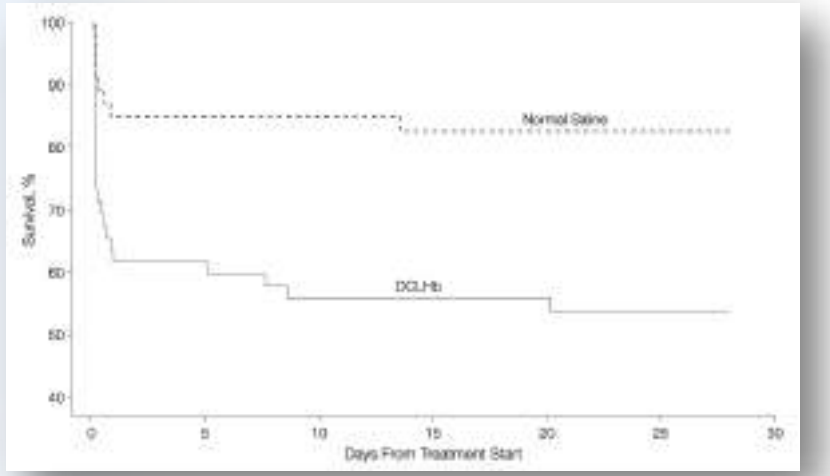
Morandi et al. Art Blood Subs 2016
Mohanto et al. J Pharm Invest 2022
Gupta et al. Shock 2017

Red Blood Cells Substitutes: Hemoglobin-Based Oxygen Carriers (HBOCs)





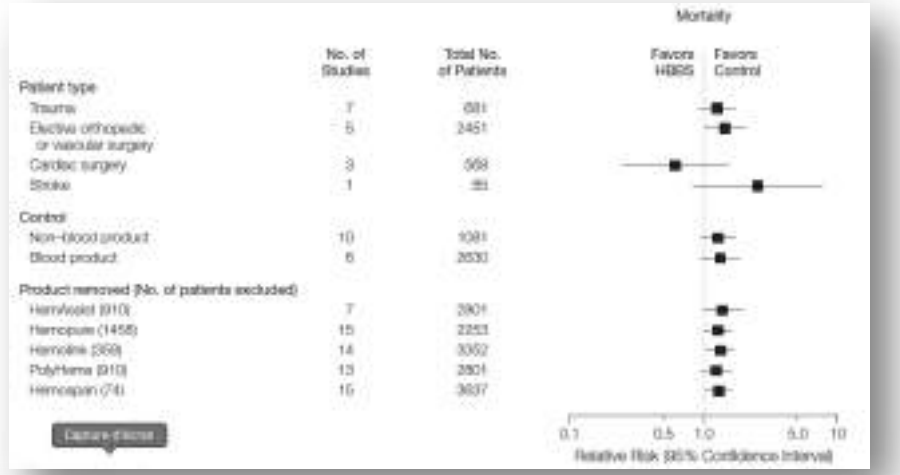
Davis et al. Transfusion 2018
Zumberg et al. Transfusion 2020
Barret et al. Transfusion 2022




Coronavirus. Le test du ver marin breton suspendu en urgence

L'Agence du médicament a suspendu en urgence ce jeudi le test d'une molécule issue du sang d'un ver marin, promu par une société bretonne. Une étude de 2011 sur des porcs aurait entraîné une létalité de 100 %. Le produit expérimental n'avait pas encore été administré à des patients.

Sloan et al. JAMA 1999
Natanson et al. Jama 2008



Vasoconstriction – HBP

Gastro-intestinals side effects

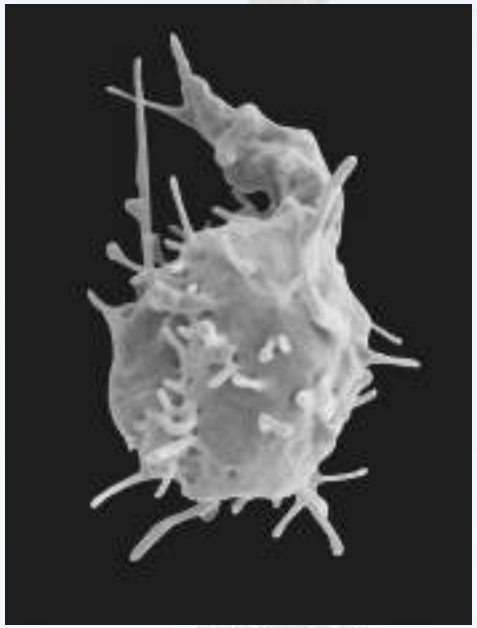
Increased liver/pancras enz.

Cardiac toxicity

Neurotoxicity

Nephrotoxicity

Platelets substitutes

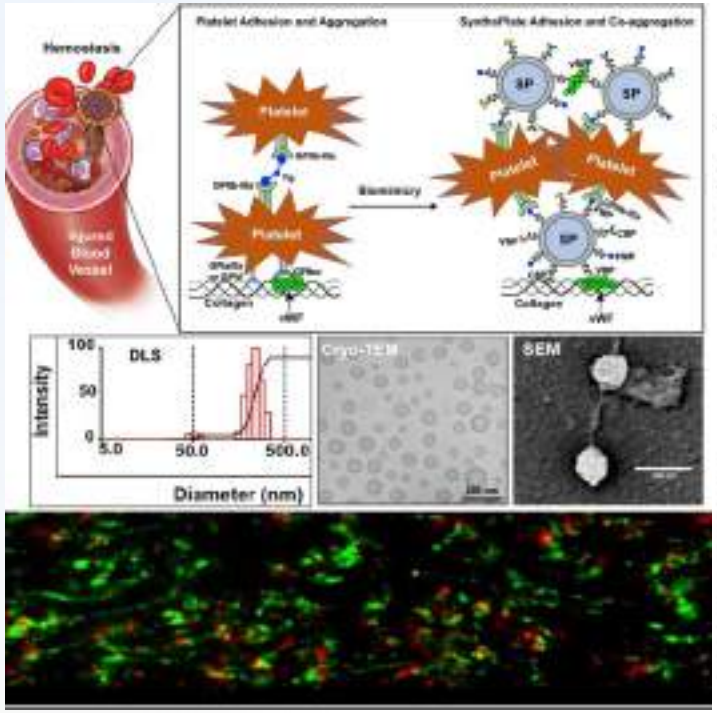


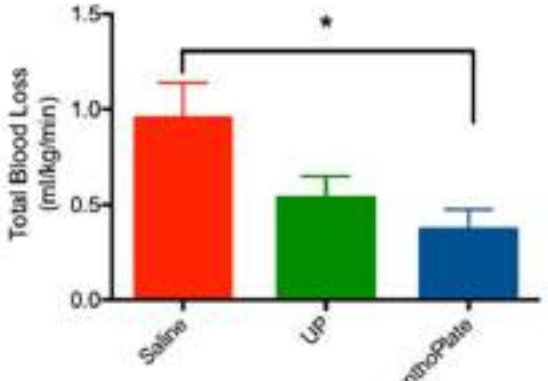
Primary hemostasis

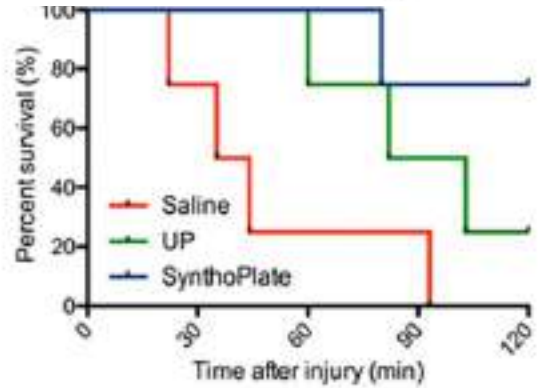
Immunomodulation

Endothelial integrity

Synthoplate

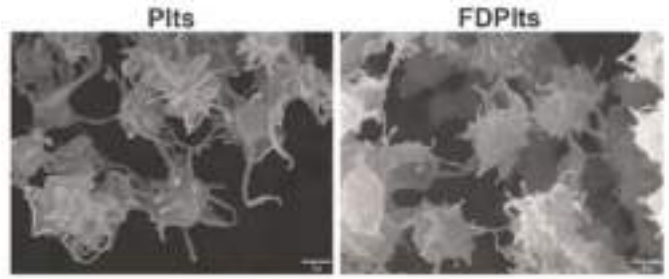


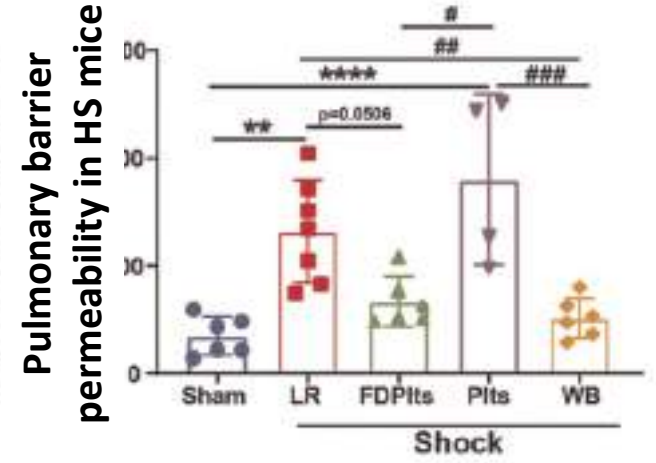




Sekkhon et al. MHSRS 2022
Hickman et al. Sci Rep 2018

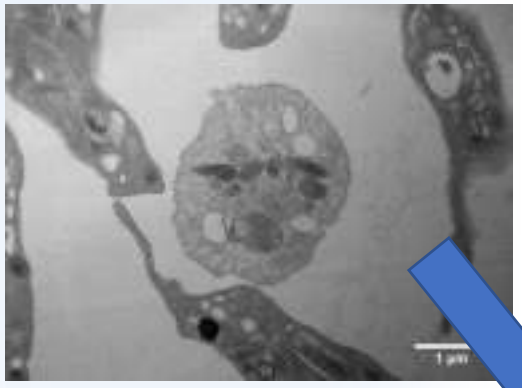
Thrombosomes

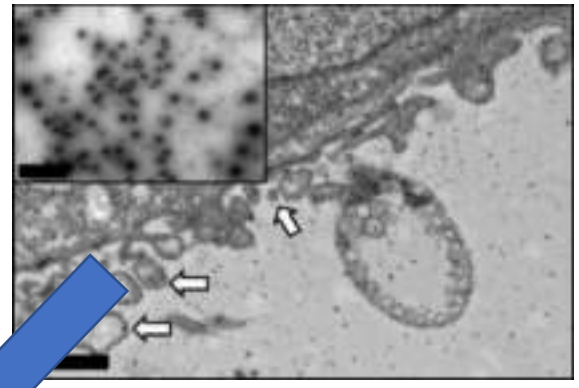




Joshi et al. Blood 2011
Trivedi J Trauma 2021

United we stand: improvement of lyophilized plasma





KaloCyte

Meledeo et al. J Trauma 2019
Valade et al. Front Imm 2021

Old product, new idea: cold-stored platelets

PLATELET PRESERVATION*

Effect of Storage Temperature on Maintenance of Platelet Viability — Deleterious Effect of Refrigerated Storage

SCOTT MURPHY, M.D., AND FRANK H. GARDNER, M.D.

Abstract Standard refrigerated storage (at 4°C) resulted in a marked shortening of the life-span of platelets labeled with ^{51}Cr and reinfused into the original donor. Storage at ambient, room temperature (22°C) preserved a normal platelet life-span. Platelets stored at this higher temperature should be adequate for transfusion purposes for as long as 96 hours. The use of cold temperatures should be abandoned in the preparation and storage of platelets for transfusion purposes.

The following exceptions or alternative procedures have been approved under 21 CFR 640.120(a) during October 2021 - December 2021.

1. **21 CFR 606.65(e) & 21 CFR 610.53(b)**

   To manufacture Apheresis Platelets, Leukocytes Reduced, suspended in 100% plasma and stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets 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.

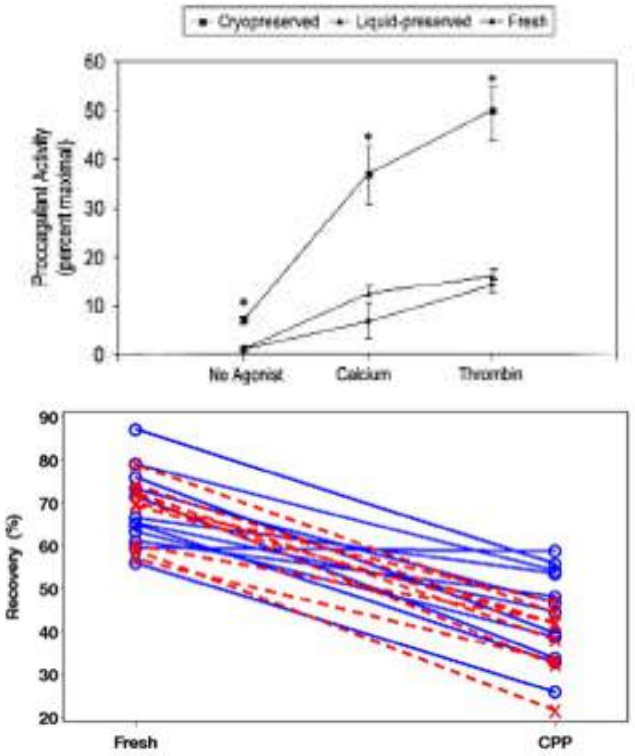
CHILLED PLATELET STUDY

C H I P S

Murphy et al. NEJM 1969

Old product, new idea: cryopreserved platelets

Parameter	Cryo-PLT After 6 hours (T6)	RT-PLT After 6 hours (T6)
Hemoglobin (mmol/L)	6.4 (5.8-6.6)	6.3 (5.7-6.5)
Hematocrit (%)	30 (27-31)	30 (27-31)
Coagulation and HMGB-1		
Thrombocytes (*10^9/L)	448 (376-509)**	511 (399-654)**
Fibrinogen (g/L)	1.3 (1.1-1.6)**	1.3 (1.0-1.4)**
PT (sec)	13.9 (12.2-14.4)**	14.2 (12.7-15.8)**
HMGB-1 (ng/mL)	21.5 (10.2-26.1)**	25.5 (13.5-33.1)**
Endothelial leakage		
Syndecan-1 (ng/mL)	105.1 (86.4-150.8)**	136.6 (108.7-173.1)**
Area FITC leakage-lung (%)	14.3 (9.5-18.0)	13.2 (7.0-20.0)
Area FITC leakage-kidney (%)	25.6 (20.7-29.8)	20.0 (13.4-28.6)



Kleinveld et al. Transfusion 2020
Martinaud et al. Transf Clin Biol
Dumont et al. 2013
Richard et al. 2015

Massive hemorrhage and no blood?

Crystal and colloid blood extenders

⇒Inability to carry oxygen

⇒ Hemodilution

⇒ Coagulopathy

⇒ Depletion of factors

⇒ (…)

Smith et al. Shock 2016
Johnson et al. Arch Surg 1979
Maegele et al. Transf 2016

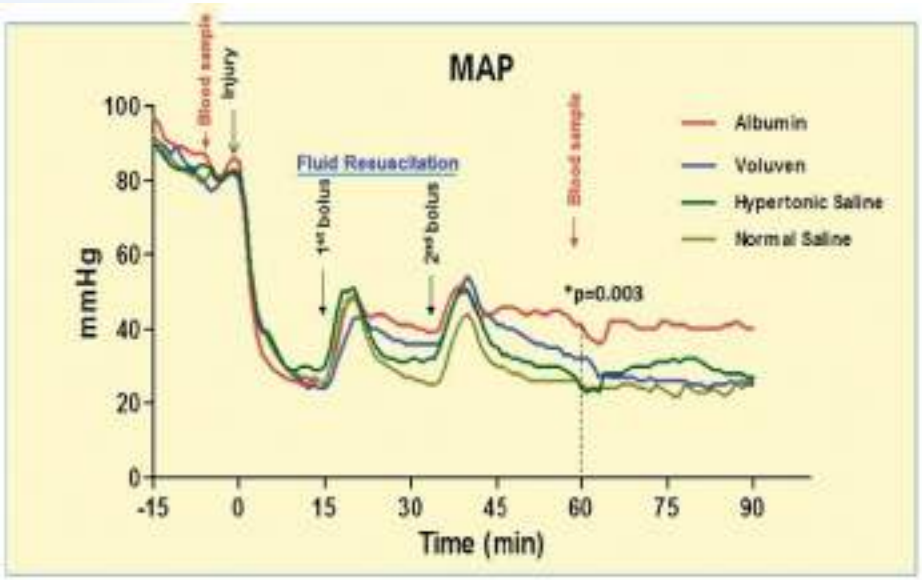


Table 3.—Coagulation Studies After Albumin Therapy

	Albumin-Treated Patients	Nonalbumin-treated Patients
Fibrinogen, mg/dL*	238 ± 106	405 ± 181
Partial thromboplastin time, s	41 ± 16	38 ± 18
Prothrombin time, s beyond control	2.6 ± 4	1.4 ± 1.3
Platelet concentration, 1 × 10³	94 ± 48	106 ± 60

Massive Trauma-hemorrhage

↓

Stop (hyper)fibrinolysis → 

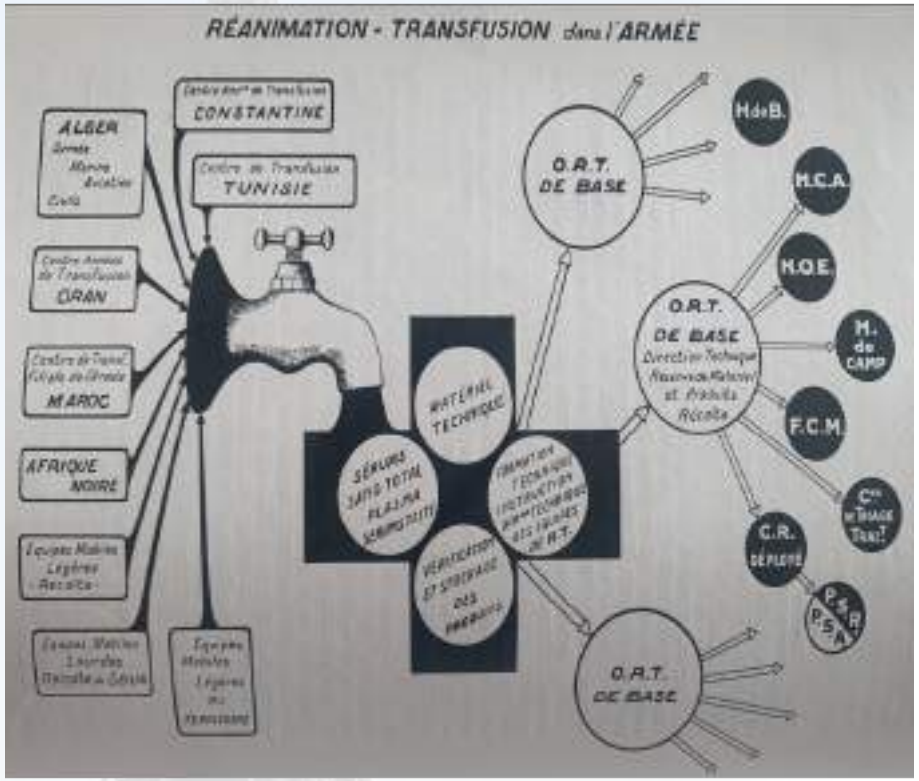
↓

Support clot formation → 

↓

Increase thrombin generation → 

Up-scaling the blood supply: looking backward



Author	% of transfusion	avg units/patient
Camp	43	4.3
Mendelson	16	7.1
Moss	36	7.5
Cary	24	6.5
Allam	50	6
Eshaya-Chauvin	16	3.9

Revue des corps de santé des armées, 1966
Vietnam studies, medical support 1965 – 1970, Neel 1991
Py et al. Transfusion 2022

Up-scaling the blood supply: team wins


Q & A