

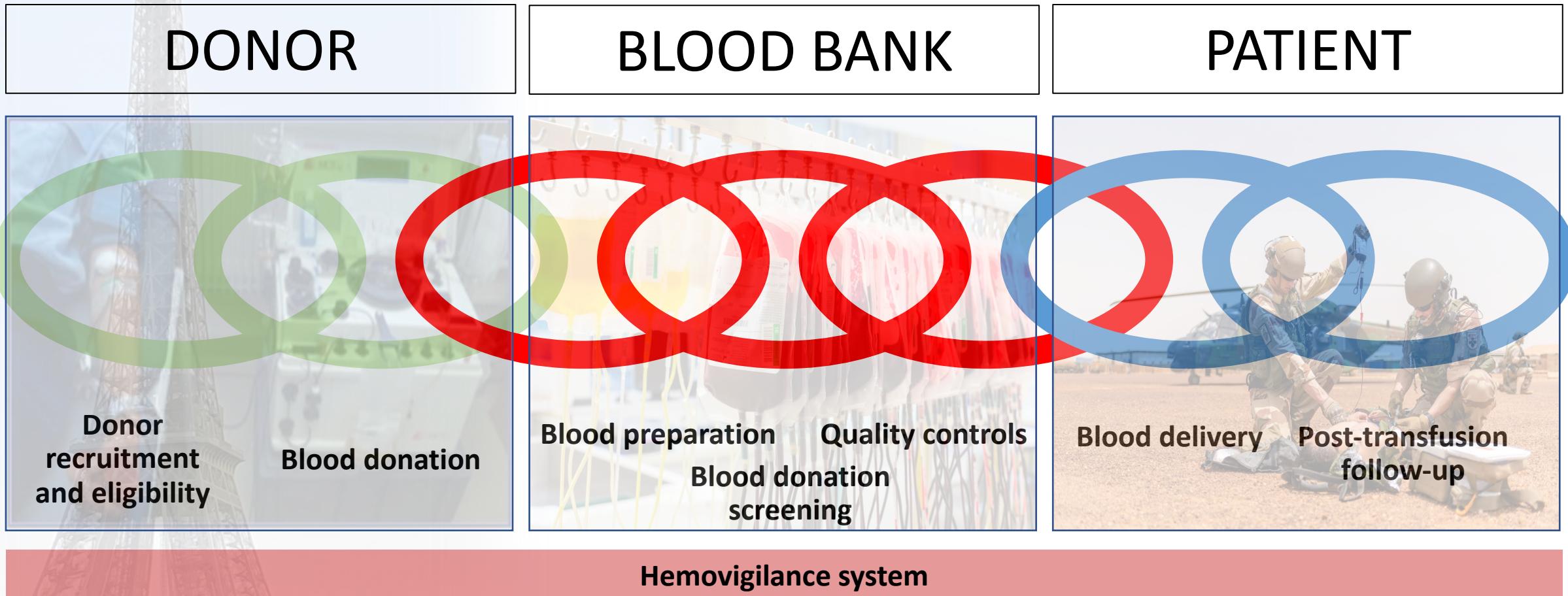
The future of blood transfusion in austere setting

PARIS SOF-CMC conference Fall 2022

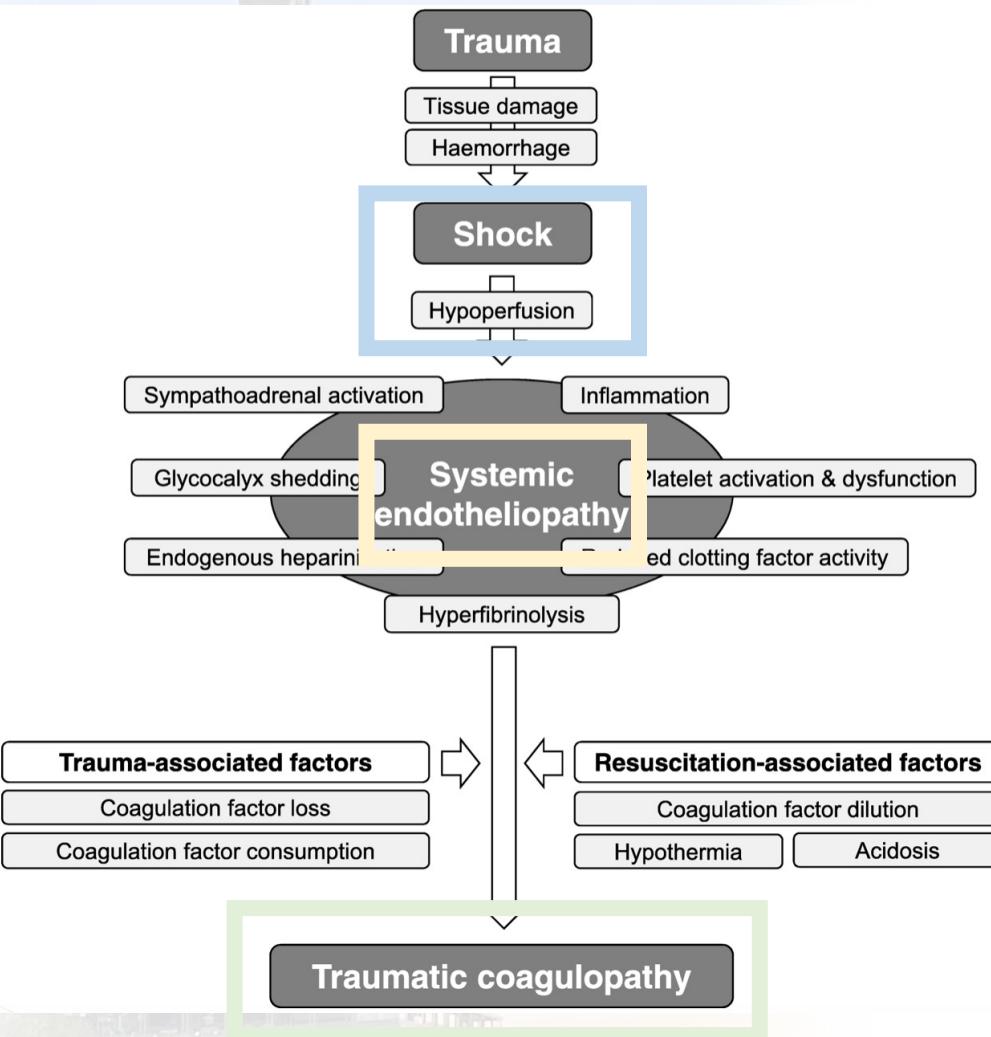
Disclaimer & disclosures

- 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

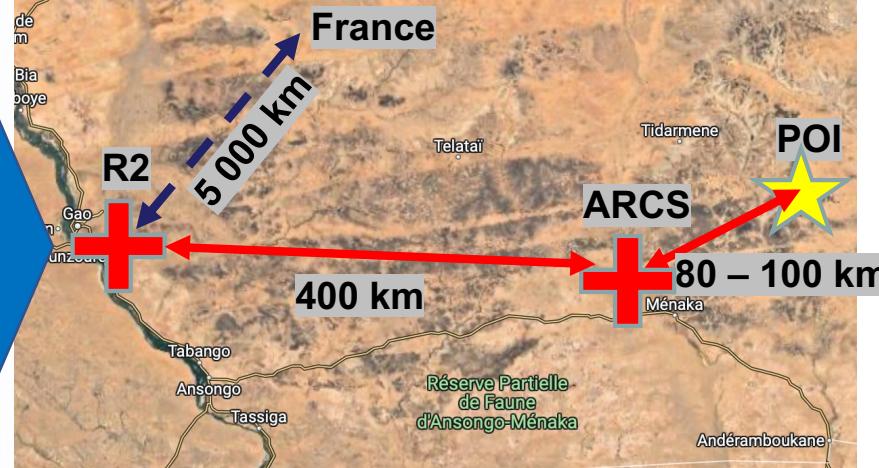


Blood Product	pRBC	Plasma	Platelets	Fibrinogen – cryo	Whole Blood
Oxygen debt (oxygen content and delivery)	Red	Yellow	Yellow	Blue	Red
Endotheliopathy (glycocalyx, leukocytes adhesion, barrier)	Yellow	Red	Red	Yellow	Yellow
Coagulopathy (fibrinolysis, factors, clot formation)	Red	Red	Red	Red	Red

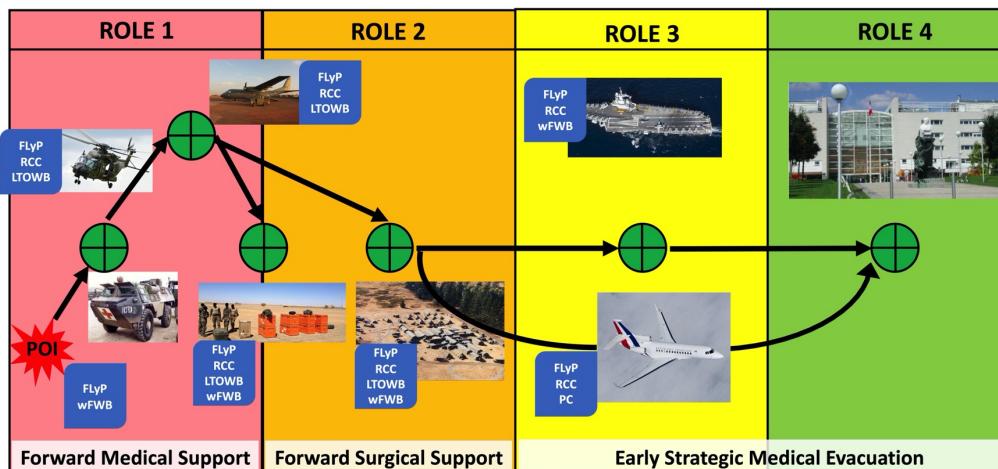
1. Transfuse as soon as possible ↓ 20 – 30% of mortality
2. Transfuse plasma and not crystalloids ↓ 20 – 30% of mortality
3. Each minutes count ↑ 5% of mortality / min
4. Transfuse platelets ↓ 20% of mortality
5. Obtain a RCC: plasma: platelets ratio close to 1:1:1 ↓ 50% of mortality

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

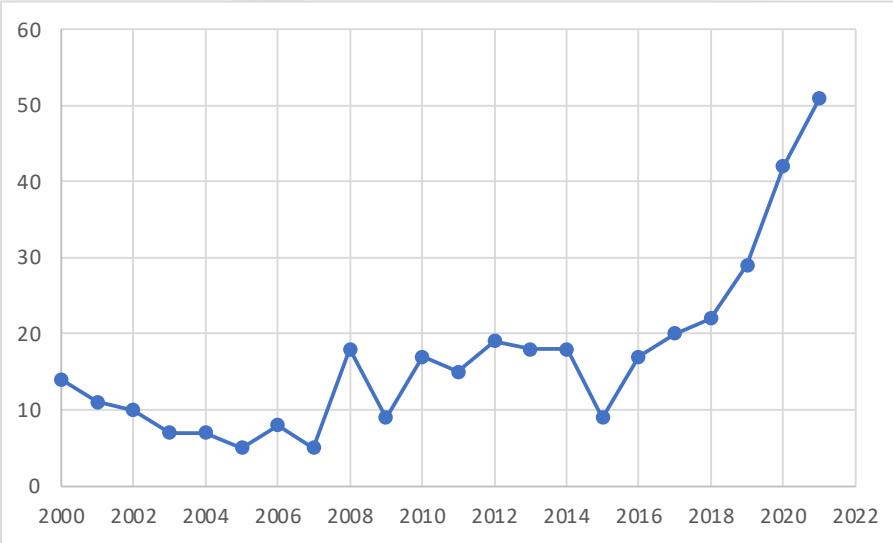


- ▷ Short time to transfusion
- ▷ End of surgery within 10h
- ▷ 11 blood products transfused
- ▷ Strategic evacuation within 24h



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

The road to winning: Low Titer group O Whole Blood

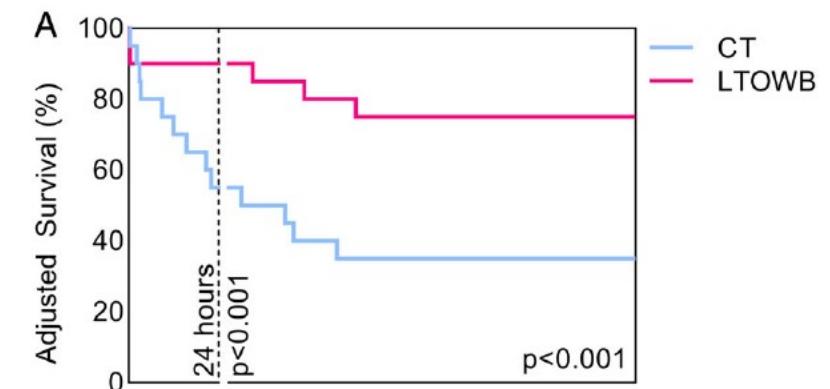


7 January, 2018

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. O₂ transportation

⇒ Hemoglobin <=> metHb

2. CO₂ transportation

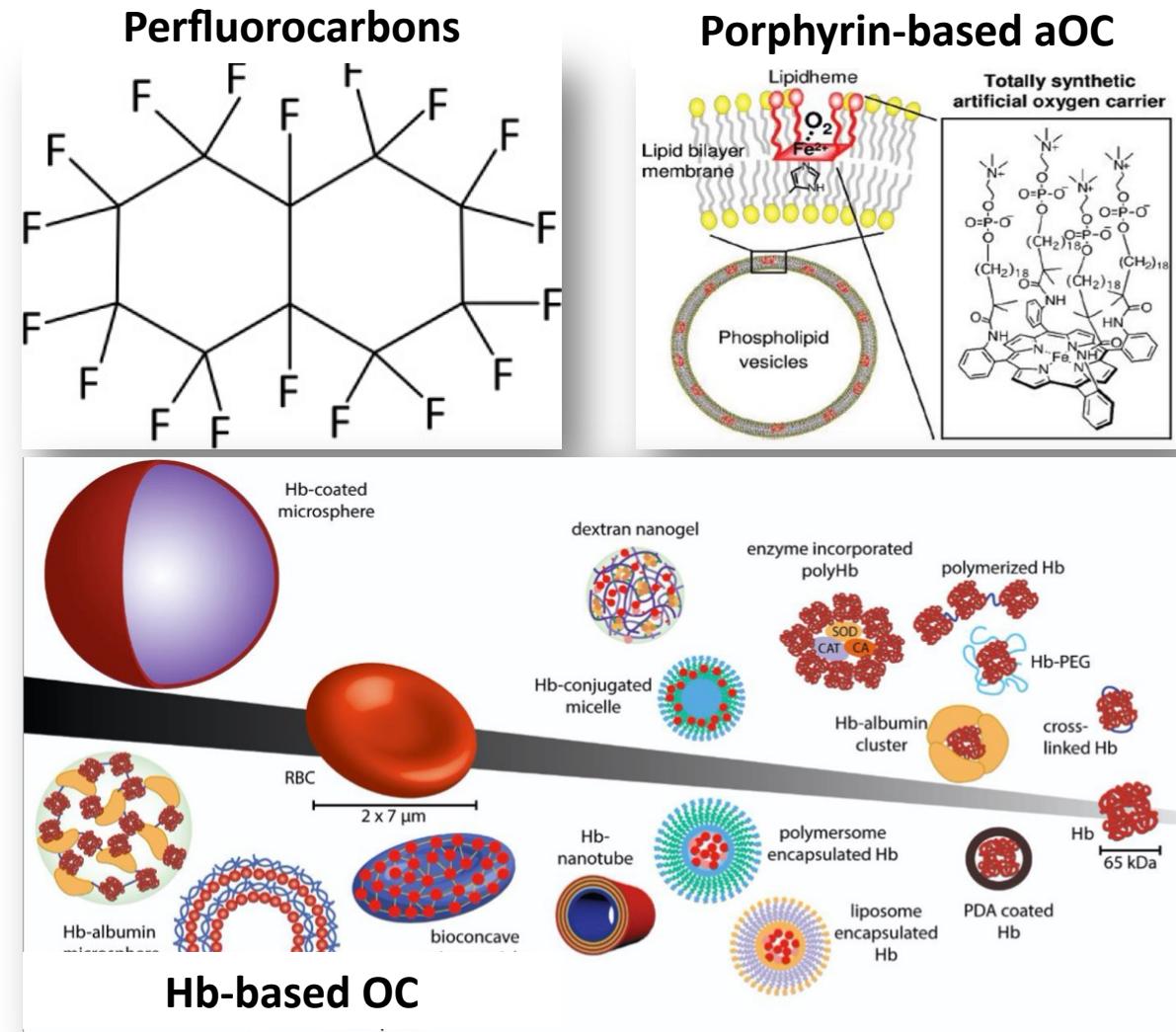
⇒ Erythrocyte carbonic anhydrase

3. Free radical scavenging

⇒ SOD and CAT

Jansman et al. *Adv Coll Interf Sci* 2018

Mohanto et al. *J Pharm Invest* 2022



Enhanced oxygen carriers: Perfluorocarbons

O₂ transportation

Immiscibility => require emulsification

Size << red cells: microcirculation

Fluosol-DA 20%

Oxygent™ (Alliance Pharmaceutical Corporation, San Diego, CA)

NanO₂® (NuvOx, Tucson, AR)

Limits

Dose limitation

Duration of required therapy

Impact of extreme hemodilution

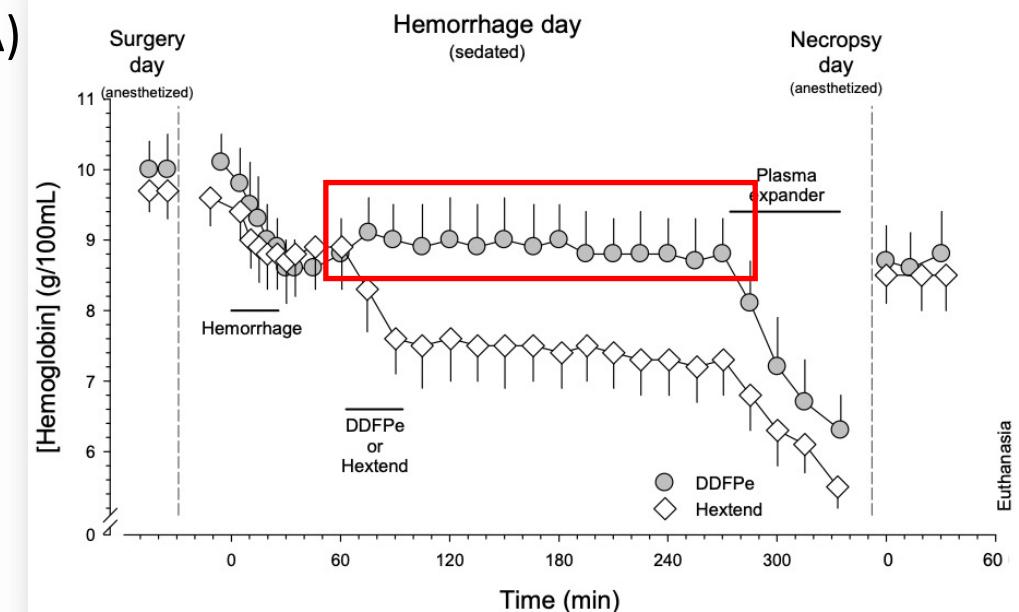
Requirement for maintenance of high O₂ concentrations

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)

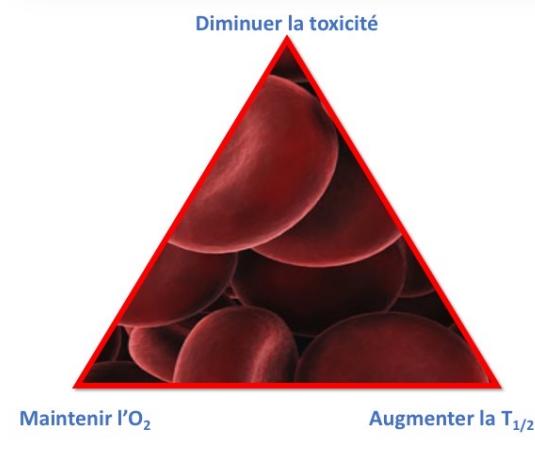
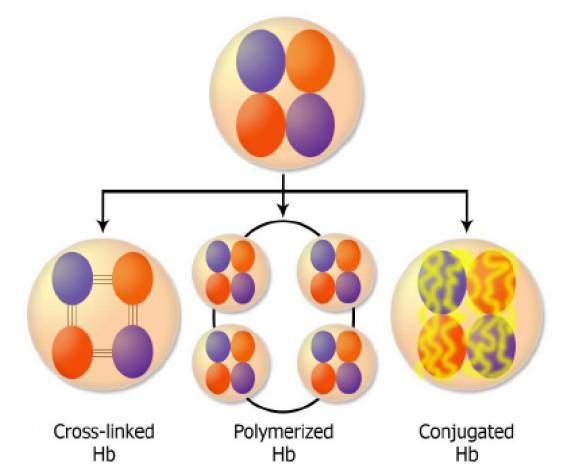
Double hemisynthetic systems

1. Heme for O₂ transport

- Human
- Bovin
- Recombined

2. « Carrier »

- Chemical
- Polymers
- Microparticule



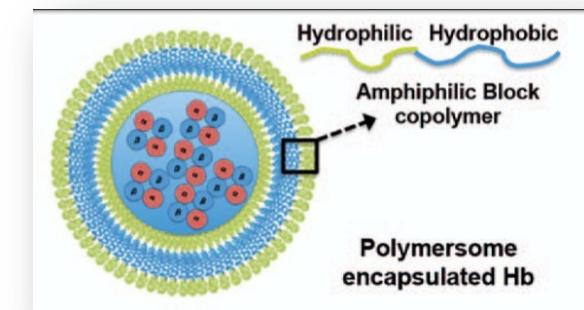
Morandi et al. Art Blood Subs 2016

Mohanto et al. J Pharm Invest 2022

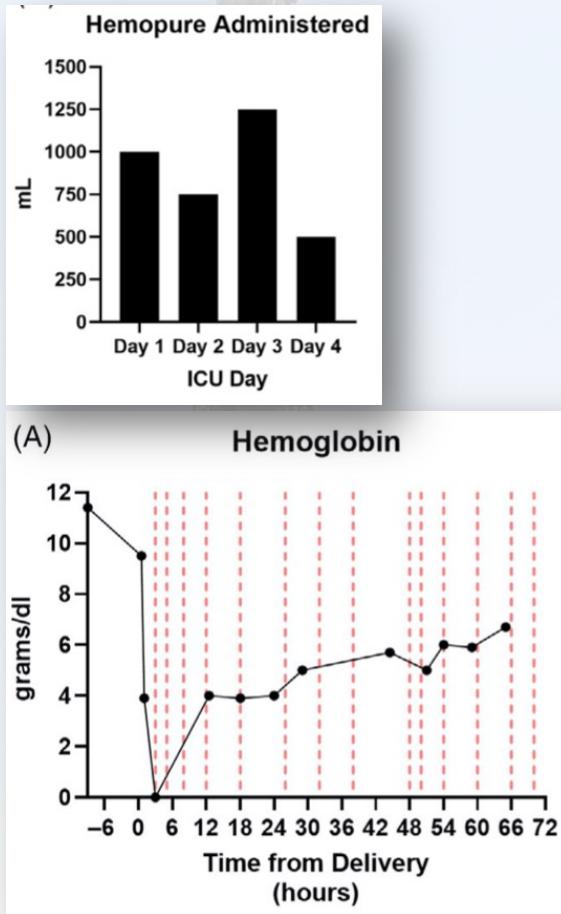
Gupta et al. Shock 2017

HBOCs formerly/currently investigated

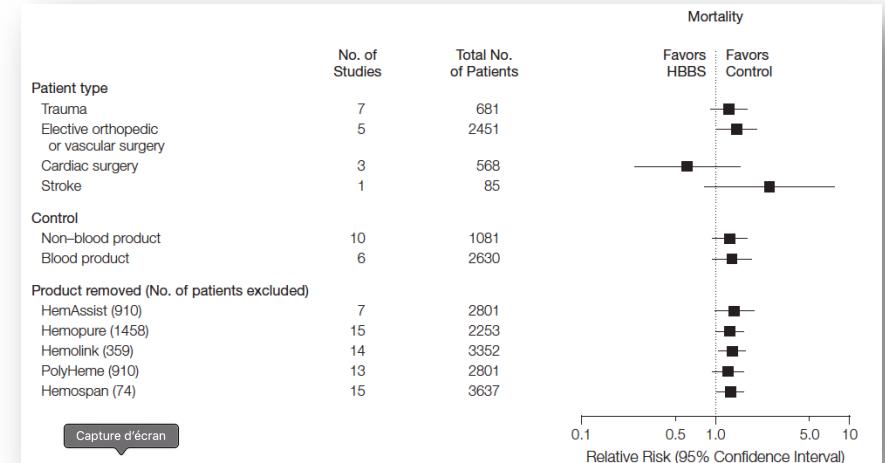
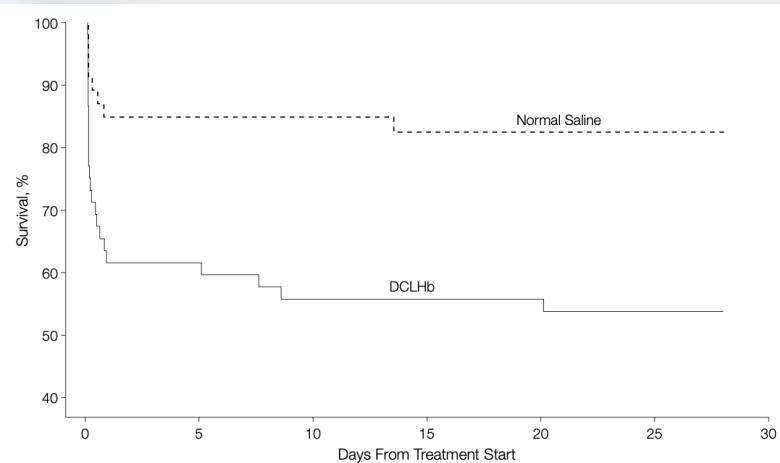
- **HemoPure®**
- **HemAssist®**
 - ✓ Stopped late 90's
 - ✓ Mortality 72% during clinical trial
- **PolyHeme®**
 - ✓ No approval (FDA, 2009)
 - ✓ Company gave up (2009)
- **HemoSpan®**
 - ✓ Toxicity led to end of the phase III trial



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.

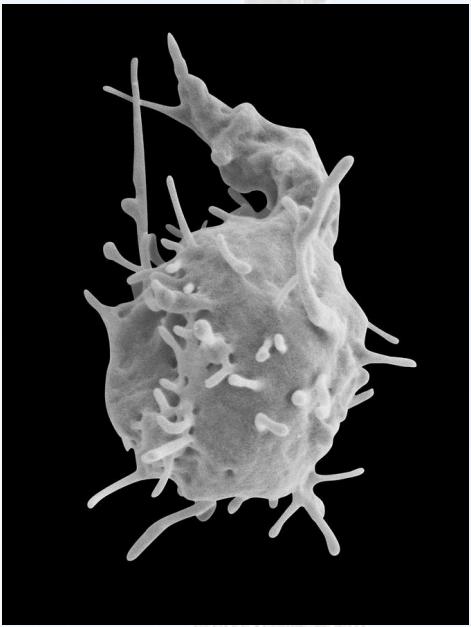
Ouest-France avec AFP.
 Modifié le 09/04/2020 à 17h13
 Publié le 09/04/2020 à 12h14



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

Vasoconstriction – HBP
 Gastro-intestinals side effects
 Increased liver/pancras enz.
 Cardiac toxicity
 Neurotoxicity
 Nephrotoxicity

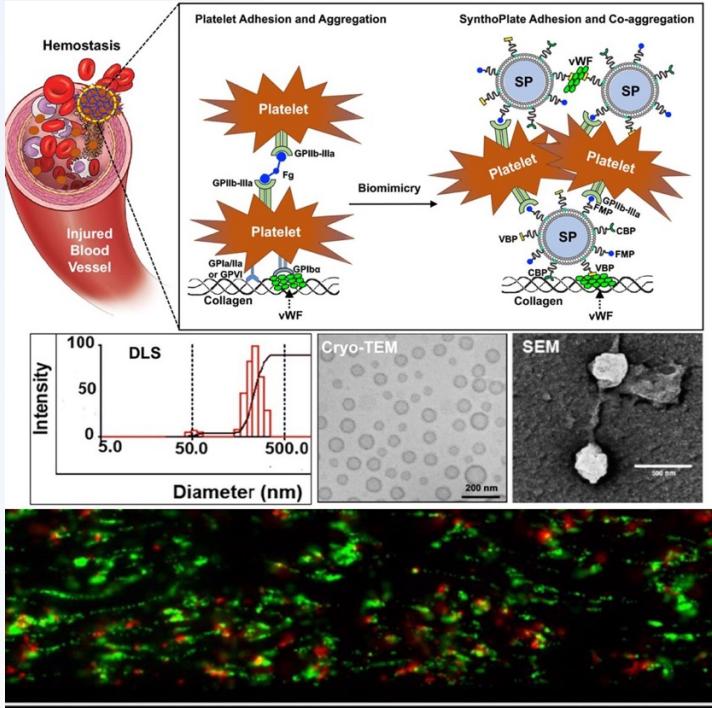
Platelets substitutes



Primary hemostasis

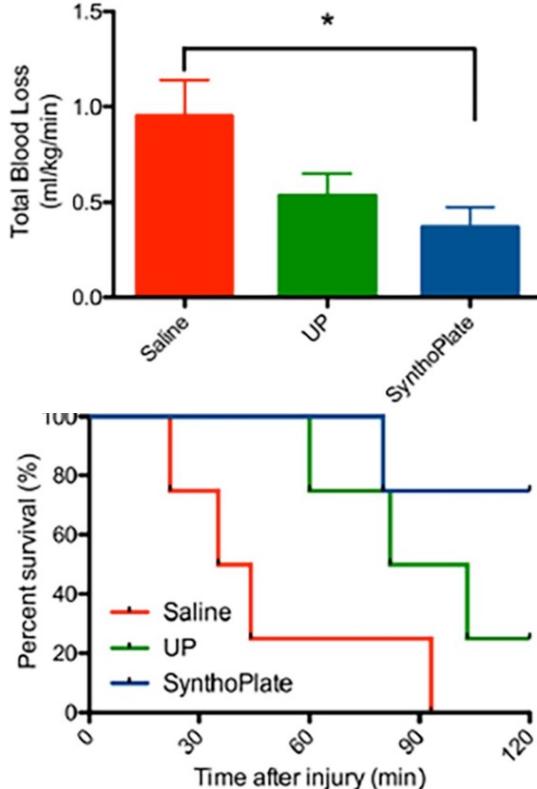
Immunomodulation

Endothelial integrity

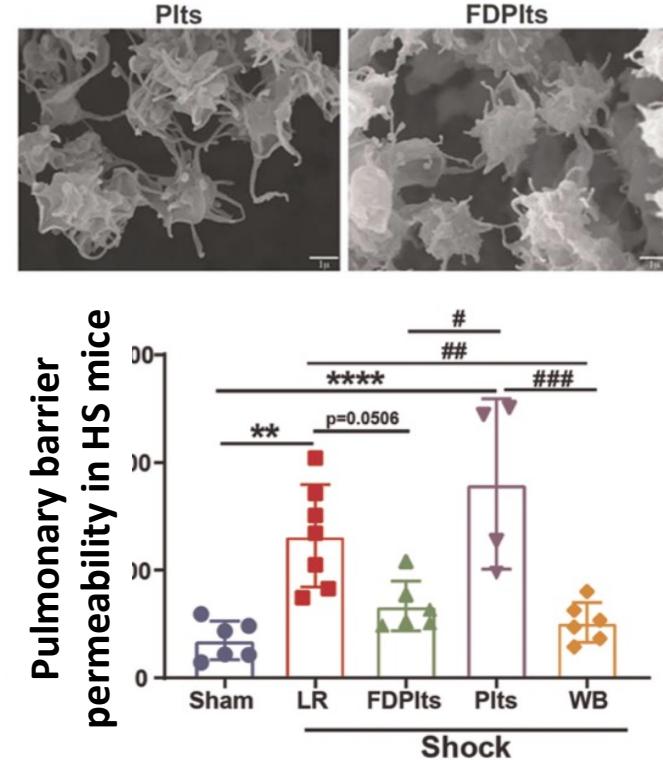


Sekhon et al. MHSRS 2022
Hickman et al. Sci Rep 2018

Synthoplate

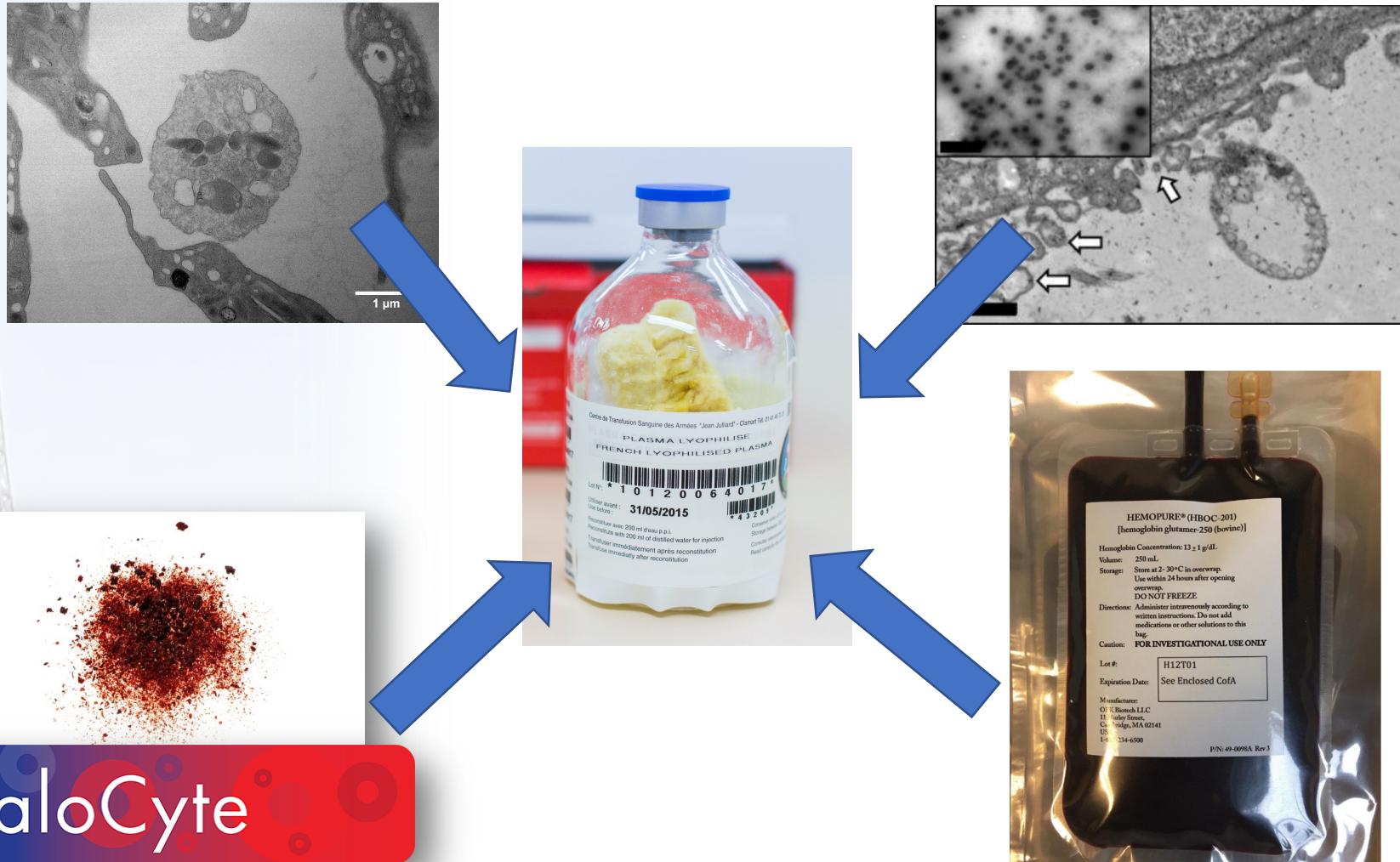


Thrombosomes



Joshi et al. Blood 2011
Trivedi J Trauma 2021

United we stand: improvement of lyophilized plasma



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

KaloCyte

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)

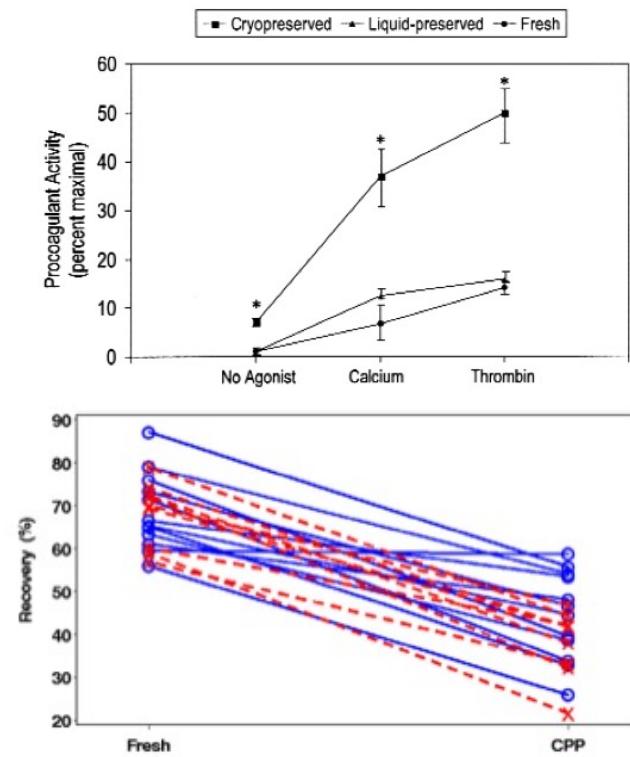
To manufacture Apheresis Platelets, Leukocytes Reduced, suspended in 100% plasma and stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets products are intended to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.



Murphy et al. NEJM 1969

Old product, new idea: cryopreserved platelets

Parameter	Cryo-PLT	RT-PLT
	After 6 hours (T6)	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

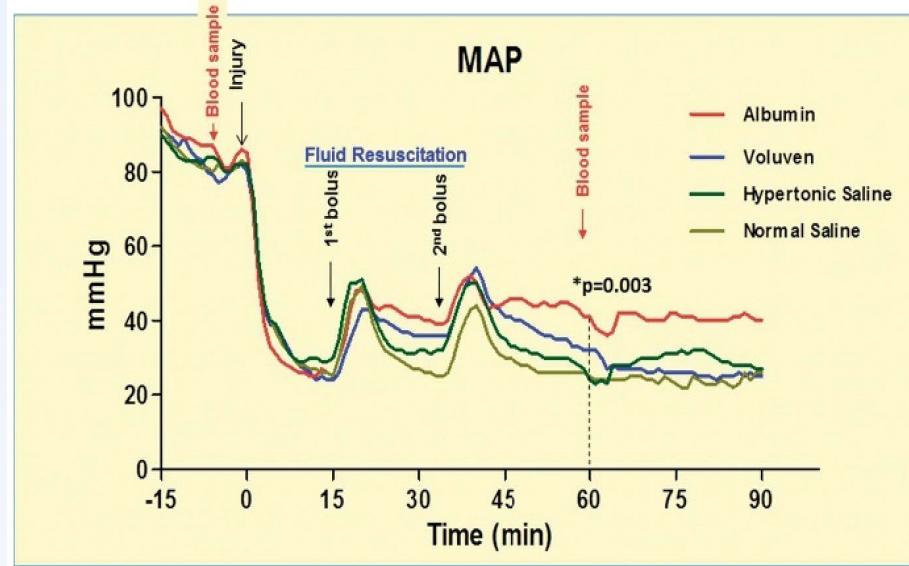


Table 3.—Coagulation Studies After Albumin Therapy

	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, 1×10^3	94 ± 48	106 ± 60

Massive Trauma-hemorrhage

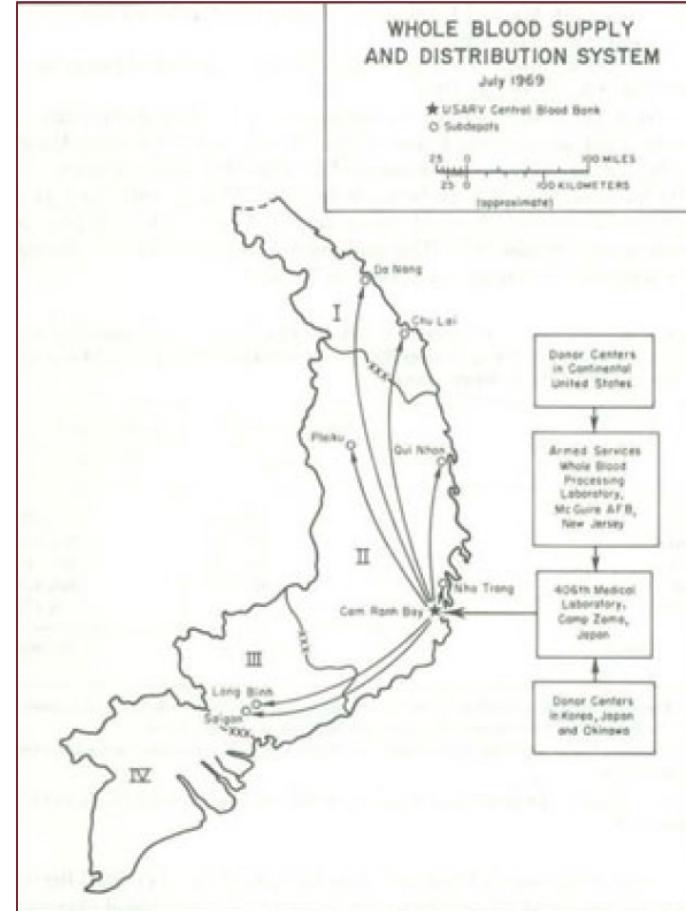
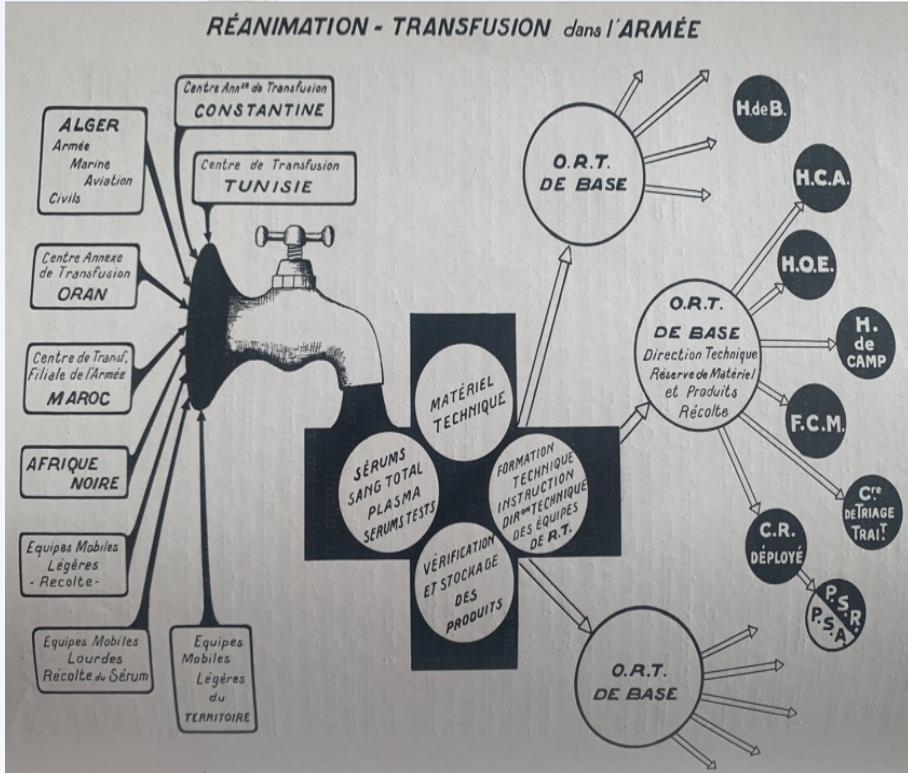
Stop (hyper)fibrinolysis

Support clot formation

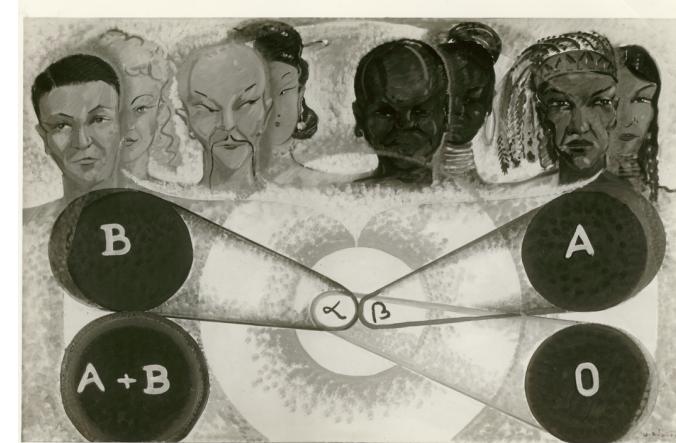
Increase thrombin generation



Up-scaling the blood supply: looking backward

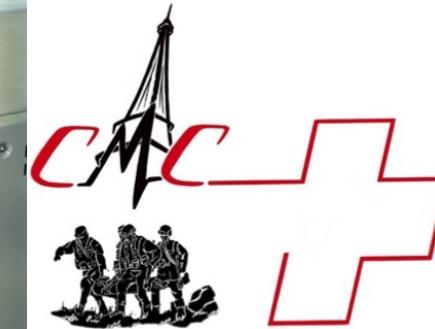


Author	% of transfusion	avg units/patient
Camp	43	4.3
Mendelson	16	7.1
Moss	36	7.5
Cary	24	6.5
Allam	50	6
Eshaya-Chauvin	16	3.9



*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