45° Convegno Nazionale di Studi di Medicina Trasfusionale
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SIMTI

PLASMA LIOFILIZZATO COME ALTERNATIVA ALL'UTILIZZO DEL PLASMA FRESCO CONGELATO

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La sottoscritta, in qualità di Relatrice
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatrice di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.

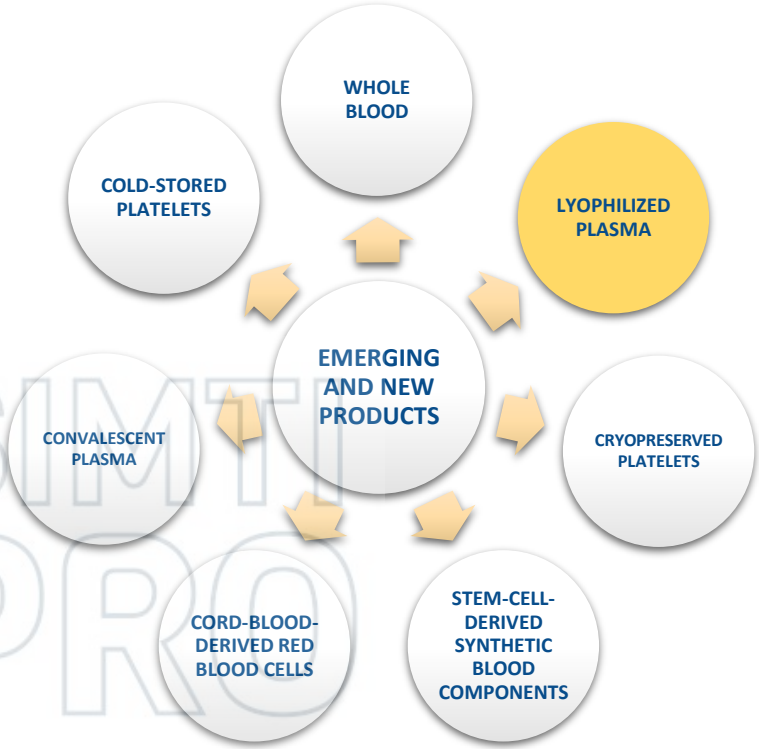
UNO SGUARDO AL FUTURO

REPORT

Vox Sanguinis ISBT

The future of blood services amid a tight balance between the supply and demand of blood products: Perspectives from the ISBT Young Professional Council

Antoine Lewin[1,2] | Eunike McGowan[3,4] | Jian Ou-Yang[5] | Lilian Antwi Boateng[6,7] | Carla Luana Dinardo[8] | Saikat Mandal[9] | Nour Almozain[10,11] | Jannison Ribeiro[12,13] | Syeldy Langi Sasongko[14] | on behalf of the Young Professional Council of the ISBT

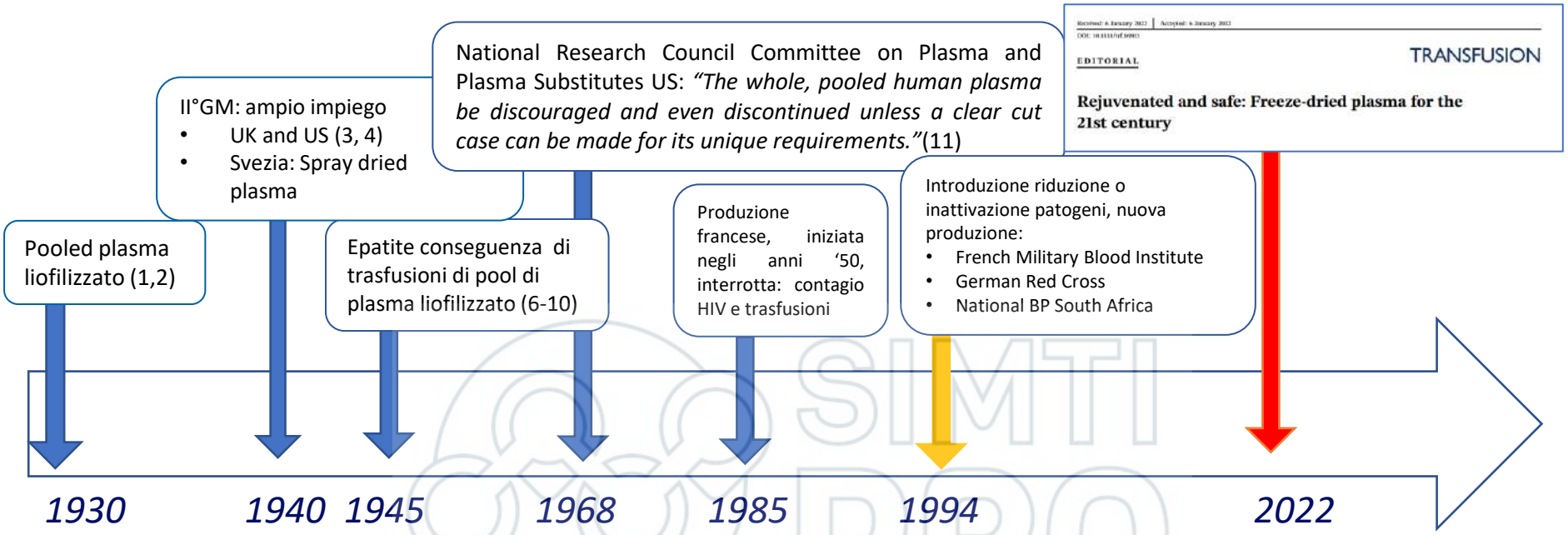


*"In the future, blood services may offer **new products**, improve access to blood donation, implement new technologies and establish research partnerships with local health authorities."*

"**Lyophilized plasma** can **expedite plasma infusion** in patients with severe coagulopathy or major bleeding. It can be **reconstituted in less than 6 min**. Relative to fresh frozen plasma, it can increase fibrinogen levels, shorten the time to transfusion, and improve prothrombin time ratio and factor II and V levels".

Lewin A, et al. 2023

PLASMA LIOFILIZZATO: ONCE UPON A TIME…



FROZEN AND DRIED PLASMA FOR CIVIL AND MILITARY USE

MAX M. STRUMIA, M.D.; JOHN J. McGRAW, M.D.

Abstract | Full Text

JAMA. 1941;116(21):2378-2382. doi:10.1001/jama.1941.02820210024004

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IL PROCESSO DI LIOFILIZZAZIONE

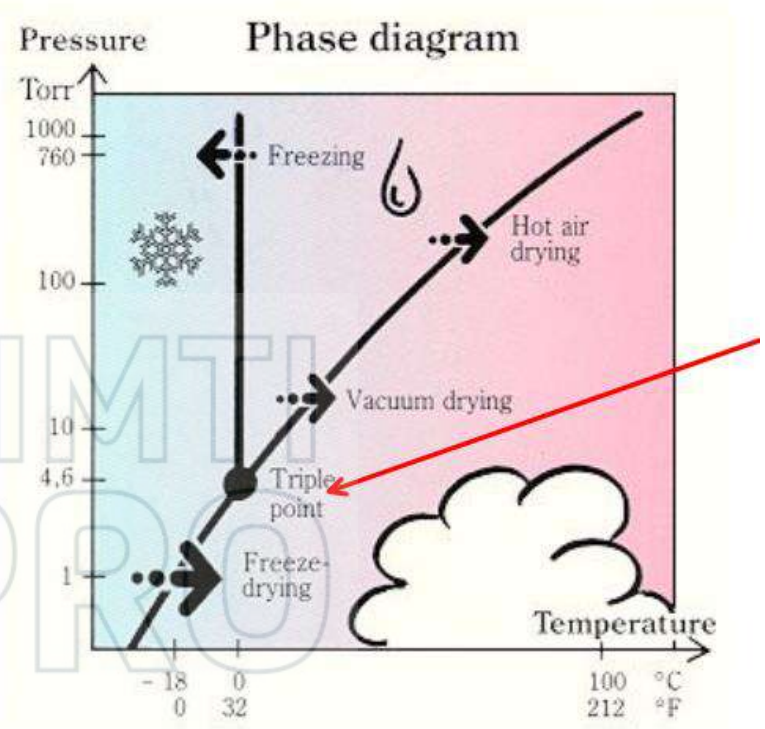
Il termine «liofilo» deriva da due vocaboli greci che sono **λιωσ=solvente** e **φιλωσ=affinità**: quando i materiali vengono sottoposti a questo processo, acquistano avidità di acqua.

Venne impiegato per la prima volta nel 1935 per indicare una sostanza disidratata.

La liofilizzazione mediante freeze-drying è l'essiccamento per sublimazione ovvero il passaggio diretto dallo *stato solido* allo *stato di vapore* del solvente congelato.

Lo spray-drying permette la trasformazione di soluzioni o sospensioni liquide acquose in polveri, attraverso in processo di atomizzazione, con conseguente evaporazione istantanea dell'acqua.

L'assenza di acqua o di umidità residua permette la lunga conservazione di tutte le attività delle sostanze biologiche che possono, poi, essere trasformate nella soluzione con semplice aggiunta del solvente.



PLASMA LIOFILO

- FREEZ-DRYING
- SPRAY-DRYING

TRAUMA, EMORRAGIA E TERAPIA TRASFUSIONALE

POSSIBILE APPLICAZIONE PRE-OSPEDALIERA: UNA PIÙ RAPIDA DISPONIBILITÀ PRESENTA VANTAGGI NEL CONTESTO DEL TRAUMA

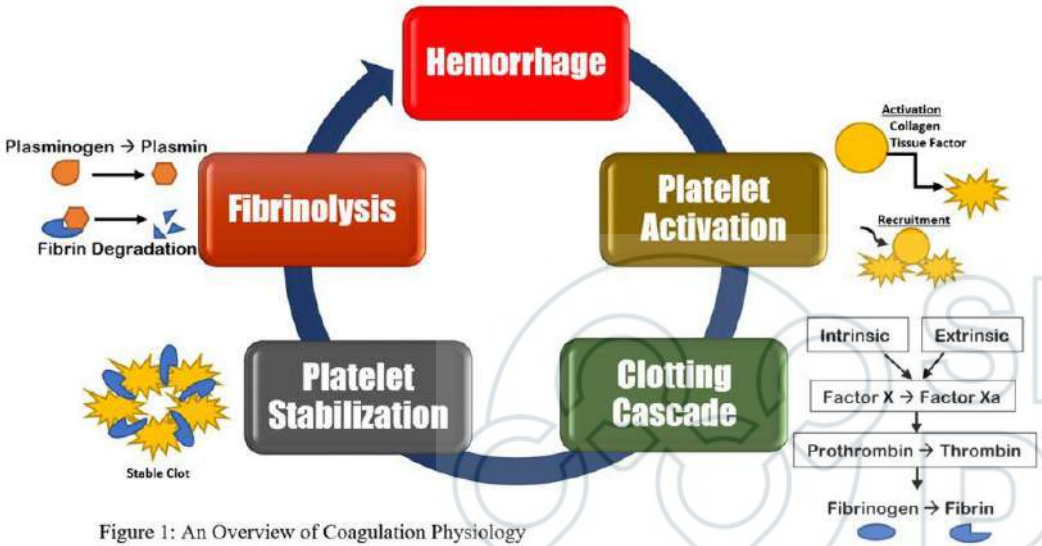


Figure 1: An Overview of Coagulation Physiology

Mc Laughlin CJ, 2023

Trauma is** responsible for **8% of global annual mortality.
*Among trauma patients, **haemorrhage** is a **leading cause of death worldwide**.*

Bleeding** is one of the **most common reasons** for patient presentation in the **prehospital setting. Peak mortality occurs at 30 min.

Zaza M, et al. 2020

- ***Emorragia*** → **perdita di GR, fattori di coagulazione, piastrine, fibrinogeno e volume plasmatico.**
- Queste **perdite** sono **aggravate dal consumo dei fattori** nel processo di coagulazione.

HYPOTHERMIA

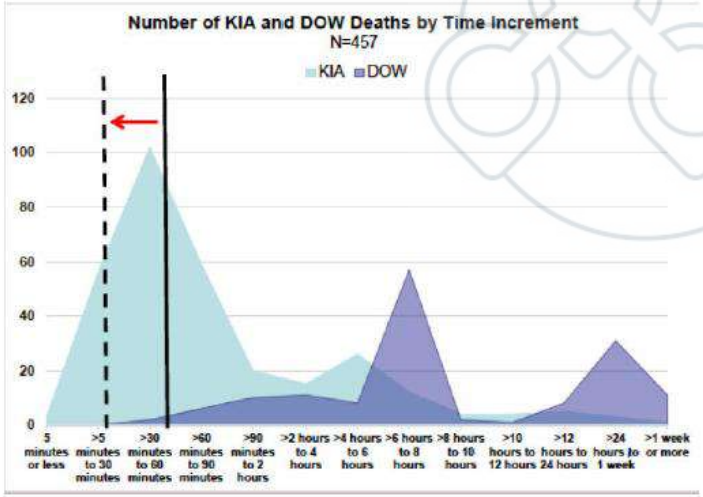
ACIDOSIS

COAGULOPATHY

DAMAGE CONTROL RESUSCITATION
with blood components mimicking WB

Irreversibile shock and Death

- L'**utilizzo di soluzioni saline (cristalloidi) può esacerbare il processo,** causando coagulopatia da diluizione e acidosi.
- **La trasfusione appropriata**, al contrario, rappresenta un **approccio vantaggioso.**



Shackleford JTS 2016

- KIA: killed in action
- DOW: death of wounds
- Black line: earlier goal to provide blood

Plasma gives more time to get whole blood into the patient (Beecher et al. 1945)

"Plasma produces superior volume expansion when compared to crystalloids, allowing less volumes infused to match volume lost, faster hemodynamic recovery, and decreased third-spaced volume …" *Zaza et al. 2020*

- ↑ fattori coagulazione
- correzione iperfibrinolisi
- miglioramento disfunzione endoteliale
- ↑ albumina

Published in final edited form as:
Lancet. 2018 July 28; 392(10144): 283–291. doi:10.1016/S0140-6736(18)31553-8.

COMBAT

Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial

Use of **prehospital plasma** during **rapid ground rescue of patients with haemorrhagic shock** before arrival at an **urban level 1 trauma centre**.

Eligible patients were **randomly assigned to receive plasma or normal saline (control)**. The primary endpoint was **mortality within 28 days of injury**. The as-treated analysis included **125 eligible patients, 65 received plasma and 60 received saline.**

The groups did not differ in mortality at 28 days (p=0·37). Due to the consistent lack of differences in the analyses, **the study was stopped for futility after 144 of 150 planned enrolments.**

During rapid ground rescue to an urban level 1 trauma centre, **use of prehospital plasma was not associated with survival benefit**. Blood products might be **beneficial in settings with longer transport times**, but the financial burden would not be justified in an urban environment with short distances to mature trauma centres.

Moore HB et al. 2018

TRASFUSIONE DI PLASMA NELLO SHOCK EMORRAGICO

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2018 VOL. 379 NO. 4

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

J.L. Sperry, F.X. Guyette, J.B. Brown, M.H. Yazer, D.J. Triulzi, B.J. Early-Young, P.W. Adams, B.J. Daley, R.S. Miller, B.G. Harbrecht, J.A. Claridge, H.A. Phelan, W.R. Witham, A.T. Putnam, T.M. Duane, L.H. Alarcon, C.W. Callaway, B.S. Zuckerbraun, M.D. Neal, M.R. Rosengart, R.M. Forsythe, T.R. Billiar, D.M. Yealy, A.B. Peitzman, and M.S. Zenati, for the PAMPer Study Group*

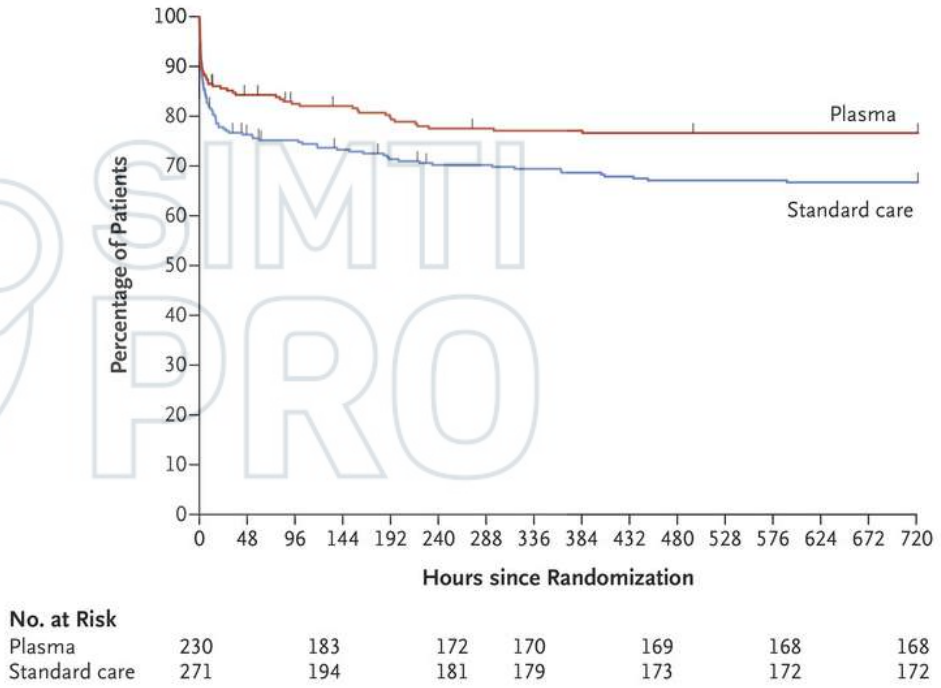
Multicenter, cluster-randomized, phase 3 superiority trial that compared the administration of **thawed plasma with standard-care resuscitation during air medical transport.**

Mortality at 30 days was significantly **lower** in the **plasma group than in the standard-care group** (p=0.03).

Kaplan–Meier curves showed an **early separation of the two treatment** groups that began **3 hours after randomization and persisted until 30 days** after randomization (**log-rank chi-square test, 5.70; P=0.02).**

No significant differences were noted with respect to multi-organ failure, acute lung injury, acute respiratory distress syndrome, nosocomial infections, or allergic or transfusion-related reactions.

PAMPer



In injured patients **at risk for haemorrhagic shock**, the **prehospital administration of thawed plasma** was safe and resulted **in lower 30-day mortality** and a **lower median pro-thrombin time ratio** than standard-care resuscitation.

Sperry JL et al. 2018

TRASFUSIONE DI PLASMA NELLO SHOCK EMORRAGICO

JAMA Surgery | Original Investigation

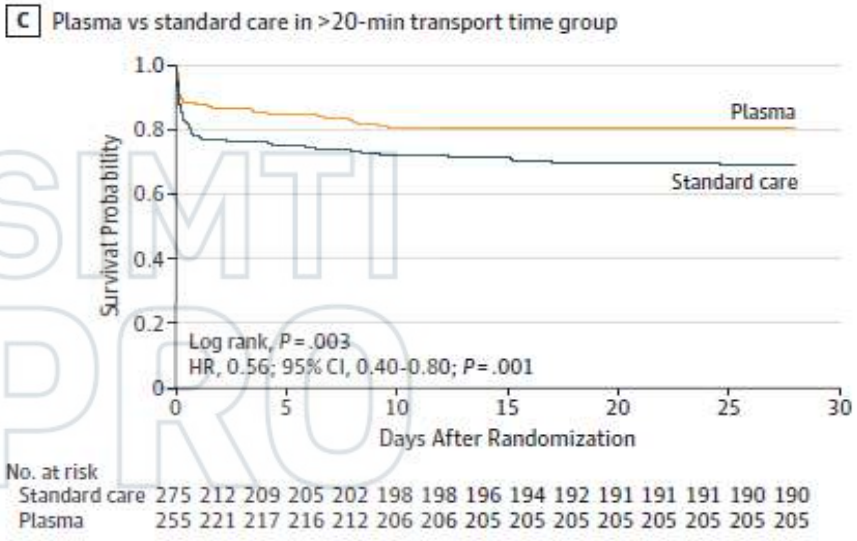
Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes

A Post Hoc Analysis of the PAMPer and COMBAT Clinical Trials

Anthony E. Pusateri, PhD; Ernest E. Moore, MD; Hunter B. Moore, MD, PhD; Tuan D. Le, MD, DrPH; Francis X. Guyette, MD, MPH; Michael P. Chapman, MD; Angela Sauaia, MD, PhD; Arsen Ghasabyan, MPH; James Chandler; Kevin McVaney, MD; Joshua B. Brown, MD; Brian J. Daley, MD; Richard S. Miller, MD; Brian G. Harbrecht, MD; Jeffrey A. Claridge, MD; Herb A. Phelan, MD, MSCS; William R. Witham, MD; A. Tyler Putnam, MD; Jason L. Sperry, MD, MPH

To facilitate a **post hoc combined analysis of the COMBAT and PAMPer** trials to examine questions that could not be answered by either clinical trial alone. We hypothesized that **prehospital transport time influenced the effects of prehospital plasma on 28-day mortality**.

Cox regression analysis showed a significant overall survival benefit for plasma (hazard ratio [HR], 0.65; 95%CI, 0.47-0.90; p = 0.01)



In 625 patients with hemorrhagic shock, it was observed **increased mortality with standard care (crystalloids) if pre-hospital transport time more than 20 minutes**. These data suggest that **prehospital plasma** is associated with a **survival benefit** when transport times are **longer than 20 minutes** and that the **benefit-risk ratio is favorable for use of prehospital plasma.**

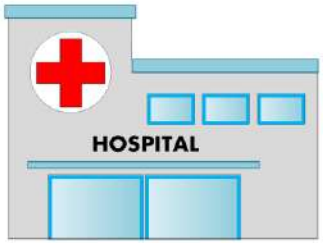
Pusateri AE et al. 2020

APPROVVIGIONAMENTO DI PLASMA FRESCO CONGELATO: DIFFICOLTÀ LOGISTICHE

PLASMA FRESCO CONGELATO

- COLD STORAGE CONDITIONS
- SUPPLY CHAIN AND SPECIALIZED TRANSPORT EQUIPMENT
- LENGHTY THAWING PROCESS

PLASMA LIOFILIZZATO



Bridge per la terapia trasfusionale nel setting pre-ospedaliero

PLASMA LIOFILIZZATO: PRODOTTI DISPONIBILI

Emocomponente prodotto nel ST

A. **French Lyophilized Plasma, FLYP (French Military Blood Institute, Centre de Transfusion Sanguine des Armees, CTSA)**
   Pool 11 donatori riduzione patogeni (amtosalene/UV)
   uso militare/uso civile ambiente austero

B. **Lyoplas N-w, (German Red Cross)**
   Aferesi da singolo donatore quarantenato
   ospedali militari e civili, servizi medici di emergenza civili

C. **Bioplasma FDP (National Bioproducts Institute, Pinetown, South Africa)**
   Pool donatori, ABO universale, trattamento S/D

Farmaceutico

Plasma liofilizzato universale trattato con S/D per trasfusione pre-ospedaliera

Approved for prehospital transfusion regulatory assessment for marketing authorisation in selected countries of the European Union

PLASMA LIOFILIZZATO: CARATTERISTICHE TECNICHE

Table 1
Data for FLyP was generated after 12 months at ambient temperature [5] and for LyoPlas after 15 months at 25°C [23].

	FLyP	LyoPlas
Process	Lyophilized pooled (<11 donors)	Lyophilized single-donor
Storage	2 years at room temperature	15 months at 2°C-25°C
Characteristics	Most factor levels normal ABO universal Leukoreduced	Most factor levels normal ABO-type specific Leukoreduced
Reconstitution	Sterile water (minutes)	Sterile water (minutes)

Sheffield et al. 2022

Long storage time
Reconstitution time
< 6 min

Shelf life 2/3 years

Stored at room temperature

To be resolved in water at time of use

Produced under inactivation process

Leukoreduced ABO-type specific or ABO universal

PLASMA LIOFILIZZATO: CARATTERISTICHE QUALITATIVE

Quality of freeze-dried (lyophilized) quarantined single-donor plasma

Jürgen Bux, Dieter Dickhörner, and Edgar Scheel

Lyophilized plasma showed characteristics similar to FFP. Since FDP requires neither complex logistics nor time-consuming thawing, it allows rapid treatment of coagulopathies.

Bux J et al. 2013

In Vitro Hemostatic Properties of French Lyophilized Plasma

Christophe Martinaud, M.D.,* Corinne Civadier, Pharm.D.,† Sylvain Ausset, M.D.,‡ Catherine Verret, M.D., M.P.H., Ph.D.,§ Anne-Virginie Deshayes, Pharm.D.,† Anne Sailliol, M.D.†

Martinaud C et al 2012

Retention of hemostatic and immunological properties of frozen plasma and COVID-19 convalescent apheresis fresh-frozen plasma produced and freeze-dried in Canada

William P. Sheffield[1,2] | Varsha Bhakta[1] | Anita Howell[1] | Craig Jenkins[1] | Katherine Serrano[1,3,4] | Nathaniel Johnson[5] | Yi-Chan J. Lin[6] | Karen Colwill[7] | Bhavisha Rathod[7] | Brianna Greenberg[8] | Anne-Claude Gingras[7,9] | David H. Evans[6] | Elissa Flaumenhaft[5] | Andrew Beckett[10] | Steven J. Drews[11,12] | Dana V. Devine[1,3,4]

Changes in protein activities or clotting times arising from freeze-drying were <15%. In vitro characteristics of TFDP or CC-TFDP were comparable to their originating plasma, making future clinical studies appropriate.

Sheffield WP et al. 2022

Table 1
Data for FlyP was generated after 12 months at ambient temperature [5] and for LyoPlas after 15 months at 25°C [23].

	FlyP		LyoPlas	
Process	Lyophilized pooled (<11 donors)		Lyophilized single-donor	
Storage	2 years at room temperature		15 months at 2°C-25°C	
Characteristics	Most factor levels normal ABO universal Leukoreduced		Most factor levels normal ABO-type specific Leukoreduced	
Reconstitution	Sterile water (minutes)		Sterile water (minutes)	
Parameter	Mean ± SD	Reference range	Mean ± SD	Reference range
PT (ratio test/control)	1.2 ± 0.1	< 1.5	Not reported	
aPTT (s)	39.0 ± 2.4	30-40	35.46 ± 2.02	26-37
INR	Not reported		1.21 ± 0.05[a]	0.8-1.2
Fibrinogen (g/l)	2.4 ± 0.3	2-4	2.31 ± 0.37	2-4
Factor V (%)	51 ± 16[a]	70-120	77.96 ± 11.65	65-100
Factor VIIIc (%)	62 ± 10	50 -150	83.68 ± 11.65	60-150
Factor XI (%)	79 ± 11	50-140	87.54 ± 13.75	65-150
Factor XIII (%)	103 ± 12	20-120	Not reported	
Protein C (%)	96 ± 9	70-120	97.6 ± 20.04	80-150
Protein S (%)	77 ± 16	70-140	71.7 ± 6.46	60-150
Antithrombin (%)	101 ± 5	80-120	90.0 ± 8.60	80-135
Alpha-2 antiplasmin (%)	95 ± 3	80-120	Not reported	
von Willebrand (%)	Not reported		90.00 ± 16.91	60-160

[a] Indicates mean value out of reference range. Where units were originally reported as units/mL(U/mL) or international units/mL (IU/mL), they have been converted to percent normal (%), where 100% is equal to 1.00 U/mL or IU/mL as appropriate.

- **Rispetto al PFC, no differenze sostanziali in termini di qualità,** per dosaggio di **proteine plasmatiche e parametri coagulativi.**
- **Trascurabile perdita attività dei fattori labili della coagulazione** (circa il 25% per il fattore VIII, generalmente aumentato nel trauma; altri come fibrinogeno, fattore XI, proteina C e antitrombina inalterati).

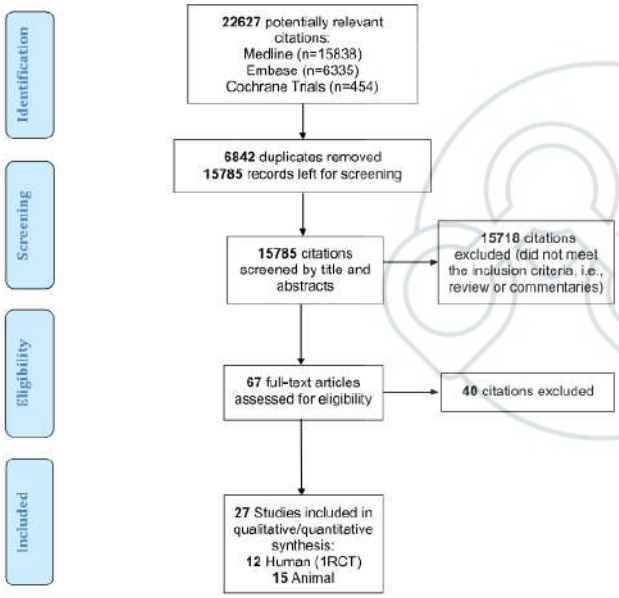
Sheffield WP al. 2022

PLASMA LIOFILIZZATO VS PFC NEL TRAUMA: SR E META-ANALYSIS

OPEN

Freeze-dried plasma for major trauma – Systematic review and meta-analysis

Garrick Mok, MD, Richard Hoang, MD, Montaha Wajid Khan, MD, Dylan Pannell, MD, PhD, Henry Peng, PhD, Homer Tien, MD, MSc, Avery Nathens, MD, PhD, Jeannie Callum, MD, Keyvan Karkouti, MD, MSc, Andrew Beckett, MD, MSc, *and* Luis Teodoro da Luz, MD, MSc, *Ottawa, Canada*



12 human studies (RCT, 1; observational, 11) and 15 animal studies

Data from two studies (n = 119) were combined for meta-analyses for mortality and transfusion of allogeneic blood products. For both outcomes, no difference was identified. For mortality, pooled odds ratio was 0.66 (95% confidence interval, 0.29–1.49), with I^2 = 0%. Use of **FDP is feasible, and no adverse events were reported.** Animal data suggest similar results for coagulation and anti-inflammatory profiles for FP and FDP.

Human data assessing freeze dried plasma use in trauma report **no difference in mortality and transfusion of blood compared with FFP**. Data from animal trauma studies report no difference in coagulation factor and anti-inflammatory profiles. Results should be interpreted **with caution because most studies were observational and have heterogeneous population (military and civilian trauma) and a moderate risk of bias**.

Well-designed **prospective observational studies** or, preferentially, **RCTs are warranted** to answer FDP's effect on laboratory (coagulation factor levels), transfusion, and clinical outcomes (organ dysfunction, length of stay and mortality).

Mock G et al. 2021

PLASMA LIOFILIZZATO *vs* PFC NEL TRAUMA: RCT

Journal of Thrombosis and Haemostasis, 16: 481–489 DOI: 10.1111/jth.13929

ORIGINAL ARTICLE

French lyophilized plasma versus fresh frozen plasma for the initial management of trauma-induced coagulopathy: a randomized open-label trial

D. GARRIGUE,*† A. GODIER,‡§ A. GLACET,*† J. LABREUCHE,¶ E. KIPNIS,*** C. PARIS,†† A. DUHAMEL,¶ E. RESCH,‡‡ A. BAUTERS,†† F. MACHURON,¶ P. RENOM,†† P. GOLDSTEIN,*† B. TAVERNIER,* A. SAILLIOL§§ and S. SUSEN†††¶¶

*CHU de Lille, Pôle d'Anesthésie-Réanimation; †CHU Lille, Pôle de l'Urgence, Lille; ‡Service d'Anesthésie-Réanimation, Fondation Ophtalmologique Adolphe de Rothschild; §NSERM, UMR-S1140, Université Paris Descartes, Sorbonne Paris Cité, Paris; ¶Université Lille, CHU Lille, EA 2694 - Santé Publique: Épidémiologie et Qualité des Soins; **Université Lille, EA 7366; ††CHU de Lille, Institut d'Hématologie-Transfusion; ‡‡EFS Hauts de France; §§Centre de Transfusion Sanguine des Armées, Clamart; and ¶¶Université Lille, Inserm, CHU Lille, U1011 – EGID, Lille, France

- Open-label, phase 3, randomised trial
- **Adult trauma patients requiring an emergency pack of 4 plasma units within 6 h of injury.**
- Randomly assigned to receive **4-FLyP units** or **4-FFP units.**
- Primary end-point: fibrinogen concentration at 45 min after randomisation.
- Secondary outcomes: time to transfusion, changes in haemostatic parameters at different time-points, blood product requirements and 30-day in-hospital mortality.
- 48 patients were randomized (FLyP, n = 24; FFP, n = 24).

TRAUCC trial: French Lyophilised Plasma (FLyP) and Fresh Frozen Plasma (FFP)

- **FLyP reduced the time from randomisation to transfusion of first plasma unit compared with FFP (14 vs 77 min)**
- FLyP achieved a higher fibrinogen concentration 45 min after randomisation (baseline-adjusted mean difference 0.29 g/L) and a greater improvement in prothrombin time ratio, factor V and factor II. **The between group differences in coagulation parameters remained significant at 6 h**
- FLyP reduced fibrinogen concentrate requirements
- **Thirty-day in-hospital mortality rate** was 22% with FLyP and 29% with FFP
- **FLyP** led to a **more rapid coagulopathy** improvement than FFP

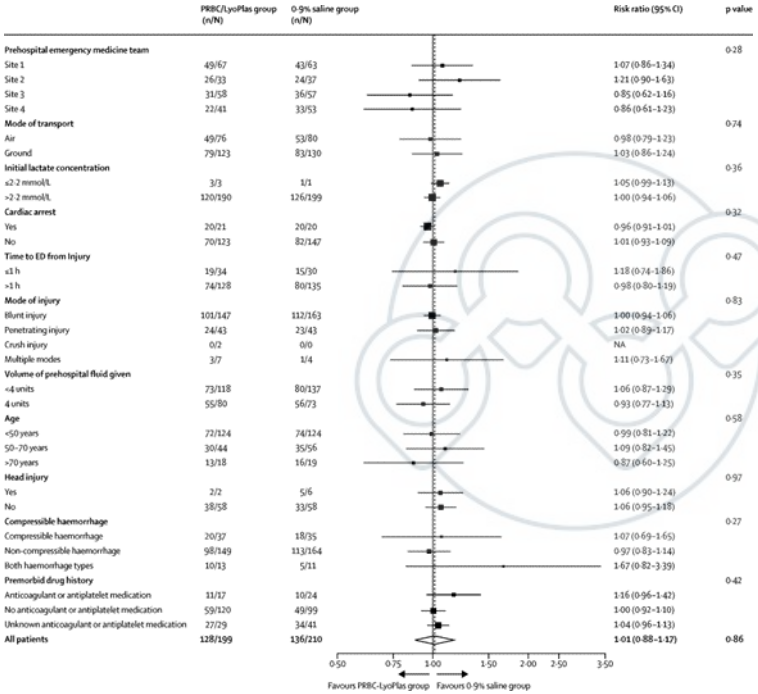
FLyP led to a **more rapid, pronounced and extended increase in fibrinogen concentrations** and **coagulopathy improvement compared with FFP** in the initial management of trauma patients.

Garrigue D et al. 2018

PLASMA LIOFILIZZATO *vs* SOC NEL TRAUMA: RCT

Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial

Nicholas Crombie, Heidi A Doughty, Jonathan R B Bishop, Amisha Desai, Emily F Dixon, James M Hancox, Mike J Herbert, Caroline Leech, Simon J Lewis, Mark R Nash, David N Naumann, Gemma Slinn, Hazel Smith, Iain M Smith, Rebekah K Wale, Alastair Wilson, Natalie Ives, Gavin D Perkins, on behalf of the RePHILL collaborative group*



	PRBC/LyoPlas group (n/N)	0·9% saline group (n/N)	Risk ratio (95% CI)	p value
Prehospital emergency medicine team				0·28
Site 1	49/67	43/63	1·07 (0·86–1·34)	
Site 2	26/33	24/37	1·21 (0·90–1·63)	
Site 3	31/58	36/57	0·85 (0·62–1·16)	
Site 4	22/41	33/53	0·86 (0·61–1·23)	
Mode of transport				0·74
Air	49/76	53/80	0·98 (0·79–1·23)	
Ground	79/123	83/130	1·03 (0·86–1·24)	
Initial lactate concentration				0·36
≤2·2 mmol/L	3/3	1/1	1·05 (0·99–1·13)	
>2·2 mmol/L	120/190	126/199	1·00 (0·94–1·06)	
Cardiac arrest				0·32
Yes	20/21	20/20	0·96 (0·91–1·01)	
No	70/123	82/147	1·01 (0·93–1·09)	
Time to ED from injury				0·47
≤1 h	19/34	15/30	1·18 (0·74–1·86)	
>1 h	74/128	80/135	0·98 (0·80–1·19)	
Mode of injury				0·83
Blunt injury	101/147	112/163	1·00 (0·94–1·06)	
Penetrating injury	24/43	23/43	1·02 (0·89–1·17)	
Crush injury	0/2	0/0	NA	
Multiple modes	3/7	1/4	1·11 (0·73–1·67)	
Volume of prehospital fluid given				0·35
<4 units	73/118	80/137	1·06 (0·87–1·29)	
4 units	55/80	56/73	0·93 (0·77–1·13)	
Age				0·58
<50 years	72/124	74/124	0·99 (0·81–1·22)	
50–70 years	30/44	35/56	1·09 (0·82–1·45)	
>70 years	13/18	16/19	0·87 (0·60–1·25)	
Head injury				0·97
Yes	2/2	5/6	1·06 (0·90–1·24)	
No	38/58	33/58	1·06 (0·95–1·18)	
Compressible haemorrhage				0·27
Compressible haemorrhage	20/37	18/35	1·07 (0·69–1·65)	
Non-compressible haemorrhage	98/149	113/164	0·97 (0·83–1·14)	
Both haemorrhage types	10/13	5/11	1·67 (0·82–3·39)	
Premorbid drug history				0·42
Anticoagulant or antiplatelet medication	11/17	10/24	1·16 (0·96–1·42)	
No anticoagulant or antiplatelet medication	59/120	49/99	1·00 (0·92–1·10)	
Unknown anticoagulant or antiplatelet medication	27/29	34/41	1·04 (0·96–1·13)	
All patients	**128/199**	**136/210**	**1·01 (0·88–1·17)**	**0·86**

0·50 0·75 1·00 1·50 2·00 2·50 3·50

Favours PRBC-LyoPlas group Favours 0·9% saline group

Lyoplas N-w

4 Pre-hospital emergency medical centres in UK

- Multicentre, allocation concealed, open-label, parallel group, randomised, controlled, phase 3 trial done in **four civilian prehospital critical care services in the UK**
- **Pre-hospital two units of pRBC** and **LyoPlas** each (n=209) or **up to 1 litre 0.9% sodium chloride** (n=223) in adult trauma patients with **haemorrhagic shock and hypotension**
- It did not show a difference for the composite endpoint **mortality and/or lactate clearance**
- The trial was stopped at 432/490 patients due to the SARS-CoV-2 pandemic.

The trial **did not show** that **prehospital PRBC–LyoPlas resuscitation was superior to 0.9% sodium chloride** for adult patients with trauma related haemorrhagic shock. **Further research is required to identify the characteristics of patients** who might benefit from prehospital transfusion and **to identify the optimal outcomes** for transfusion trials in major trauma.

Crombie N et al. 2022

PLASMA LIOFILIZZATO *vs* SOC: RCT

JAMA Network | Open

Original Investigation | Emergency Medicine

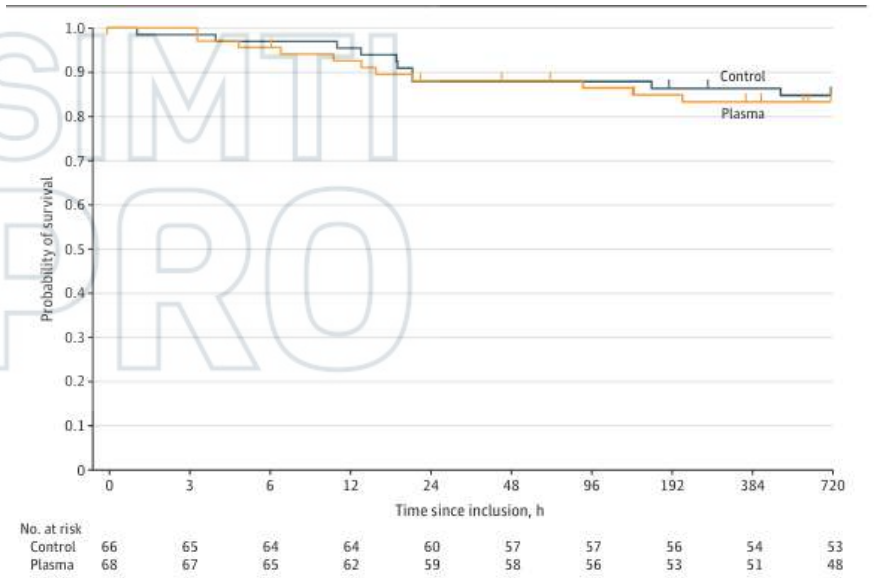
Prehospital Lyophilized Plasma Transfusion for Trauma-Induced Coagulopathy in Patients at Risk for Hemorrhagic Shock
A Randomized Clinical Trial

Daniel Jost, MD; Sabine Lemoine, MD; Frédéric Lemoine, CRA; Clément Derkenne, MD; Sébastien Beaume, MD; Vincent Lanoë, CRA; Olga Maurin, MD; Emilie Louis-Delaurière, CRA; Maëlle Delacote, MD; Pascal Dang-Minh, MD; Marilyn Franchin-Frattini, MD; René Bihannic, PharmD; Dominique Savary, MD; Albrice Levrat, MD; Clémence Baudouin, MD; Julie Trichereau, MD; Marina Salomé, CRA; Benoit Frattini, MD; Vivien Hong Tuan Ha, MD; Romain Jouffroy, MD; Edouard Seguineau, MD; Rudy Titreville, MD; Florian Roquet, MD, PhD; Olivier Stibbe, MD; Benoit Vivien, MD, PhD; Catherine Verret, MD, PhD; Michel Bignand, MD; Stéphane Travers, MD; Christophe Martinaud, MD, PhD; Michel Arock, MD, PhD; Mathieu Raux, MD, PhD; Bertrand Prunet, MD, PhD; Sylvain Ausset, MD, PhD; Anne Sailliol, MD, PhD; Jean-Pierre Tourtier, MD, PhD; for the Prehospital Lyophilized Plasma (PREHO-PLYO) Study Group

FLyP

French ALS teams during ground transportation to a level 1 trauma center

- Multicenter randomised clinical trial **comparing either plasma or standard care with normal saline infusion (control).** The primary outcome was **INR on arrival at the hospital**. Secondary outcomes included the need for massive **transfusion and 30-day survival**.
- 150 randomised patients, 134 were included in the analysis with 68 in the plasma group and 66 in the control group.
- The groups **did not differ significantly in the need for massive transfusion** (7 [10.3%] vs 4 [6.1%]; relative risk, 1.78 [95% CI, 0.42-8.68];p = 0.37) or **30-day survival** (hazard ratio for death, 1.07 [95% CI, 0.44-2.61]; p = 0.89).



In this **randomised clinical trial** including severely injured patients at risk for hemorrhagic shock and associated coagulopathy, **prehospital transfusion of lyophilized plasma was not associated with significant differences in INR values *vs* standard care with normal.**

Jost D et al. 2022

PLASMA LIOFILIZZATO *vs* SOC: RCT

ORIGINAL ARTICLE

Pre-hospital freeze-dried plasma for critical bleeding after trauma: A pilot randomized controlled trial

Biswadev Mitra PhD[1,2] | Ben Meadley PhD[3,4] | Stephen Bernard MD[2,4,5] | Marc Maegele PhD[6,7] | Russell L. Gruen PhD[8] | Olivia Bradley BEH[4] | Erica M. Wood MBBS[2,9] | Zoe K. McQuilten PhD[2,9] | Mark Fitzgerald MD[10,11,12] | Toby St. Clair BEH[3,4] | Andrew Webb MSc[13] | David Anderson MBChB[3,4,5] | Michael C. Reade DPhil[2,14,15,16]

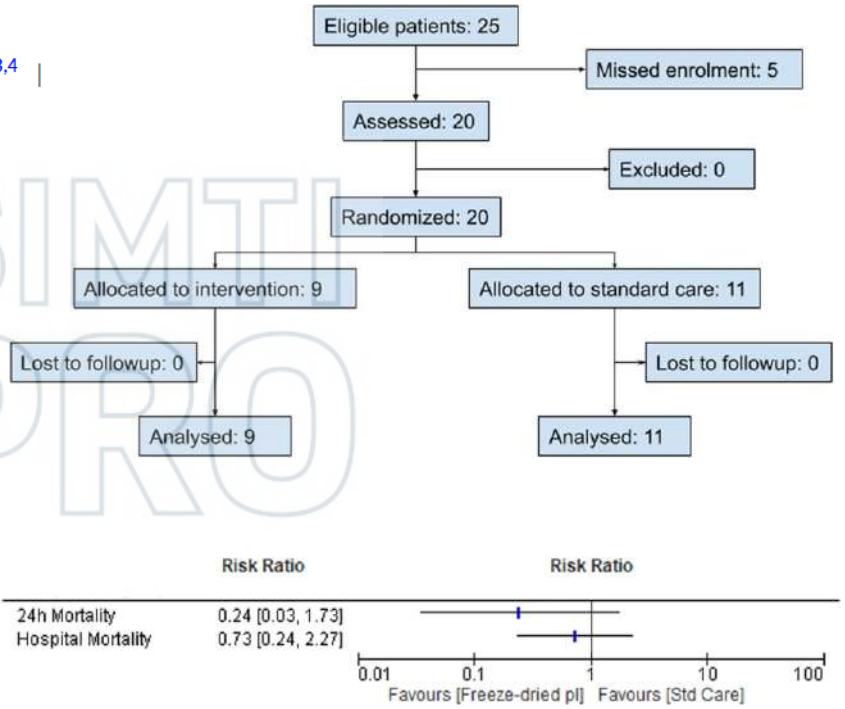
Pilot trial to assess the feasibility of transfusing *freeze-dried plasma* with *red blood cells (RBCs)* using in an Australian aeromedical prehospital setting.

Patients managed with prehospital RBCs randomized to receive 2 units of freeze-dried plasma (Lyoplas N-w) or standard care (no plasma).

- Primary outcome: proportion of eligible patients enrolled and provided the intervention.
- Secondary outcomes: preliminary data on effectiveness, including mortality censored at 24 h and at hospital discharge, and adverse events.

Mortality may have been lower in the freeze-dried plasma group at 24 h (RR 0.24, 95% CI 0.03-1.73) and at hospital discharge (RR 0.73, 95% CI 0.24-2.27). No serious adverse events related to the trial interventions were reported.

Lyoplas N-w



This **first reported experience of freeze-dried plasma** use in Australia **suggests prehospital administration** is **feasible.** Given longer prehospital times typically associated with HEMS attendance, there is potential clinical benefit from this intervention and rationale for a definitive trial.

Mitra B et al. 2023

PLASMA LIOFILIZZATO *vs* SOC: REVISIONE DELLA LETTERATURA

Original Articles

Prehospital Freeze-Dried Plasma in Trauma: A Critical Review

William P. Sheffield[a,b,*], Kanwal Singh[c,d], Andrew Beckett[c,d,e], Dana V. Devine[f]

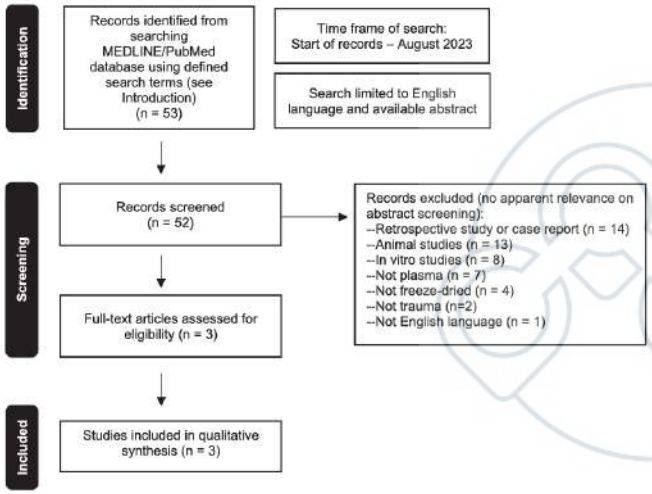


Figure 1. PRISMA [46] diagram of systematic search strategy.

	RePHILL [7]	PRE-HO PLYO [8]	Mitra et al. [9]
PMID	35271808	35881397	37103482
Nature	RCT	RCT	RCT (pilot)
Study duration	2016-2021	2016-2019	2021 (5 months)
Publication year	2022	2022	2023
Setting	UK multicentre air/ground EMS; open-label prehospital treatment	French multicentre EMS; open-label prehospital treatment	Australian single air EMS; open-label prehospital treatment
Inclusion	Trauma patients 16 years or over assessed for transfusion, SBP < 90 mm Hg or no radial pulse	Adult trauma patients SBP < 70 mM Hg or shock index > 1.1	Adult trauma patients assessed to require transfusion in a 5-month set time period
Exclusion	Blood products prerandomization, pregnancy, prisoners, isolated head injury	Pregnancy, prisoners, allergy to amotosalen, coagulation factors prior to randomization, DNR	>90 years, no venous access, known pregnancy, active palliative care
Consent	Assumed/deferred	Assumed/deferred	Not specified
Intervention	Up to 2 units PRBC + 2 units LyoPlas vs up to 4 × 250 mL normal saline	Up to 4 units FLyP (and saline as needed for hemodynamic goals) vs up to 1000 mL normal saline	1-unit PRBC + 2 units LyoPlas vs 1-unit PRBC alone
Randomization and blinding	1:1, allocation concealed until randomization	1:1, allocation concealed until randomization	1:1, allocation concealed until randomization
Enrolment and rationale	438 to give 80% power to detect 10% difference in primary outcome	140 to give 80% power to detect mean difference in INR of 0.3	Eligible patients in 5 month set time interval
Patients (*n*)	432	150	25
Age	Medians 38 (27-57), 39 (24-59) (IQR)	Medians 36.6 (26.8-49.5) vs 33.6 (25.2-47.6) (IQR)	Medians (IQR) 48 (40-51) vs 34 (19-54)
Male (%)	82% in both arms	86.8 vs 77.3	77.8 vs 63.6
Blunt injury (%)	78 vs 80	58.8 vs 60.6	Not specified
	RePHILL	PRE-HO PLYO	Mitra et al.
Prehospital crystalloid (mL)	Means 422 vs 437	Median 700 (475-1000) vs 1000 (700-1350) (IQR)	Not specified
Tranexamic acid (%)	87 vs 92	83.8 vs 90.9	0
Primary outcome	Composite of mortality + failure to clear lactate	INR at hospital arrival	% of patients enrolled
Analysis	ITT, model-based	ITT	ITT
Outcome	No difference between groups, 64% vs 65%, $P = .996$	No difference between groups, Median 1.21 vs 1.20, $P = .88$	80% of patients were enrolled and 76% received the intervention

DNR, Do Not Resuscitate; EMS, Emergency Medical Services; INR, International Normalized Range; IQR, interquartile range; ITT, intention to treat; SBP, systolic blood pressure; UK, United Kingdom.

Available high-level evidence ***does not support*** **a benefit of prehospital administration of FDP to trauma patients**. **Lack of evidence of benefit** in those clinical settings subjected to RCT investigation **is not necessarily evidence of lack of benefit** in all scenarios. It is possible that there is an unidentified **subset of trauma patients** who could benefit most from its use.

Sheffield WP al. 2024

PLASMA LIOFILIZZATO CARATTERISTICHE QUALITATIVE

Characterization and first-in-human clinical dose-escalation safety evaluation of a next-gen human freeze-dried plasma

Jose A. Cancelas[1] | Shawnagay Nestheide[1] | Neeta Rugg[1] | Anna Eckerman[2] | Victor W. Macdonald[3] | Matthew L. Charles[2] | Luke Markstrom[2] | Andrew J. Atkinson[3] | Melissa R. King[4] | Michele Snyder[4] | David Burgess[4] | James Murto[2] | Manoj K. Valiyaveettil[3] | Joan C. Pehta[5] | Stephen A. Penegor[2]

Clinical dose escalation safety trial in healthy volunteer subjects of a next-generation product, stored in plastic bag containers with rapid reconstitution for immediate infusion.

- **Characterisation and clinical safety data of the first, next-generation FDP stored in plastic bags** with rapid reconstitution. **Coagulation** and **chemistry parameters of FFP** and their derivative FDP units **were compared.**
- **First-in-human, dose-escalation safety evaluation of FDP**, involving **24 healthy volunteers** who donated either whole blood or apheresis plasma to create autologous FDP, in **three dose cohorts (270, 540, and 810 ml)**
- **Cohort 3 was randomised, double-blind** with a cross-over arm that **compared FDP versus FFP** using descriptive analysis for AEs, coagulation, haematology, and chemistry parameters.
- ***FDP coagulation factors, clotting times, and product quality (pH, total protein, and osmolality) post-lyophilization*** were preserved.

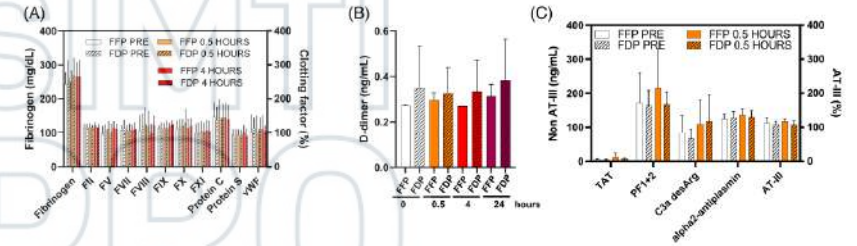


FIGURE 5 Time kinetics of clotting factor levels and pro-thrombotic indicators in plasma before and after infusions in Cohort 3. (A) Fibrinogen, prothrombin (FII), factor V (FV), factor VII (FVII), factor VIII:Coagulant (FVIII), factor IX (FIX), factor X (FX), factor XI (FXI), protein C, protein S, and von Willebrand factor antigen (vWF). Protein C levels higher than 200% were found outside the linearity range and used as of 200% for quantitative calculations. (B) D-dimer. Level of sensitivity was 0.27 ng/ml. For specimens with levels lower than 0.27 ng/ml, a level of 0.27 ng/ml was used for quantitative calculations. (C) Thrombin–antithrombin (TAT) complexes, prothrombin fragment 1 + 2 (PF1 + 2), complement C3a desArg fragment, alpha2-antiplasmin, and antithrombin III (AT-III). Data are presented as average + one SD. No statistically significant differences between the levels of any of the parameters analyzed before or after the infusions of FFP or FDP were found

Cancelas JA et al. 2022

This first next-generation FDP product preserves the potency and safety of FFP in a novel rugged, compressible, plastic container, for rapid transfusion.

GUIDELINES Open Access

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

Rolf Rossaint[1*], Arash Afshari[2], Bertil Bouillon[3], Vladimir Cerny[4,5], Diana Cimpoesu[6], Nicola Curry[7,8], Jacques Duranteau[9], Daniela Filipescu[10], Oliver Grottke[1], Lars Grønlykke[11], Anatole Harrois[9], Beverley J. Hunt[12], Alexander Kaserer[13], Radko Komadina[14], Mikkel Herold Madsen[2], Marc Maegele[15], Lidia Mora[16], Louis Riddez[17], Carolina S. Romero[18], Charles-Marc Samama[19], Jean-Louis Vincent[20], Sebastian Wiberg[11] and Donat R. Spahn[13]

Pre-hospital blood product use
Recommendation 4
No clear recommendation or suggestion in favour or against the use of pre-hospital blood products can be provided at this time

The pre-hospital use of blood products is technically feasible; however, logistical hurdles and the scarcity of universal blood group donors, along with health economic challenges and financial burdens, remain subjects of ongoing investigation and debate.

"**Due to conflicting data and the financial burden involved in the design and implementation of pre-hospital pRBC and plasma transfusion programmes.., no clear recommendation or suggestion in favour or against the use of pre-hospital blood products can be provided at this time**. The decision to commit to routine pre-hospital use of blood products requires careful consideration by all stakeholders and must be adapted to local circumstances and settings"

Prehospital use of freeze-dried plasma may have logistic benefits over thawed/frozen plasma and retrospective evidence has demonstrated feasibility, positive effects on coagulation, and when administered as bolus followed by pre-hospital pRBC, a capacity to reduce pRBC requirements.

Rossaint R et al. 2023

PRODOTTO FARMACEUTICO

TABLE 1 Screening tests of blood coagulation and inhibition

Parameters	OctaplasLG final product specification	Reference range plasma	Frozen OctaplasLG ($N = 12$)	Freeze-dried OctaplasLG Lyo ($N = 3$)	FFP ($N = 12$)
aPTT (s)	23–40	28–40	28 (27–31)	29 (28–31)	30 (26–35)
PT (s)	n.s.	12.5–16.5	11.8 (11.2–12.6)	11.4 (11.4–11.5)	11.4 (10.0–14.1)
RT (s)	n.s.	<20	14.6 (14.2–14.9)	13.9 (13.1–14.3)	17.4 (14.7–19.7)[a,b]
TT (s)	n.s.	14–20	14.7 (13.9–16.6)	12.4 (12.1–12.8)	14.1 (11.9–15.7)[b]
Thrombin (nM)	n.s.	n.s.	147 (111–175)	163 (161–166)	66 (33–118)[a,b]
Lag time (min)	n.s.	n.s.	6.3 (5.5–7.5)	6.0 (6.0–6.0)	8.0 (5.5–11.0)[a,b]
AUC (nM × min)	n.s.	n.s.	1376 (1219–1528)	1476 (1438–1525)	1116 (803–1358)[a,b]
Clotting time (min)	n.s.	n.s.	417 (206–465)	342 (311–374)	379 (330–451)
MCF (mm)	n.s.	n.s.	20 (18–23)	22 (21–22)	22 (16–28)
Factor II (IU/ml)	n.s.	0.65–1.54	1.08 (0.98–1.14)	1.15 (1.12–1.21)	1.29 (1.05–1.51)[a]
Factor V (IU/ml)	≥0.5	0.54–1.45	0.93 (0.90–1.00)	0.90 (0.90–0.90)	0.99 (0.80–1.25)
Factor VII (IU/ml)	n.s.	0.62–1.65	1.07 (0.97–1.21)	1.13 (1.10–1.20)	1.35 (0.85–1.74)
Factor VIII (IU/ml)	≥0.5	0.45–1.68	1.08 (0.80–1.30)	0.93 (0.80–1.00)	1.32 (0.61–1.80)[a]
Factor IX (IU/ml)	n.s.	0.45–1.48	1.15 (0.99–1.27)	1.20 (1.10–1.37)	1.32 (1.06–1.54)
Factor X (IU/ml)	n.s.	0.68–1.48	1.09 (0.98–1.12)	1.25 (1.22–1.29)	1.19 (1.08–1.52)
Factor XI (IU/ml)	≥0.5	0.42–1.44	0.93 (0.90–1.00)	0.80 (0.80–0.80)	0.99 (0.69–1.20)[a]
Factor XII (IU/ml)	n.s.	0.40–1.52	1.19 (1.03–1.40)	1.00 (0.95–1.03)	0.98 (0.54–1.37)[a,b]
Factor XIII (IU/ml)	n.s.	0.65–1.65	0.92 (0.85–0.98)	0.90 (0.88–0.92)	0.88 (0.64–1.20)
VWF:RCo (IU/ml)	n.s.	0.45–1.75	0.87 (0.78–0.94)	0.95 (0.89–1.07)	1.08 (0.57–1.42)[a]
ADAMTS13 (IU/ml)	n.s.	n.s.	0.99 (0.83–1.24)	0.92 (0.88–0.94)	0.92 (0.58–1.38)
Antithrombin (IU/ml)	n.s.	0.80–1.25	0.96 (0.91–1.02)	1.06 (1.02–1.11)	1.14 (0.91–1.36)[a]
HCII (IU/ml)	n.s.	0.65–1.35	1.23 (1.14–1.36)	1.18 (1.12–1.24)	1.27 (0.67–1.71)
Protein C (IU/ml)	≥0.7	0.58–1.64	1.00 (1.00–1.00)	1.03 (1.00–1.10)	0.97 (0.76–1.16)
Protein S activity (IU/ml)	≥0.3	0.65–1.45	0.66 (0.60–0.80)	0.67 (0.60–0.70)	1.02 (0.69–1.40)[a,b]
Protein S antigen (IU/ml)	n.s.	0.65–1.45	0.87 (0.81–0.93)	0.81 (0.80–0.82)	1.05 (0.73–1.39)[a]
Plasmin inhibitor (U/ml)	≥0.2	0.72–1.32	0.43 (0.40–0.50)	0.47 (0.40–0.50)	1.33 (1.11–1.49)[a,b]
Plasminogen (IU/ml)	n.s.	0.68–1.44	0.87 (0.82–0.90)	0.86 (0.83–0.88)	0.96 (0.70–1.18)
A1AT (mg/ml)	n.s.	n.s.	1.32 (1.02–1.47)	1.26 (1.15–1.42)	1.48 (0.93–1.71)
A1AT Ag (mg/ml)	n.s.	1.10–2.60	1.17 (1.04–1.24)	1.16 (1.16–1.17)	1.20 (0.80–1.46)
C1-INH (IU/ml)	n.s.	0.60–1.24	1.18 (1.02–1.45)	1.17 (1.08–1.22)	1.56 (1.17–1.97)[a,b]

Note: Mean (minimum–maximum) levels are presented.
[a]Statistically significant differences between OctaplasLG and FFP are indicated, that is, p-value < .05.
[b]Statistically significant differences between OctaplasLG Lyo and FFP are indicated, that is, p-value < .05.
Abbreviations: A1AT, α_1-antitrypsin; ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; Ag, antigen; aPTT, activated partial thromboplastin time; AUC, area under the curve; C1-INH, C1-inhibitor; FFP, fresh frozen plasma; HCII, heparin cofactor II; IU, international units; MCF, maximum clot firmness; N, number of batches; n.s., not specified; PT, prothrombin time; RT, reptilase time; TT, thrombin time; VWF:RCo, ristocetin cofactor activity of von Willebrand factor.

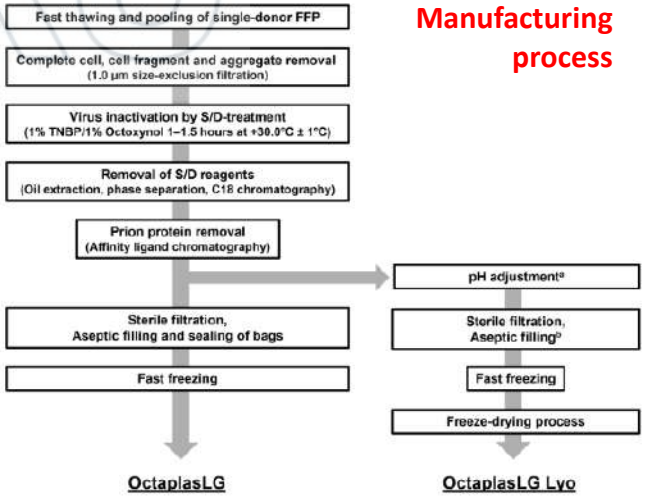
Heger, Grueber 2022

INDICAZIONI

- Complesse carenze di fattori della coagulazione come la coagulopatia dovuta a grave insufficienza epatica o trasfusioni massicce.
- Terapia sostitutiva nei deficit di fattori della coagulazione, quando uno specifico concentrato di fattori della coagulazione non è disponibile per l'uso o in situazioni di emergenza quando non è possibile una diagnosi di laboratorio precisa.
- Rapida inversione degli effetti degli anticoagulanti orali, quando un concentrato di complesso protrombinico non è disponibile per l'uso o la somministrazione di vitamina K è insufficiente a causa della compromissione della funzionalità epatica o in situazioni di emergenza.
- Emorragie potenzialmente pericolose durante la terapia fibrinolitica, utilizzando ad es. attivatori tissutali del plasminogeno , in pazienti che non rispondono alle misure
- Procedure terapeutiche di plasmaferesi, comprese quelle nella porpora trombotica trombocitopenica

FIGURE 1 Flow-chart of the OctaplasLG and OctaplasLG Lyo manufacturing process. [a]The pH value is adjusted in stepwise manner by using citric acid, phosphoric acid and low pressure. [b]The sterile filtered plasma is filled under aseptic conditions into sterile and depyrogenated type I glass vials (200–210 ml plasma per vial). FFP, fresh frozen plasma; S/D, solvent/detergent; TNBP, tri(n-butyl)phosphate.

Manufacturing process



Approvazione EMA
Feb. 2023

JOINT ACTION GAPP PRO

GAPP-PRO – **Piloting Gapp model approach for assessing and authorizing novel substances of human origin preparation process".**

- La Joint Action europea ha lo scopo di testare e perfezionare la metodologia della precedente JA GAPP con l'obiettivo di:

  Simulare i processi di autorizzazione su nuovi prodotti nei diversi ambiti di attività della donazione e trapianto delle sostanze di origine umana (ad es. trapianto di microbiota, latte materno, collirio ecc.);

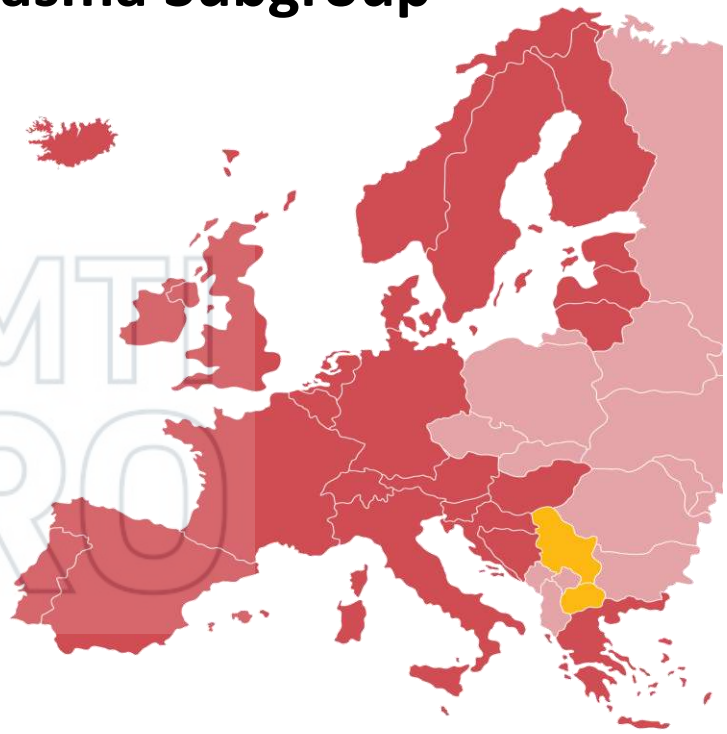
  Verificare la capacità di implementazione del modello nei diversi Stati Membri, con particolare riferimento ad una comune valutazione dei livelli di rischio;

- Testare la metodologia in un'ottica di multi-country assessment;
- Formare gli assessor;
- Testare la fattibilità di mettere in atto dei joint assessment anche attraverso il coinvolgimento di stakeholder dei settori dei dispositivi medici e delle terapie avanzate.

- **Volto a testare e perfezionare la metodologia di autorizzazione di nuovi processi e prodotti relativi a sostanze di origine umana.**
- **Tra i prodotti/processi innovativi in corso di valutazione anche il plasma liofilizzato.**

EUROPEAN BLOOD ALLIANCE

Dried Plasma Subgroup



The **main focus** of the **Dried plasma WG:**

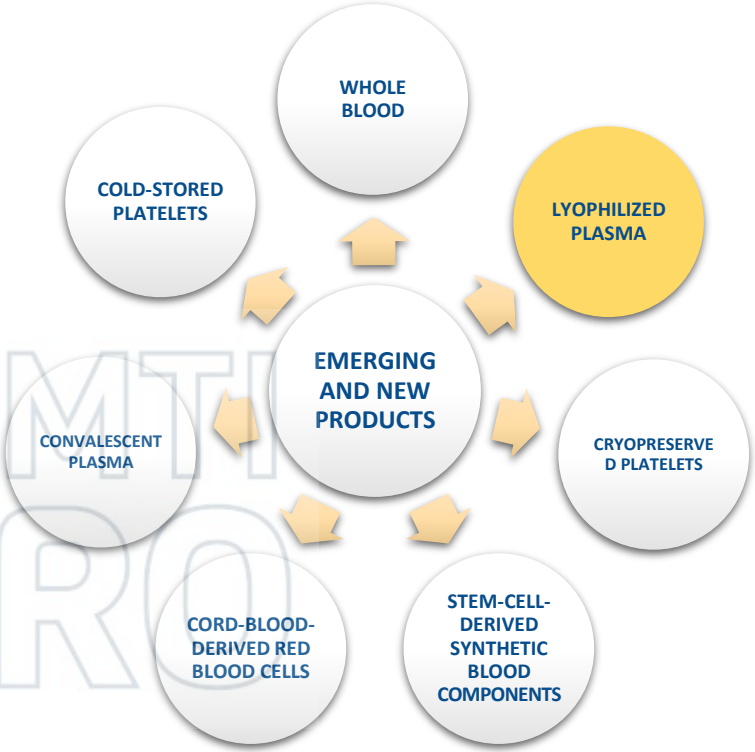
- Support the **inclusion** of dried plasma in the **EDQM Blood Guide**
- Understand **the demand** and **clinical use** ➢ **Survey of EBA member states**

Challenges:

- Availability of the technology for local production
- Source limitations: Demand of plasma for fractionation
- Regulatory aspects: Blood product versus drug

CONCLUSIONI

- **Approccio attualmente valutabile** nel contesto **pre-ospedaliero emergenziale militare e civile.**
- **Possibile estensione**, in un futuro, **ad un più ampio utilizzo clinico**, in considerazione degli evidenti vantaggi tecnici e logistici?
- Sono necessari **ulteriori studi** volti ad identificare le **caratteristiche dei pazienti** che potrebbero beneficiarne dell'utilizzo nel contesto emergenziale, con una migliore definizione e standardizzazione di **outcomes primari e secondari**, e con il **supporto degli strumenti POC.**
- E' necessaria una **valutazione opportuna in relazione al rapporto costo/beneficio** anche alla luce dell'attuale contesto geopolitico che rende più insistente la richiesta di tali prodotti.



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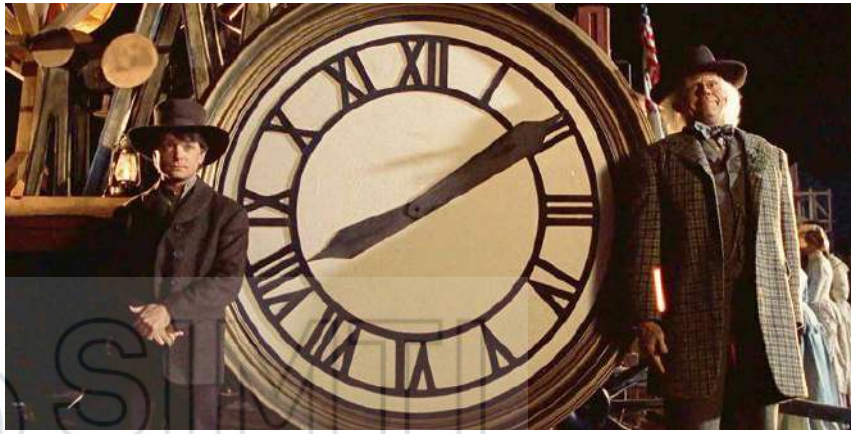

Jean-Jacques Lataillade
Alberto Mancin
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Markus Jarnig

Grazie

Sooner or later, everything old is new again!
Stephen King