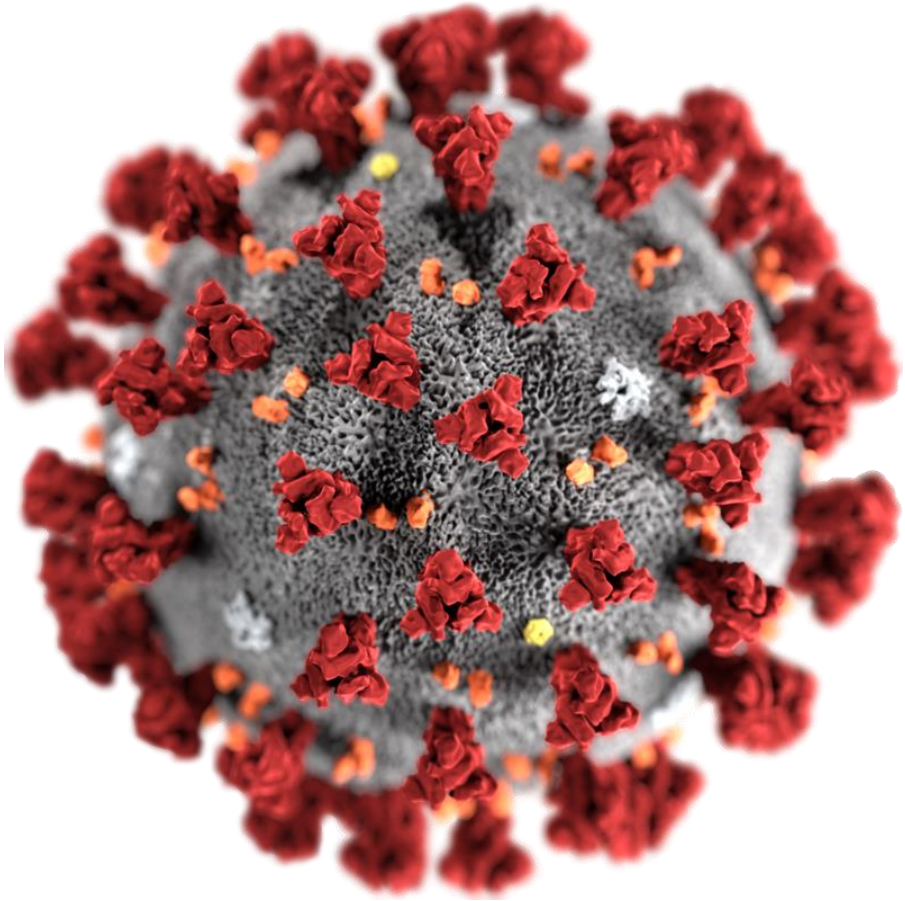
Medicina transfusional i teràpia cel·lular en temps de pandèmia



Plasma convalescent

Dr. Enric Contreras Barbeta

Banc de Sang i Teixits

Contingut

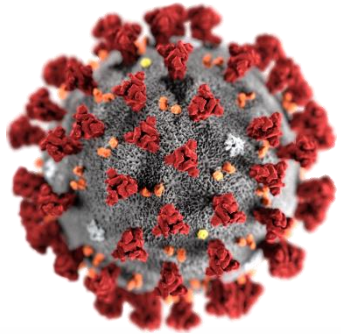
1. Us de plasma convalescent. Antecedents històrics

2. COVID-19. Tractament amb plasma convalescent
   - Primeres experiències
   - Primeres dades
   - Últimes aportacions

3. De plasma convalescent a plasma vacunal

4. Contribució a l'autosuficiència d'hemoderivats

5. Conclusions



Les primeres immunoteràpies passives

Antitoxines diftèrica i tetànica

1890. **Emili Von Behring** demostra que el sèrum de cavalls infectats provoca immunitat (tètanus i diftèria)

Durant la guerra de Corea es van tractar milers de soldats afectats per la febre hemorràgica de Corea (Hantavirus) amb **plasma convalescent** procedent de soldats curats

Treatment of Ebola Hemorrhagic Fever with Blood Transfusions from Convalescent Patients

K. Mupapa, M. Massamba, K. Kibadi, K. Kuvula, A. Bwaka, M. Kipasa, R. Colebunders, and J. J. Muyembe-Tamfum on behalf of the International Scientific and Technical Committee

Kinshasa University, Ministry of Public Health, and Kikwit General Hospital, Kikwit, and National Institute for Biomedical Research, Kinshasa, Democratic Republic of the Congo; Institute of Tropical Medicine, Antwerp, Belgium

J Infect Dis 1999; 179 Supl 1: S18-S23

Table 2. Characteristics of 8 Ebola-infected female convalescent blood transfusion recipients.

Patient	Age (years)	No. of days between onset of symptoms and transfusion	Blood volume (cm^3)	Received blood from donor no.	Outcome
1	27	7	400	1	Survived
2	12	11	150	2	Survived
3	15	13	150	3	Survived
4	54	9	250	2	Survived
5	44	15	250	4	Survived
6	25	13	250	4	Survived
7	40	11	450	5	Survived
8	48	4	400	2	Died

Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

Interim Guidance for National Health Authorities and Blood Transfusion Services

Version 1.0 September 2014

World Health Organization

Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients

Soo Y, Cheng Y, Wong R et al. Clin Microbiol Infect 2004 Jul;10(7):676-8.

Table 2. Comparison of treatment outcome between patients in the plasma-treated and steroid-treated groups

	Plasma group[a]	Steroid group[b]	p
Discharge rate by day 22 following onset of illness	73.4% (n = 14)	19% (n = 4)	0.001
Discharge rate by day 22 after adjustment for co-morbidities	77.8% (14/18)	23% (3/13)	0.004
Death rate	0%	23.8% (n = 5)	0.049

[a]Three doses of methylprednisolone, followed by convalescent plasma.
[b]Four or more doses of methylprednisolone.

Use of convalescent plasma therapy in SARS patients in Hong Kong

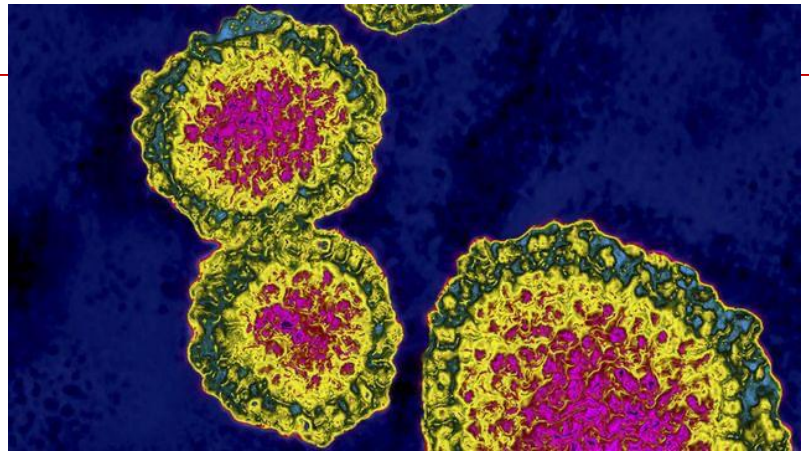
Cheng Y, Wong R, Soo Y et al. Eur J Clin Microbiol Infect Dis 2005; 24(1): 44-46

Characteristic	Good outcome[a]	Poor outcome[b]	*P* value	Logistic regression *P* value
No. of patients	33	47		
Age	37.9±12.5	50.2±15.1	<0.001	0.009
Admission LDH (IU/l)	268.6±117.6	334±183.7	0.08	0.014
Mean day of plasma infusion[c]	11.7±2.3	16.0±6.0	<0.001	0.012
Mean plasma volume	253.6±99.9	297.23±141.4	0.11	0.174
PCR positive and seronegative for SARS[d]	20	10	<0.001	0.006

Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection FREE

Hung I, To K, Lee C-K et al. Clinical Infectious Diseases 2011; 52(4): 447-456

In conclusion, this study has demonstrated that convalescent plasma treatment may have a place in the treatment of patients with severe H1N1 2009 infection. The treatment effectively reduced the viral load and dampened the cytokine response with reduced mortality. A double-blind randomized controlled trial with hyperimmune intravenous immunoglobulin on patients with severe influenza infection is warranted in the future.



Plasma Convalescent COVID-19
primeres sèries de casos

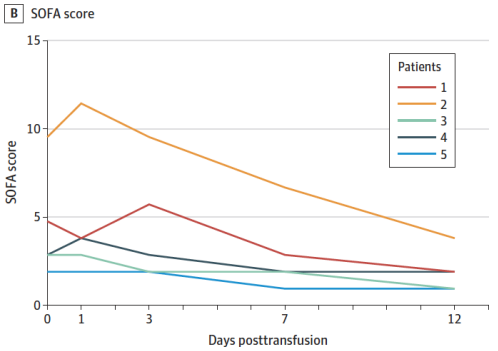
JAMA | Preliminary Communication

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Shen C, Wang Z, Zhao F et al. JAMA 2020; 323(16): 1582-1589

DESIGN, SETTING, AND PARTICIPANTS Case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PaO_2/FiO_2 <300; and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.

Ct value[c] (viral load proxy)					
On admission to hospital	23.0	19.7	18.9	38.0	28.0
Lowest value during hospitalization[d] (highest viral load)	19.2	19.7	18.9	26.6	26.5
Just before plasma transfusion	28.5	22.0	33.0	26.6	35.9
Day 1 posttransfusion	30.0	23.7	38.5	28.0	Negative
Day 3 posttransfusion	34.4	25.0	Negative	Negative	Negative
Day 7 posttransfusion	38.0	32.0	Negative	Negative	Negative
Day 12 posttransfusion	Negative	Negative	Negative	Negative	Negative



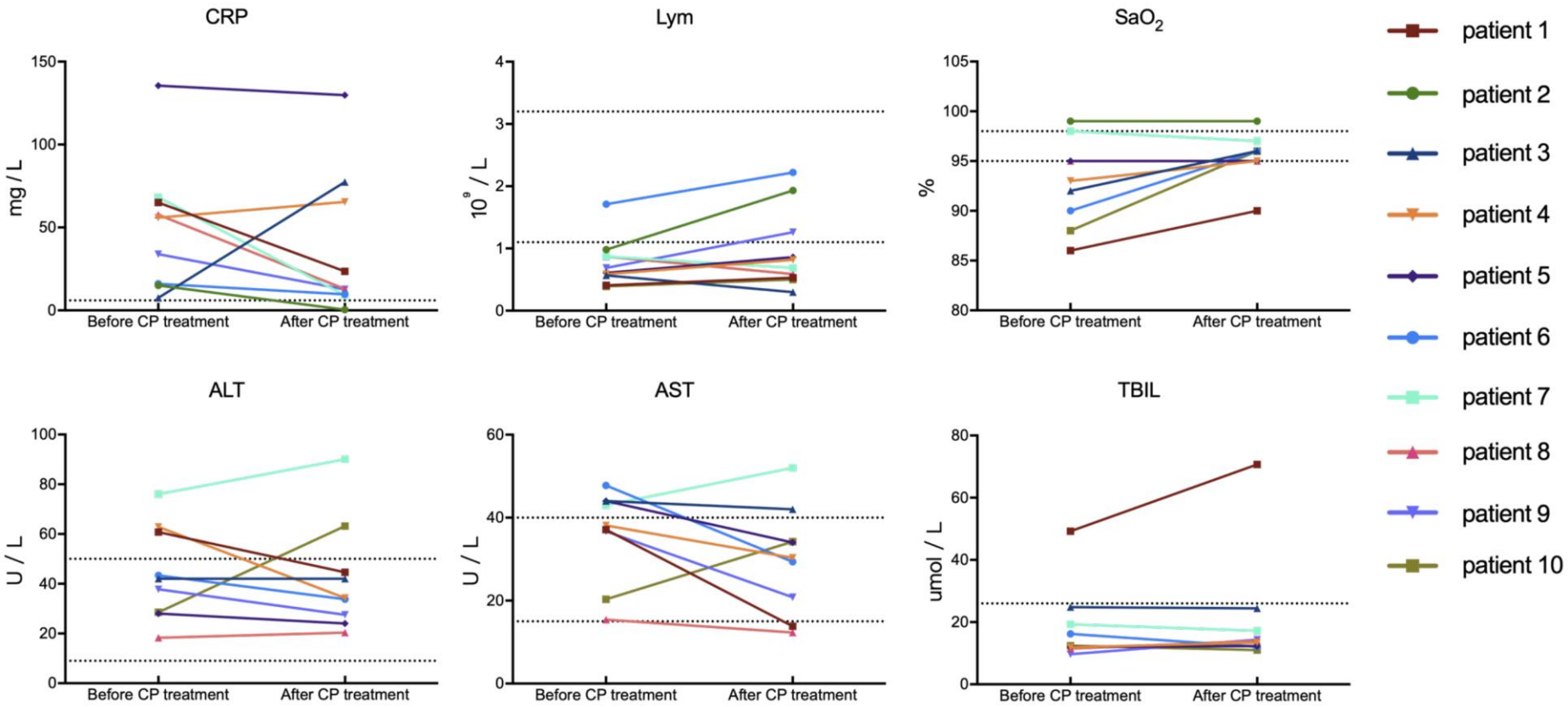
Length of hospital stay, d	Remains hospitalized	Remains hospitalized	53	51	55
Current status as of March 25, 2020	Stable, still receiving mechanical ventilation	Stable, still receiving mechanical ventilation	Discharged home	Discharged home	Discharged home

Plasma Convalescent COVID-19

primeres sèries de casos

The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study

Duan K, Liu B, Li C et al. https://doi.org/10.1101/2020.03.16.20036145



Plasma Convalescent COVID-19

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Ref. Ares(2020)7213671 - 30/11/2020

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety, innovation

Brussels,
SANTÉ B4/DF/

An EU programme of COVID-19 convalescent plasma collection and transfusion

Guidance on collection, testing, processing, storage, distribution and monitored use

GOBIERNO DE ESPAÑA · MINISTERIO DE SANIDAD

CCST COMITÉ CIENTÍFICO SEGURIDAD TRANSFUSIONAL

DIRECTRICES PARA LA OBTENCIÓN DE PLASMA DE DONANTES CONVALECIENTES DE LA COVID-19

Comité Científico para la Seguridad Transfusional (CCST)

BANC DE SANG I TEIXITS

NOTA TÈCNICA:	**NT -EM-DI-011 (Versió 2)**
Document relacionat:	**T-DI-EM-006**
Data:	**17/03/2021**

ACTUALITZACIÓ DEL PROTOCOL PER A LA SELECCIÓ DE DONANTS DE PLASMA CONVALESCENT COVID-19

Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma			
Manufacturer (listed alphabetically)	**Assay**	**Qualifying Result**	**Date of Listing under this EUA**
Abbott	SARS-CoV-2 IgG (ARCHITECT and Alinity i)	Index (S/C) ≥ 4.5	February 4, 2021
Abbott	AdviseDx SARS-CoV-2 IgG II (ARCHITECT and Alinity i)	≥ 840 AU/mL	March 9, 2021
Beckman Coulter	Access SARS-CoV-2 IgG	S/CO ≥ 3.3	February 4, 2021
EUROIMMUN	Anti-SARS-CoV-2 ELISA (IgG)	Ratio ≥ 3.5	February 4, 2021

BST S/Co > 6

(≥ 1/160 neutralising antibodies)

Jaaskelainen et al. 2020; Patel et al. 2020

Cedida per Silvia Sauleda

Plasma Convalescent COVID-19

Des de l'inici de la pandèmia hem obtingut 6000 plasmes convalescents COVID-19

Plasma Convalescent COVID-19
un allau de dades

- Malalts crítics
- Malalts amb pneumònia
- Malalts greus
- Malalts lleus
- Malalts amb altres patologies

Early safety indicators of COVID-19 convalescent plasma in 5000 patients

Joyner M, Scott Wright R, Fairweather, D et al. J Clin Ivest 2020; 130(9): 4791-4797

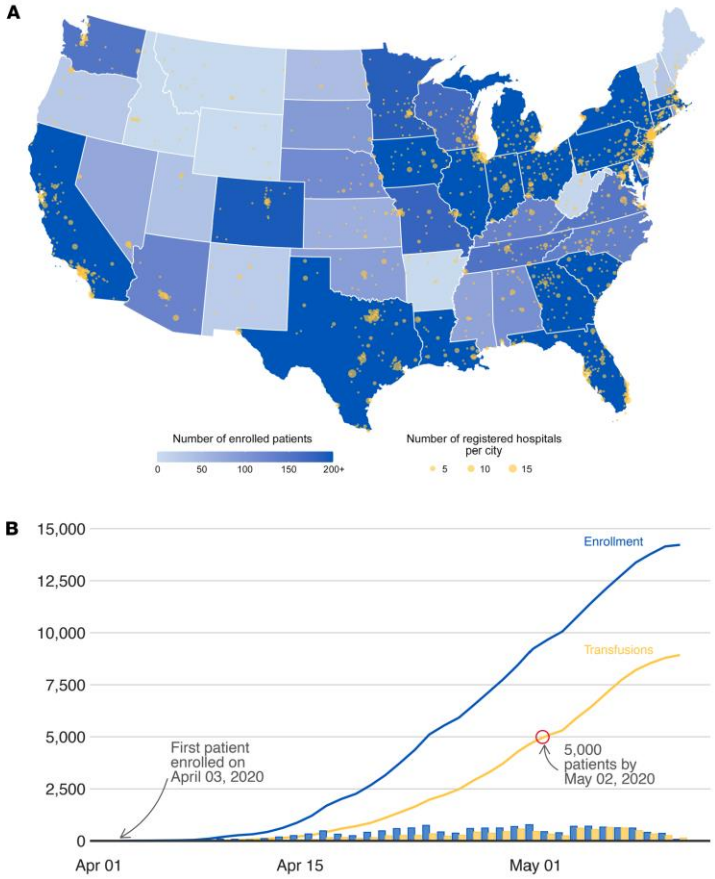


Table 2. Serious adverse event characteristics (*n* = 5,000)

Four-hour reports	Reported (*n* = 36)	Related[A] (*n* = 25)	Estimate (95% CI)
Mortality	15	4	0.08% (0.03%, 0.21%)
Transfusion-associated circulatory overload	7	7	0.14% (0.07%, 0.29%)
Transfusion-related acute lung injury	11	11	0.22% (0.12%, 0.39%)
Severe allergic transfusion reaction	3	3	0.06% (0.02%, 0.18%)
Seven-day reports			
Mortality	602		14.9% (13.8%, 16.0%)[B]

CONCLUSION. Given the deadly nature of COVID-19 and the large population of critically ill patients included in these analyses, the mortality rate does not appear excessive. These early indicators suggest that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19.

FDA U.S. FOOD & DRUG ADMINISTRATION

EMERGENCY USE AUTHORIZATION (EUA) OF COVID-19 CONVALESCENT PLASMA FOR TREATMENT OF HOSPITALIZED PATIENTS WITH COVID-19

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product high titer COVID-19 convalescent plasma to treat hospitalized patients with COVID-19. Available evidence suggests potential benefit is associated with transfusion of high titer COVID-19 convalescent plasma early in the course of disease and those hospitalized with impaired humoral immunity. Transfusion of COVID-19 convalescent plasma to hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit.

Convalescent plasma for covid-19

Authorisation in the US was premature, and a missed opportunity

Lise J Estcourt, David J Roberts

the bmj | *BMJ* 2020;370:m3516 | doi: 10.1136/bmj.m3516

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

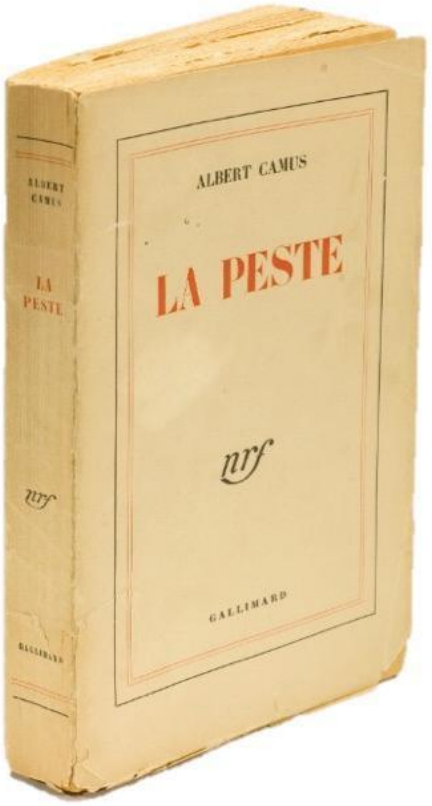
journal homepage:
https://www.journals.elsevier.com/transfusion-medicine-reviews/

COVID-19 Convalescent Plasma: Now Is the Time for Better Science

"Le mal dans le monde vient presque toujours de l'ignorance, et les bonnes intentions peuvent faire autant de mal que la malveillance si elles manquent de compréhension"- Albert Camus, *The Plague*, 1947

Sunny Dzik, Transfus Med Rev 2020; 34(3): 141-144

- Transfusion-Associated Circulatory Overload in the Critically Ill
- Complement and Coagulation
- Antibody-Dependent Enhancement of COVID-19 Disease
- Unexpected Findings Are Best Understood by Randomized Trials



Cochrane Library

Cochrane Database of Systematic Reviews

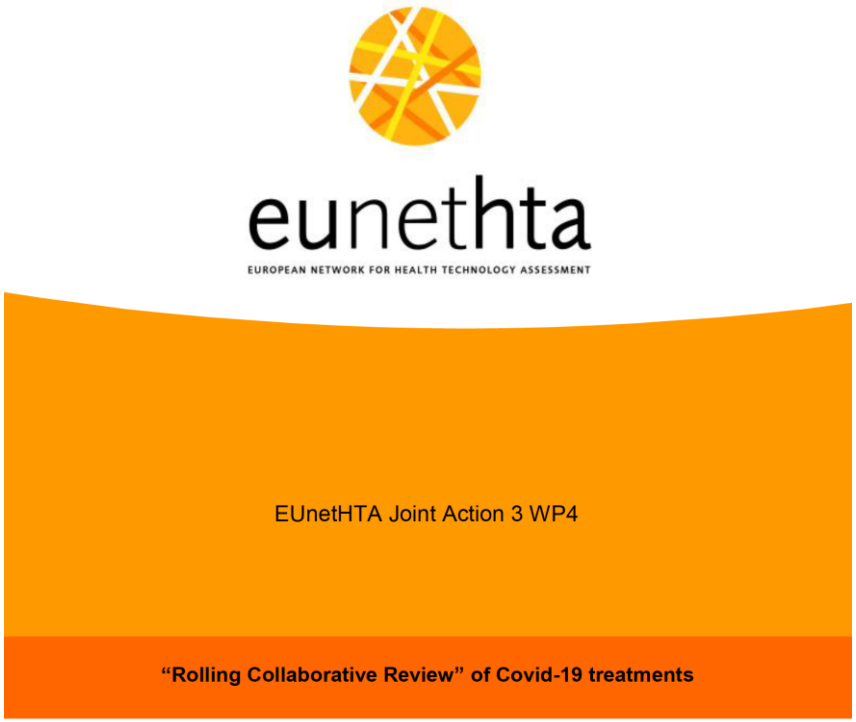
Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review (Review)

Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N

AUTHORS' CONCLUSIONS

Implications for practice

The currently available evidence on the safety and effectiveness of convalescent plasma and hyperimmune immunoglobulin for treatment of people hospitalised with COVID-19 is of very low certainty.



4.4 Scientific conclusion about status of evidence generation

Currently the evidence for CPT for COVID-19 is in the early stages and it is difficult to draw reliable conclusions from it. Proxy measures such as viral conversion rates are promising but as yet there is no high quality evidence of effectiveness for clinical outcomes. With the large number of RCTs which are expected to report in 2020 or early 2021 good quality evidence is expected to be available in the near future.

JAMA Clinical Guidelines Synopsis

Management of Critically Ill Adults With COVID-19

Poston JT, Patel B, Davis A. JAMA 2020; 323 (18)

Therapy

1. In adults receiving mechanical ventilation who do not have ARDS, routine use of systematic corticosteroids is suggested against (weak recommendation, LQE). In those with ARDS, use of corticosteroids is suggested (weak recommendation, LQE).
2. In COVID-19 patients receiving mechanical ventilation who have respiratory failure, use of empiric antimicrobial/antibacterial agents is suggested (no evidence rating); assess for deescalation.
3. In critically ill adults with fever, use of pharmacologic agents for temperature control is suggested over nonpharmacologic agents or no treatment. Routine use of standard IV immunoglobulins is not suggested. Convalescent plasma is not suggested. There is insufficient evidence to issue a recommendation on use of any of the following: antiviral agents, recombinant interferons, chloroquine/hydroxychloroquine, or tocilizumab.

REVIEW ARTICLE

DOI: 10.1111/vox.12926

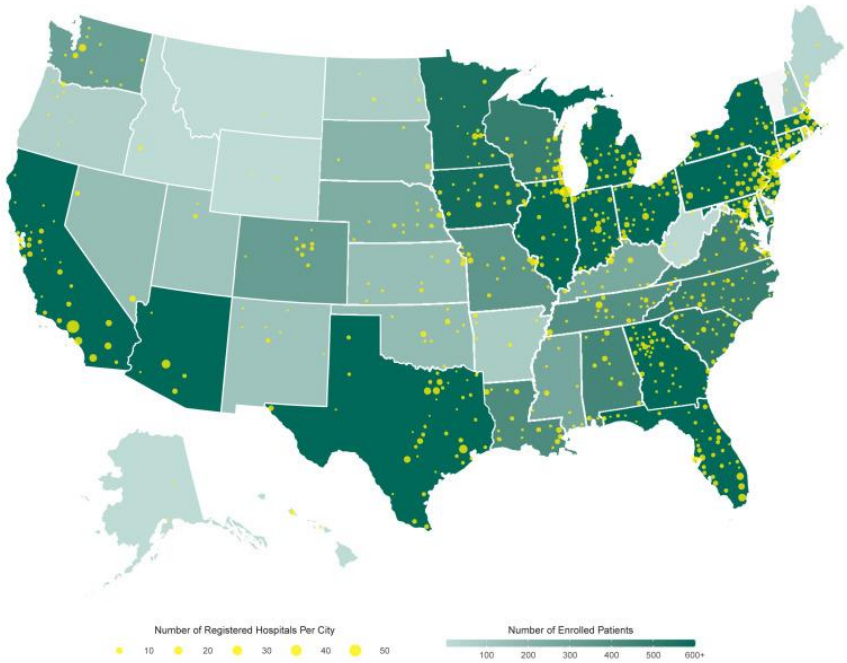
Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how?

Tiberghien P, de Lamballerie X, Morel P et al. Vox Sanguinis 2020; 115: 488-494

Una acurada avaluació clínica ha de permetre establir ràpidament si el plasma convalescent, **administrat en fases inicials de la malaltia a pacients amb alt risc d'evolucionar malament**, pot reduir el deteriorament del pacient i, per tant, la mortalitat

Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience

Joyner M, Senefeld J, Klassen S. et al. https://doi.org/10.1101/2020.08.12.20169359



35.322 pacients transfosos amb plasma convalescent

Conclusions and Relevance The relationships between reduced mortality and both earlier time to transfusion and higher antibody levels provide signatures of efficacy for convalescent plasma in the treatment of hospitalized COVID-19 patients. This information may be informative for the treatment of COVID-19 and design of randomized clinical trials involving convalescent plasma.

Plasma Convalescent COVID-19
ultimes dades

Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)

Agarwal A, Mukherjee A, Kumar G et al. BMJ 2020; 371; m3939

EDITORIALS

Convalescent plasma is ineffective for covid-19

Lessons from the Placid Trial

PLACID trial

Conclusion

Although the use of convalescent plasma seemed to improve resolution of shortness of breath and fatigue in patients with moderate covid-19 and led to higher negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment, this did not translate into a reduction in 28 day mortality or progression to severe disease. Areas of future research could include effectiveness of convalescent plasma among neutralising antibody negative patients and the use of convalescent plasma with high neutralising antibody titres. The challenge will be to find both suitable patients and suitable plasma donors. Additionally, this challenge could limit the use of convalescent plasma to a small subset of patients.

- No titulació d'anticossos neutralitzants
- No s'especifica el moment de l'administració del plasma convalescent

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

Simonovich V A, Burgos Pratx L D, Scibona P et al. NEJM 2020, November 24

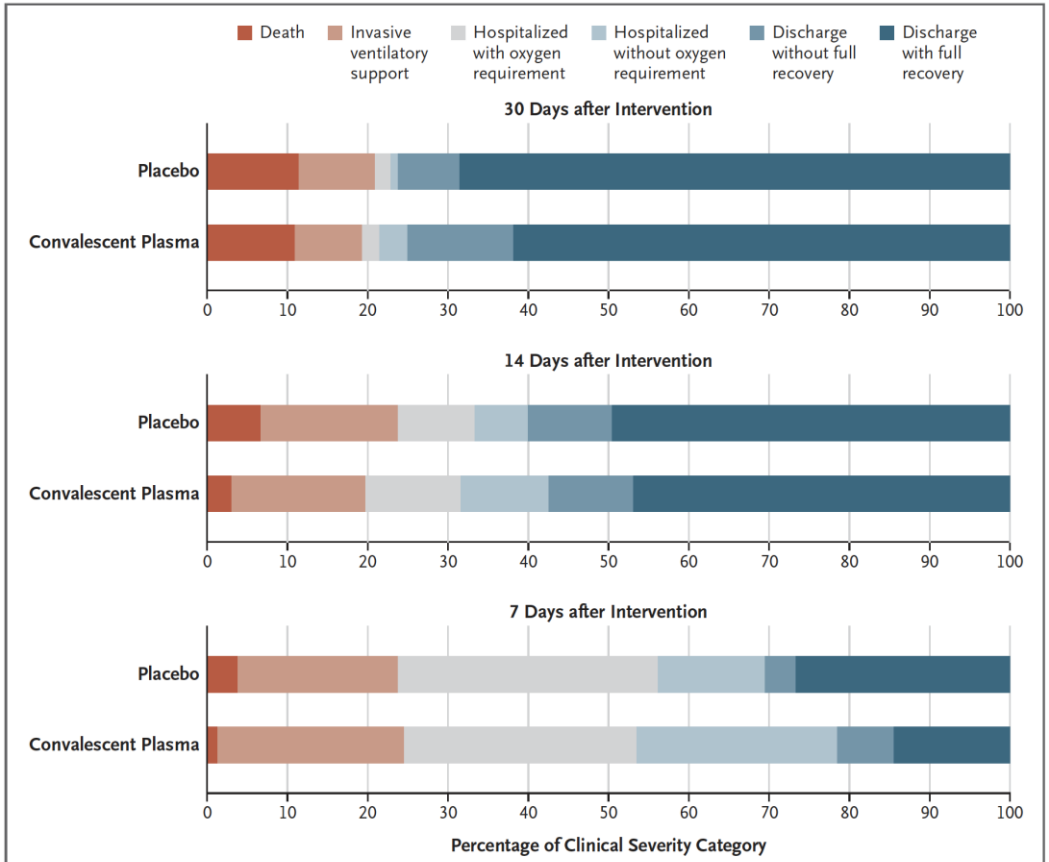


Figure 2. Clinical Outcomes among Patients Treated with Convalescent Plasma as Compared with Placebo.
The distribution of the clinical status according to the ordinal scale is shown at 30 days, 14 days, and 7 days after the intervention.

Plasma Convalescent COVID-19
ultimes dades

JAMA | Original Investigation

Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19
A Systematic Review and Meta-analysis

Janiaud P, Axfords C, Schmitt A et al. JAMA 2021; 325(12): 1185-1195

CONCLUSIONS AND RELEVANCE Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

STUDY SELECTION The RCTs selected compared any type of convalescent plasma vs placebo or standard of care for patients with confirmed or suspected COVID-19 in any treatment setting.

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

Libster R, Pérez Marc G, Wappner D et al. NEJM 2021, January 6

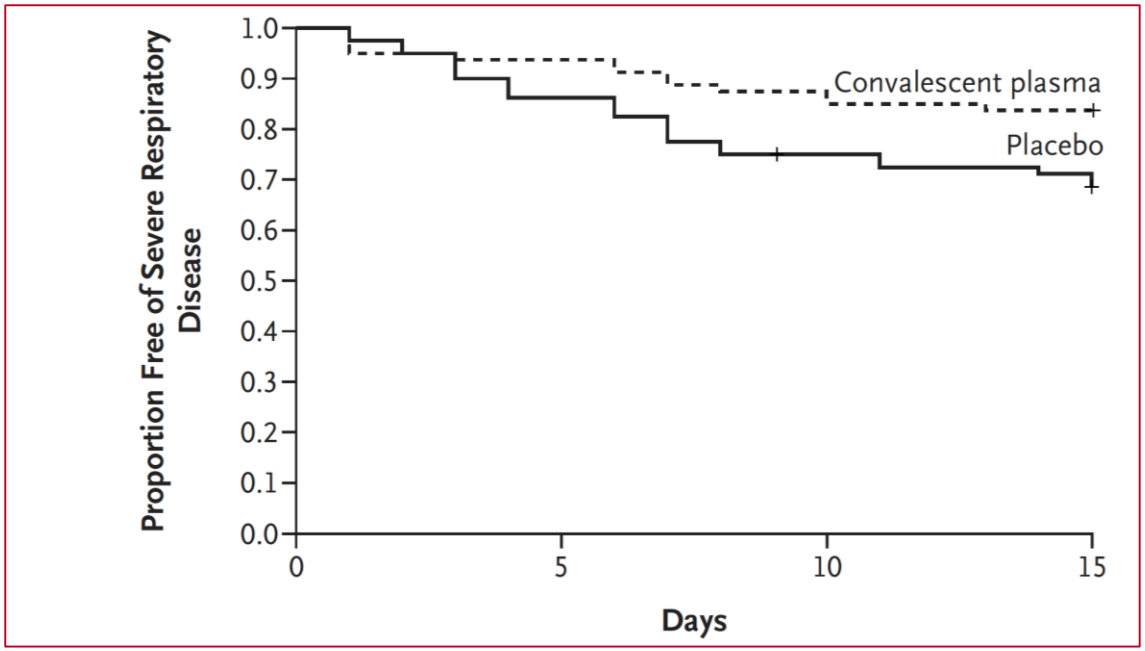


Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

Patient Group	Patients with Severe Respiratory Disease	Relative Risk (95% CI)	Relative Risk Reduction
	no./total no. (%)		*percent*
Placebo group	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08–0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34–1.31)	31.4

FUNDACIÓ **LLUITA** CONTRA LA SIDA
I LES MALALTIES INFECCIOSES

Convalescent Methylene Blue Treated (MBT) Plasma for Early Treatment in Non-hospitalised Individuals with SARS-CoV-2 Infection: a Randomized Double Blind Study (COnV-ert)

Version 1.0, 9th September 2020

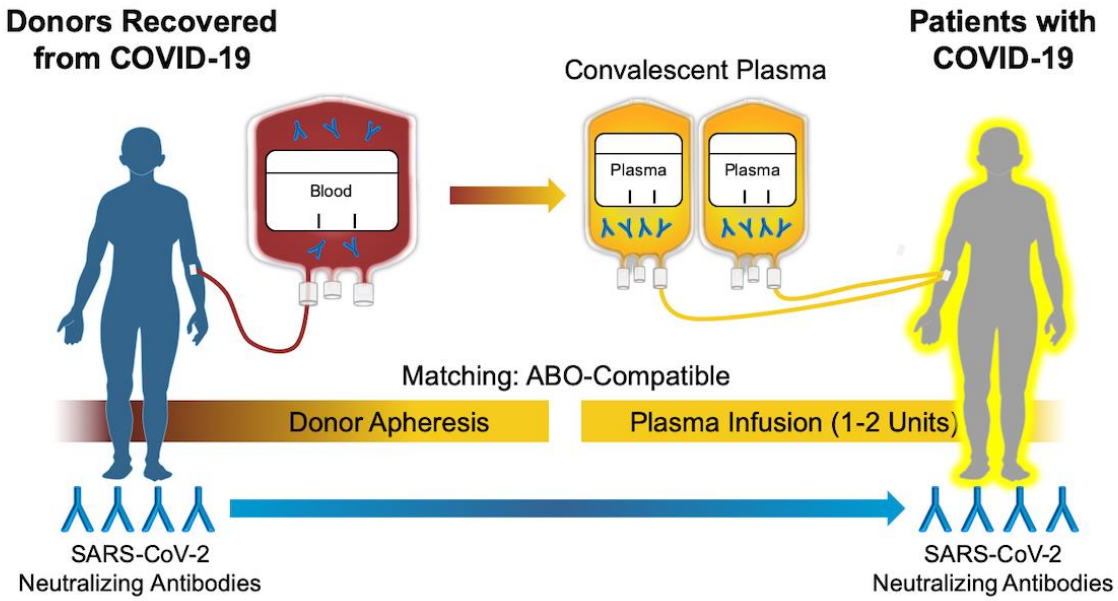
Sponsor:

Fundació FLS de Lluita contra la Sida, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
Hospital Universitari Germans Trias i Pujol
Carretera de Canyet s/n
08916 Badalona (Barcelona)

Principal Investigator:

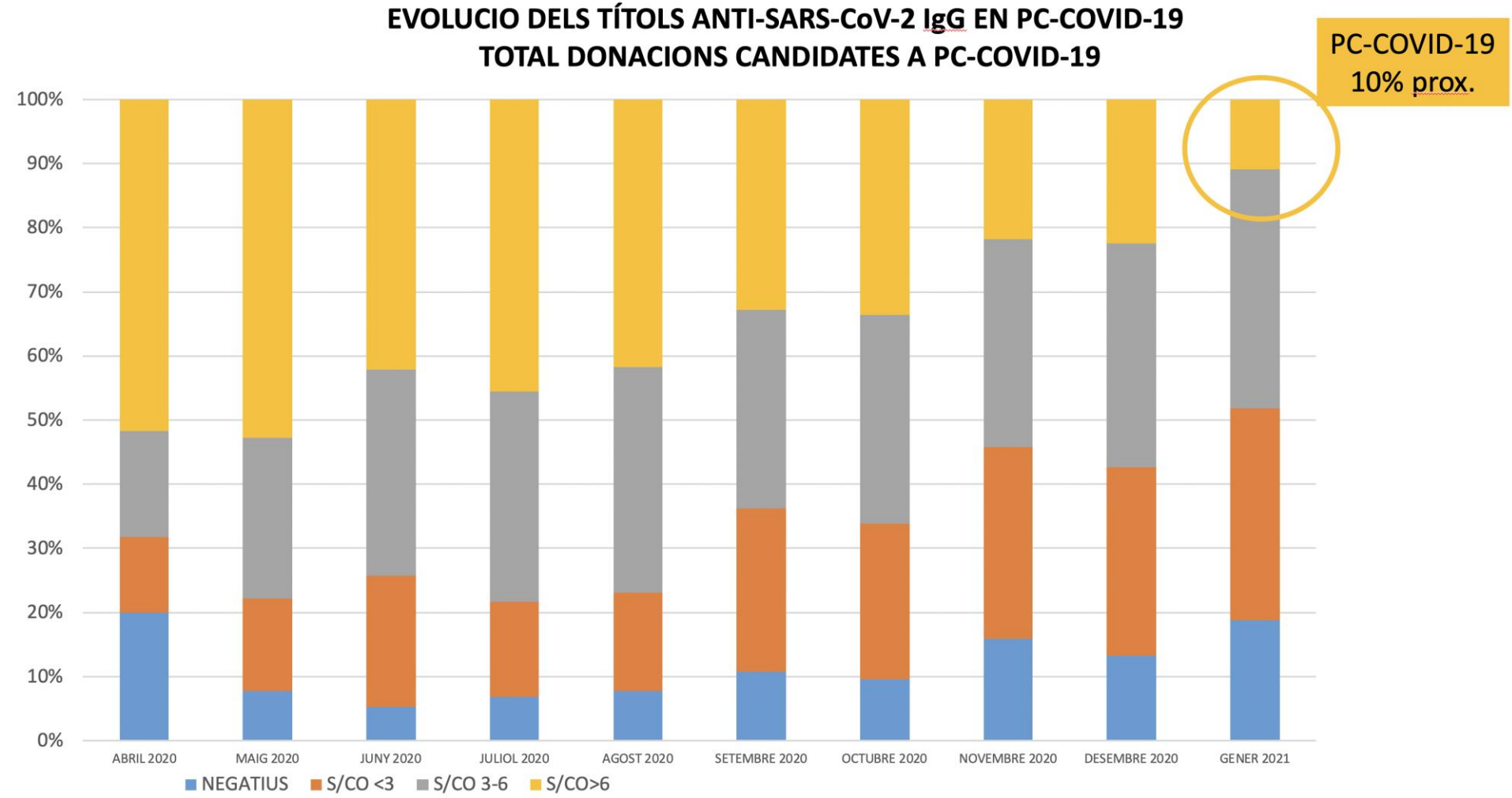
Oriol Mitjà, MD, PhD
Hospital Universitari Germans Trias i Pujol

ESTUDIO OBSERVACIONAL SOBRE EL IMPACTO CLÍNICO (SEGURIDAD/EFICACIA) DE LA TRANSFUSIÓN DE PLASMA CONVALECIENTE EN PACIENTES COVID-19 DE LA RED HOSPITALARIA DE CATALUÑA



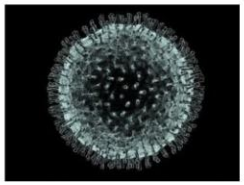
Tractament de la COVID19 amb plasma convalescent

- Administració precoç
- Títols alts d'anticossos
- Adults grans
- Patologia de base



Cedida per Silvia Sauleda

SARS-CoV-2 anti-Spike anticossos neutralitzants



DONANTS PC-COVID-19
Títols alts (S/Co>6) N=151

★★★

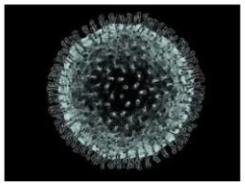
5.191 ± 4.878 UA/mL

(706-31.740)

PREVENCIÓ DE RISCOS-BST
N=121

17.748 ± 12.104 UA/mL

(1748 – 59.051)



+

DONANTS PC-COVID-19 Vacunats
Pfizer/AstraZeneca N=56

34.135 ± 23.511 UA/mL

(5.463 - >80.000)

3,4x

7x

Cedida per Silvia Sauleda

An EU programme of COVID-19 convalescent plasma collection and transfusion

Recipients of COVID-19 vaccines who have never been infected with COVID-19 do not meet the definition of 'convalescent' plasma donors. Given the increasing number of approved vaccines and the existence of virus variants that can escape neutralization, it is preferable to ensure that CCP collected from donors contains antibodies directly related to their immune response to infection with the SARS-CoV-2 virus that is prevalent in the local population. However, vaccinated individuals may donate standard plasma. If that plasma is shown to contain high titre neutralizing SARS-CoV-2 antibodies, blood establishments may consider redesignating it for clinical use as an equivalent to CCP.

Eligible CCP donors who received a COVID-19 vaccine after recovery from disease may donate CCP. Possible administration of COVID-19 vaccines for the purpose of boosting immunity of convalescent plasma donors should be investigated in clinical trials. This guidance related to vaccination is in line with the current approach in the United States[4].

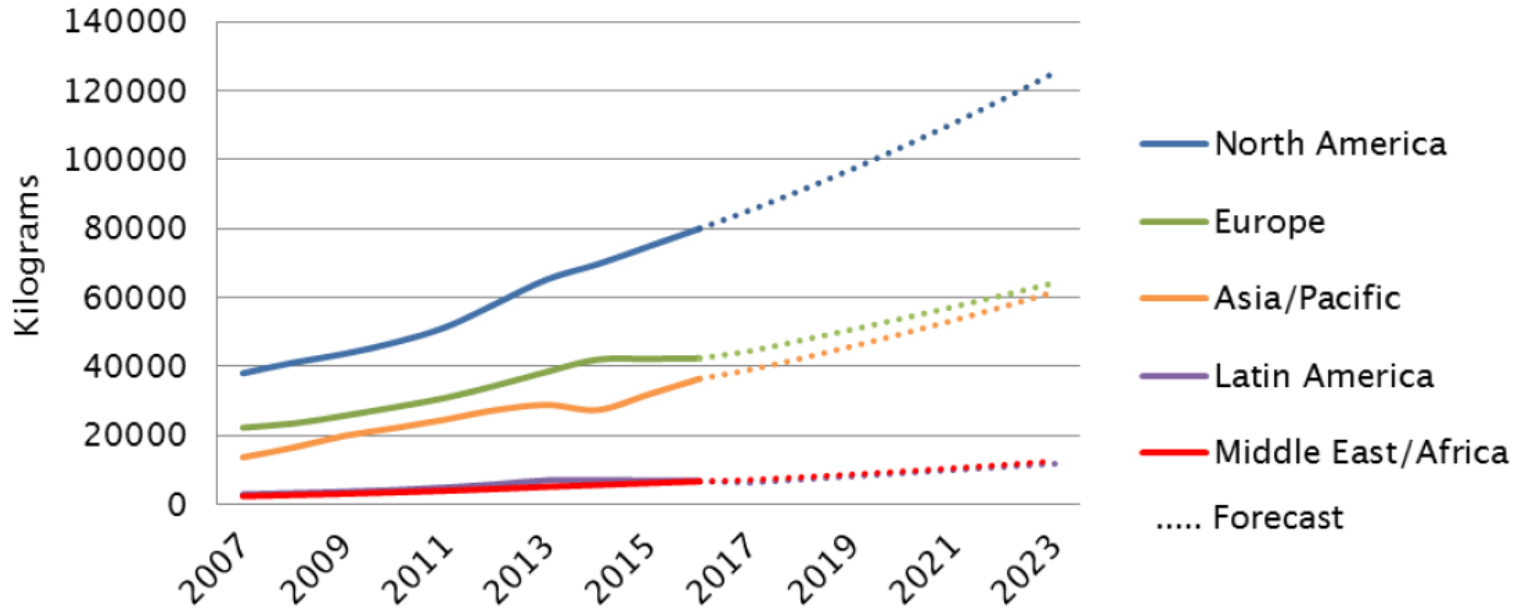
Plasma vacunal com alternativa al plasma convalescent en el tractament de la COVID-19. Caracterització del component i estudi observacional

Pendent autorització CEIM H. Clínic

Plasma Convalescent COVID-19
contribució a l'autosuficiència d'hemoderivats

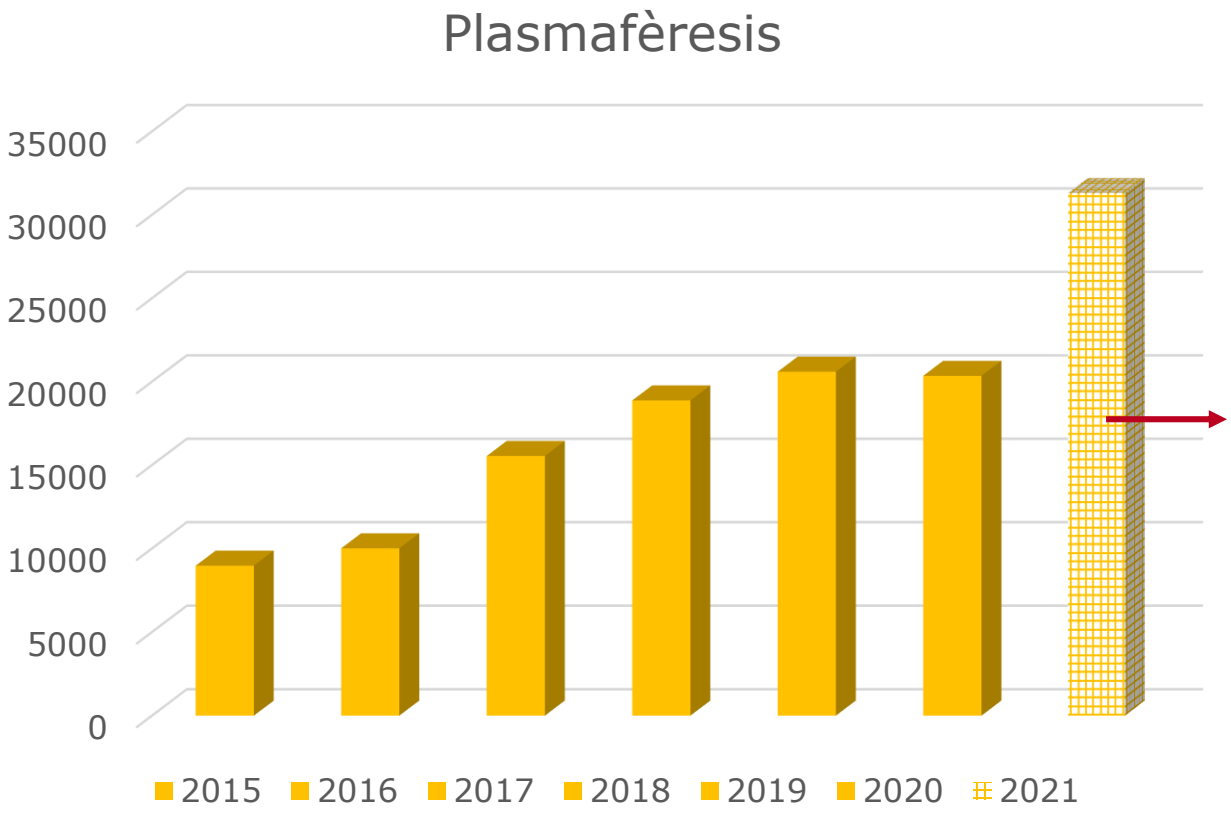
les donacions voluntàries a Catalunya permeten cobrir menys del 50% de les necessitats d'Igs

Figure 2.3: Global IG Demand – Actual and Projected



Data from MRB (2015) Forecast of the Global Immunoglobulin Market (2014–2023).

Plasma Convalescent COVID-19
contribució a l'autosuficiència d'hemoderivats

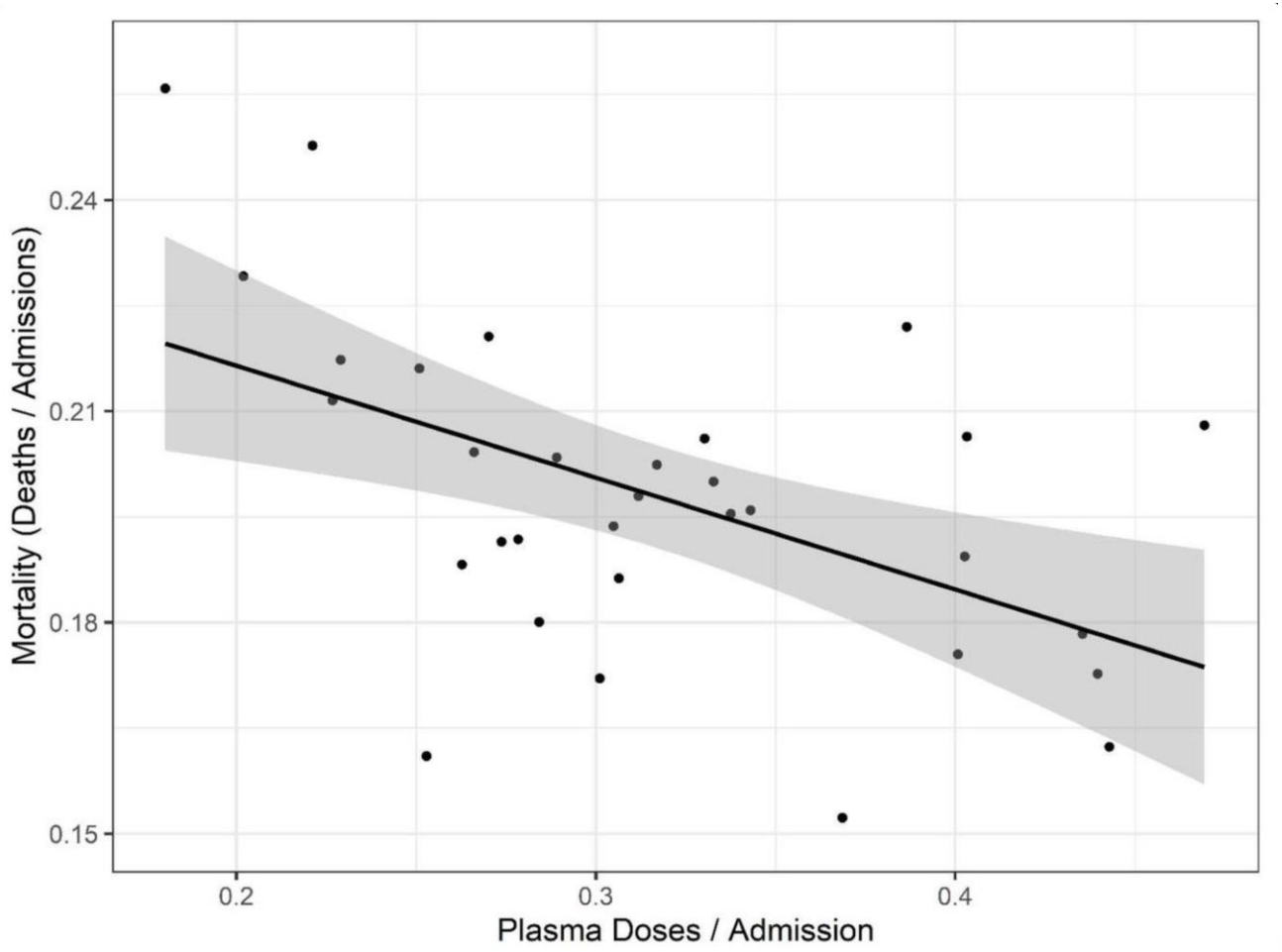


Més del 25% de les plasmafèresis corresponen a plasma convalescent

Convalescent Plasma Use in the United States was inversely correlated with COVID-19 Mortality:

Did Convalescent Plasma Hesitancy cost lives?

Casadevall A, Dragotakes Q, Johnson PV et al. https://doi.org/10.1101/2021.04.07.21255089



en resum ...

- L'evidència científica disponible **no recolza** l'ús generalitzat del plasma convalescent pel tractament de la COVID-19

- Sembla que l'administració de plasma convalescent a pacients adults amb símptomes lleus o moderats pot prevenir una COVID severa sempre i quan s'administri de forma **precoç** i el plasma contingui **títols alts d'anticossos**

- El plasma procedent de pacients que s'han recuperat de la COVID-19 i han estat vacunats (**plasma vacunal**) conté uns títols molt alts d'anticossos neutralitzants i pot ser una alternativa al plasma convalescent.

- A curt termini es disposarà de resultats d'assaigs clínics i estudis observacionals que aportaran **més evidència científica** en relació al plasma convalescent i al vacunal.

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