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Medical Faculty Carl Gustav Carus, TU-Dresden
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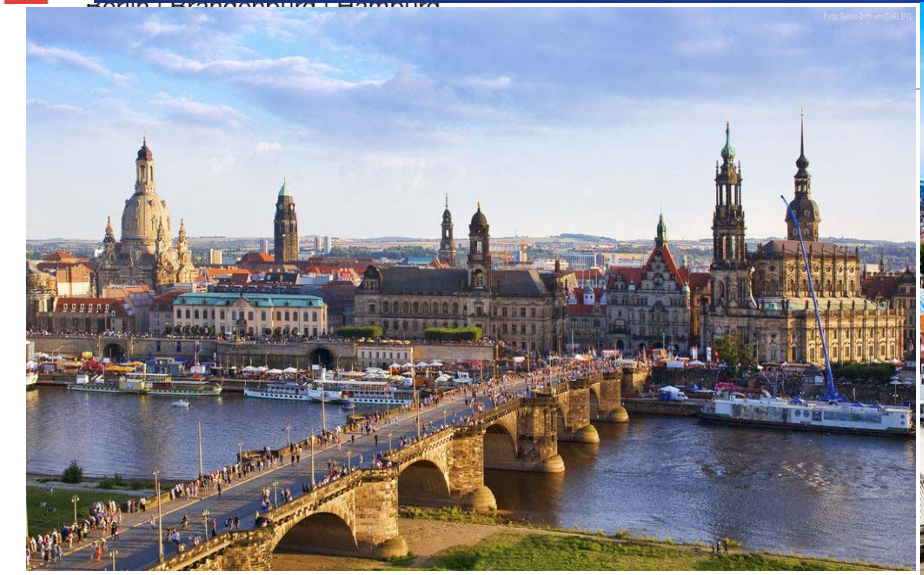

Covid-19 Convalescent plasma

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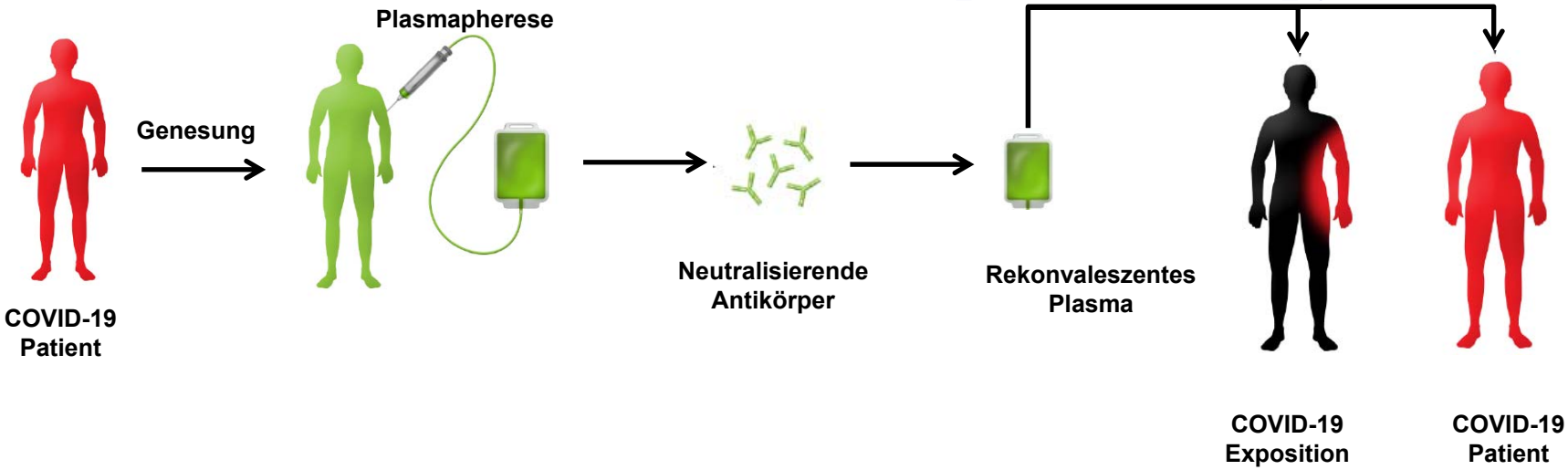
Rationale for convalescent plasma therapy



- **Immune reaction in ill patient**
- **Induction of neutralizing antibodies**
- **Collection of convalescent plasma containing neutralizing antibodies**
- **Transfusion into patients with acute disease or as prophylaxis to people at risk**

Mod. aus Casadevall and Pirovski 2020

Rationale I

Why convalescent plasma for COVID-19?

Neutralizing humoral immune response after infection with SARS-CoV, MERS-CoV and SARS-CoV-2:

- Rapid and sustained humoral immune response after infection with SARS-CoV and MERS-CoV (abundance of data, see example next slides)
- Now first data available confirming this also for immune reaction against SARS-CoV-2
- **Neutralizing capacity of these antibodies (shown for SARS-CoV- and SARS-CoV-2 antibodies)**

Experience on use of Convalescent Plasma in SARS and MERS:

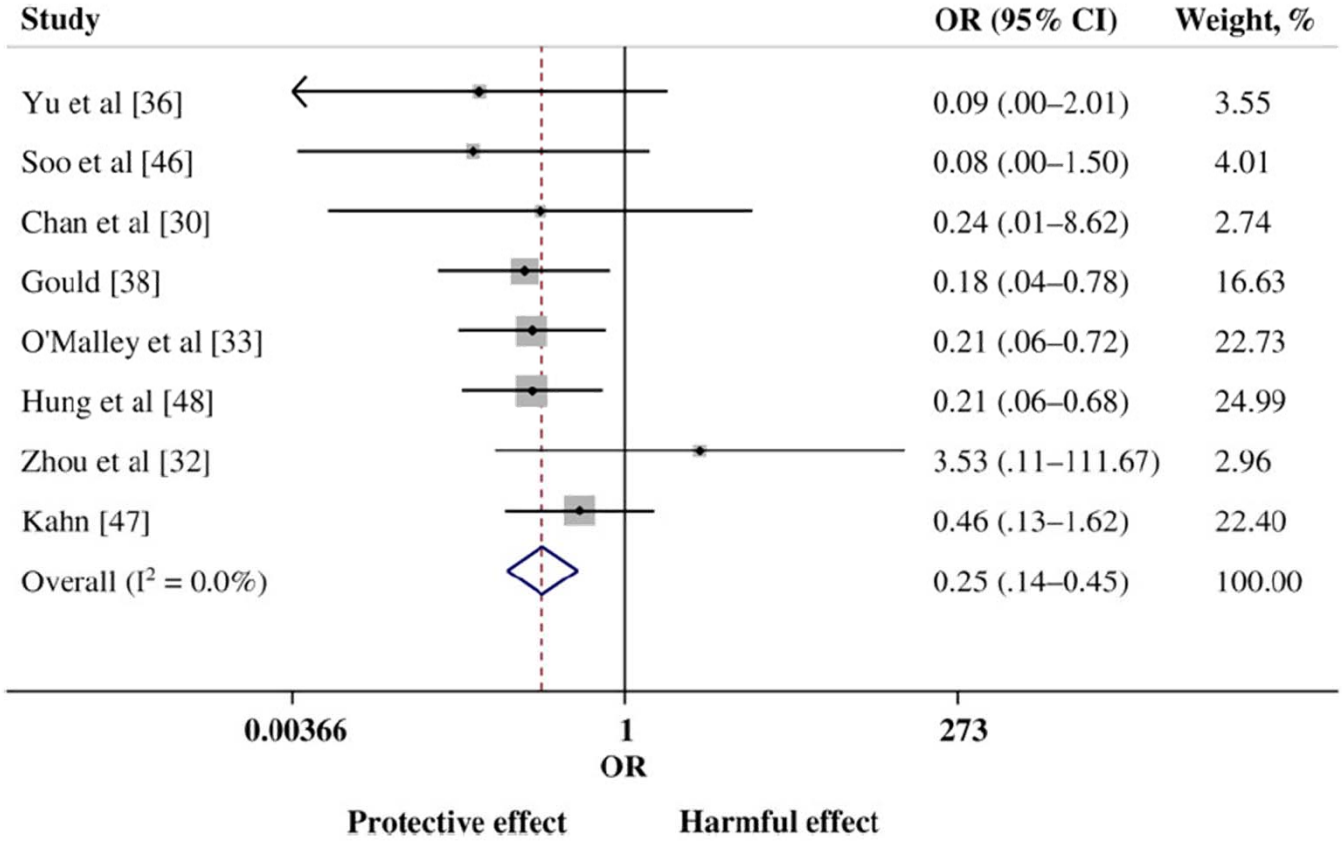
- CP: safe and feasible
- Efficacy: advantages have been reported regarding survival, length of ventilation, length of stay on ICU or in hospital

(see meta-analysis Mair-Jenkins et al. 2015, next slide)

BUT: no randomized control – retrospective analyses

Metanalysis for convalescent plasma for treatment of acute viral respiratory infections (H1N1, H5N1, SARS)

27 Studies included in the review, <u>none of the study was placebo –controlled</u>!



Mair-Jenkins et al J Infect Dis 2015:211:80-90

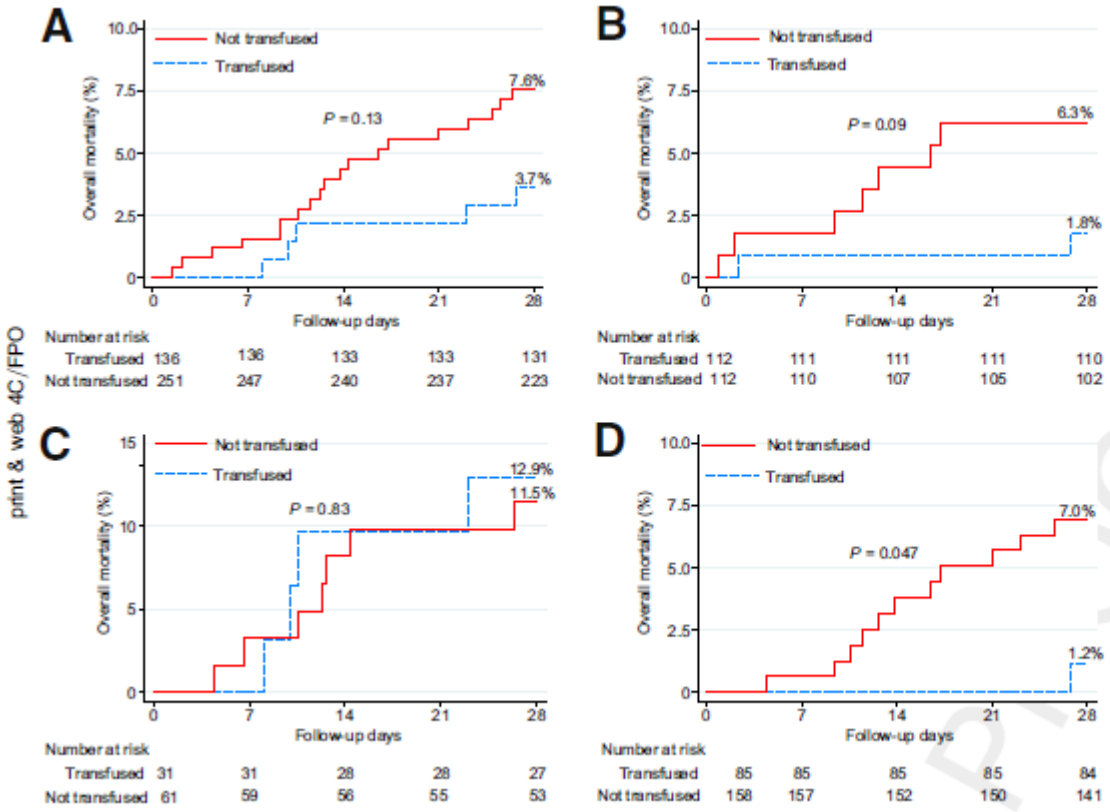
Mortality rate decreases from 7.0% to 1.2% in COVID-19 patients transfused with CCP containing high titer neutralising antibody capacity within 72hrs of hospital admission

The American Journal of Pathology, Vol. ■, No. ■, ■ 2020

ELSEVIER

The American Journal of PATHOLOGY

ajp.amjpathol.org



Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality

Eric Salazar,*† Paul A. Christensen,* Edward A. Graviss,*‡ Duc T. Nguyen,‡ Brian Castillo,* Jian Chen,* Bevin V. Lopez,§ Todd N. Eagar,*† Xin Yi,*† Picheng Zhao,* John Rogers,* Ahmed Shehabeldin,* David Joseph,* Christopher Leveque,* Randall J. Olsen,*†‡ David W. Bernard,*† Jimmy Gollihar,¶ and James M. Musser*†‡

Figure 2 Kaplan-Meier curves for mortality within 28 days post-day 0 for secondary matched cohorts. **A:** All secondary matched patients. **B:** Secondary matched patients transfused within 72 hours of admission. **C:** Secondary matched patients transfused >72 hours after admission. **D:** Secondary matched patients transfused within 72 hours of admission with plasma with anti–receptor binding domain IgG titer ≥1:1350.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem,

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

* The median concentration is a SARS-CoV-2 S IgG titer of 1:3200.

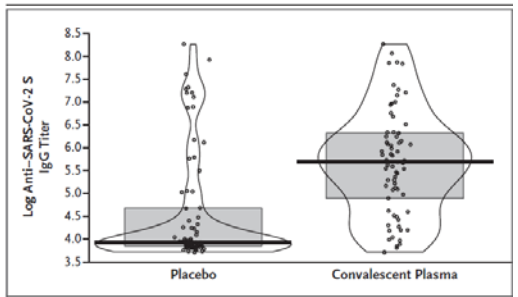


Figure 2. SARS-CoV-2 Serum Titers, According to Trial Group.
Shown are IgG antibody titers against SARS-CoV-2 spike (S) protein in the convalescent plasma and placebo groups 24 hours after infusion. The horizontal bars indicate medians, and the shaded gray areas interquartile ranges. Each circle represents one patient.

This article was published on January 6, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2033700

blood® Brief Report

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CLINICAL TRIALS AND OBSERVATIONS

Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19

Thomas Hueso,[1,2] Cécile Pouderoux,[3] Hélène Péré,[4,5] Anne-Lise Beaumont,[6] Laure-Anne Raillon,[3] Florence Ader,[3,7] Lucienne Chatenoud,[8,9]

KEY POINTS

- As a proof of concept, COVID-19 convalescent plasma represents an interesting approach in B-cell–depleted patients with protracted COVID-19.
- COVID-19 convalescent plasma induces a decrease in temperature and inflammatory parameters within 1 week associated with oxygen weaning.

Anti-CD20 monoclonal antibodies are widely used for the treatment of hematological malignancies or autoimmune disease but may be responsible for a secondary humoral deficiency. In the context of COVID-19 infection, this may prevent the elicitation of a specific SARS-CoV-2 antibody response. We report a series of 17 consecutive patients with profound B-cell lymphopenia and prolonged COVID-19 symptoms, negative immunoglobulin G (IgG)-IgM SARS-CoV-2 serology, and positive RNAemia measured by digital polymerase chain reaction who were treated with 4 units of COVID-19 convalescent plasma. Within 48 hours of transfusion, all but 1 patient experienced an improvement of clinical symptoms. The inflammatory syndrome abated within a week. Only 1 patient who needed mechanical ventilation for severe COVID-19 disease died of bacterial pneumonia. SARS-CoV-2 RNAemia decreased to below the sensitivity threshold in all 9 evaluated patients. In 3 patients, virus-specific T-cell responses were analyzed using T-cell enzyme-linked immunospot assay before convalescent plasma transfusion. All showed a maintained SARS-CoV-2 T-cell response and poor cross-response to other coronaviruses. No adverse event was reported. Convalescent plasma with anti–SARS-CoV-2 antibodies appears to be a very promising approach in the context of protracted COVID-19 symptoms in patients unable to mount a specific humoral response to SARS-CoV-2. (*Blood*. 2020;136(20):2290-2295)

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Running title: Convalescent plasma for COVID-19

The RECOVERY Collaborative Group*

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the Appendix.

09. März 2021 Prepub RECOVERY TRIAL

630 **Table 2: Primary, Secondary and Subsidiary Outcomes**

	Convalescent plasma (n=5795)	Usual Care (n=5763)	RR (95% CI)	p value
Primary outcome				
Mortality at 28 days	1398 (24%)	1408 (24%)	1.00 (0.93-1.07)	0.93
Secondary outcomes				
Median duration of hosp				
Discharged from hospita				
Invasive mechanical ver				
Invasive mechanica				
Death				
Subsidiary outcomes				
Use of ventilation †	860/3564 (24%)	863/3441 (25%)	0.96 (0.89-1.04)	0.36
Non-invasive ventilation	822/3564 (23%)	821/3441 (24%)	0.97 (0.89-1.05)	0.43
Invasive mechanical ventilation	226/3564 (6%)	237/3441 (7%)	0.92 (0.77-1.10)	0.36
Successful cessation of invasive mechanical ventilation ‡	87/302 (29%)	112/315 (36%)	0.77 (0.59-1.03)	0.07
Renal replacement therapy §	258/5729 (5%)	249/5713 (4%)	1.03 (0.87-1.22)	0.71

No benefit for convalescent plasma with regard to primary and secondary endpoints. Also not in Subgroups

Data are n (%) or n/N (%). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes.
* Analyses exclude those on invasive mechanical ventilation at randomisation.
† Analyses exclude those on invasive or non-invasive ventilation at randomisation.
‡ Analyses exclude those not receiving invasive mechanical ventilation at randomisation.
§ Analyses exclude those on renal replacement therapy at randomisation.

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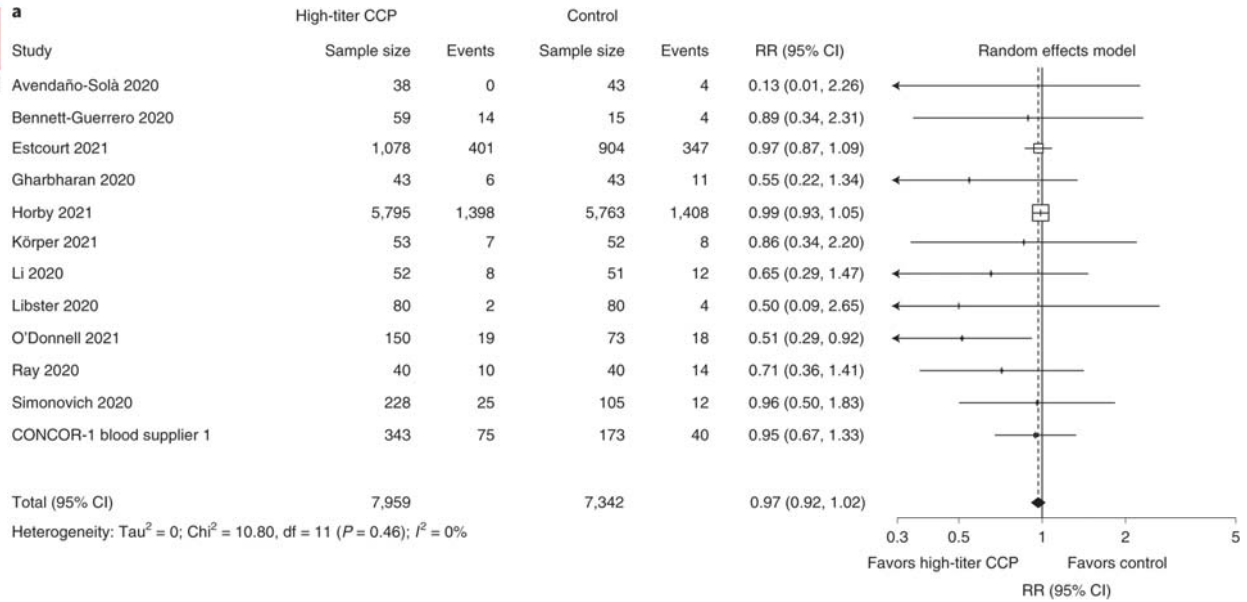
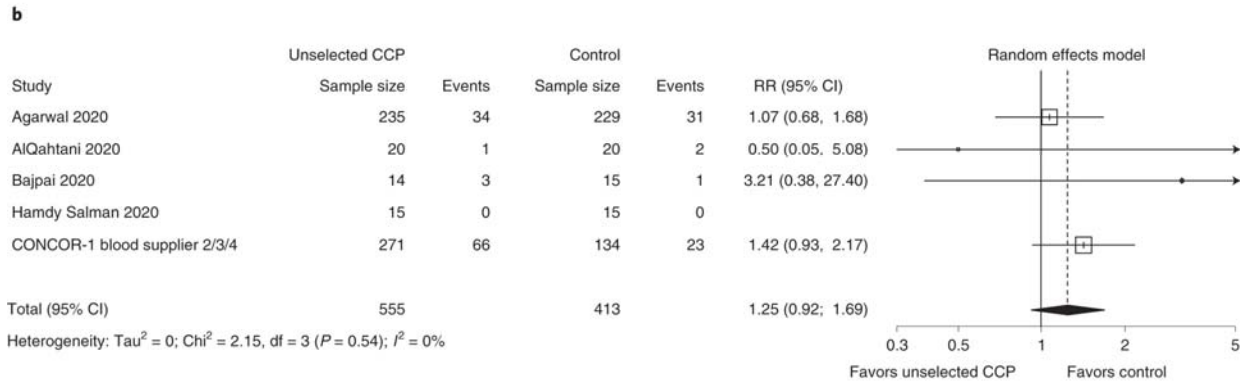
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01488-2
Check for updates

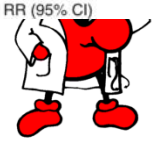
OPEN

Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial

Philippe Bégin[1,2,87], Jeannie Callum[3,4,5,6,87], Erin Jamula[7], Richard Cook[8], Nancy M. Heddle[6,7,9], Alan Tinmouth[6,10,11], Michelle P. Zeller[6,7,9], Guillaume Beaudoin-Bussières[12,13], Luiz Amorim[14], Renée Bazin[15], Kent Cadogan Loftsgard[16], Richard Carl[17], Michaël Chassé[2,18], Melissa M. Cushing[19,20], Nick Daneman[21], Dana V. Devine[22,23], Jeannot Dumaresq[24,25], Dean A. Fergusson[6,10,26], Caroline Gabe[7], Marshall J. Glesby[27], Na Li[7,28,29], Yang Liu[7], Allison McGeer[30,31], Nancy Robitaille[32,33,34], Bruce S. Sachais[20,35], Damon C. Scales[36,37], Lisa Schwartz[38], Nadine Shehata[6,39,40], Alexis F. Turgeon[41,42], Heidi Wood[43], Ryan Zarychanski[44], Andrés Finzi[12,13], the CONCOR-1 Study Group* and Donald M. Arnold[7,9,87]







Akronym:	**CAPSID**
EudraCT number:	**2020-001310-38**
Sponsor's ID:	**CAPSID2020-DRK-BSD**
Sponsor:	**DRK Blutspendedienst Baden-Württemberg-Hessen**
Lead Investigators:	**H.Schrezenmeier, E.Seifried**
Trial Coordinator:	**S.Körper**

- A **randomized, prospective, multicenter, open label clinical trial** of convalescent plasma compared to best supportive care for treatment of patients with severe COVID-19.
- Patients who are randomized to best supportive care and with progressive disease at evaluation on day 14 are allowed to change to **cross over arm** to convalescent plasma treatment.
- Sample Size: **53 patients per treatment group (total n=106)** dropout rate of 10%.
- Convalescent plasma dose: **3 treatments, each 250-325 ml** on day 1, 3 and 5.
- Study duration: **12 months**

CAPSID

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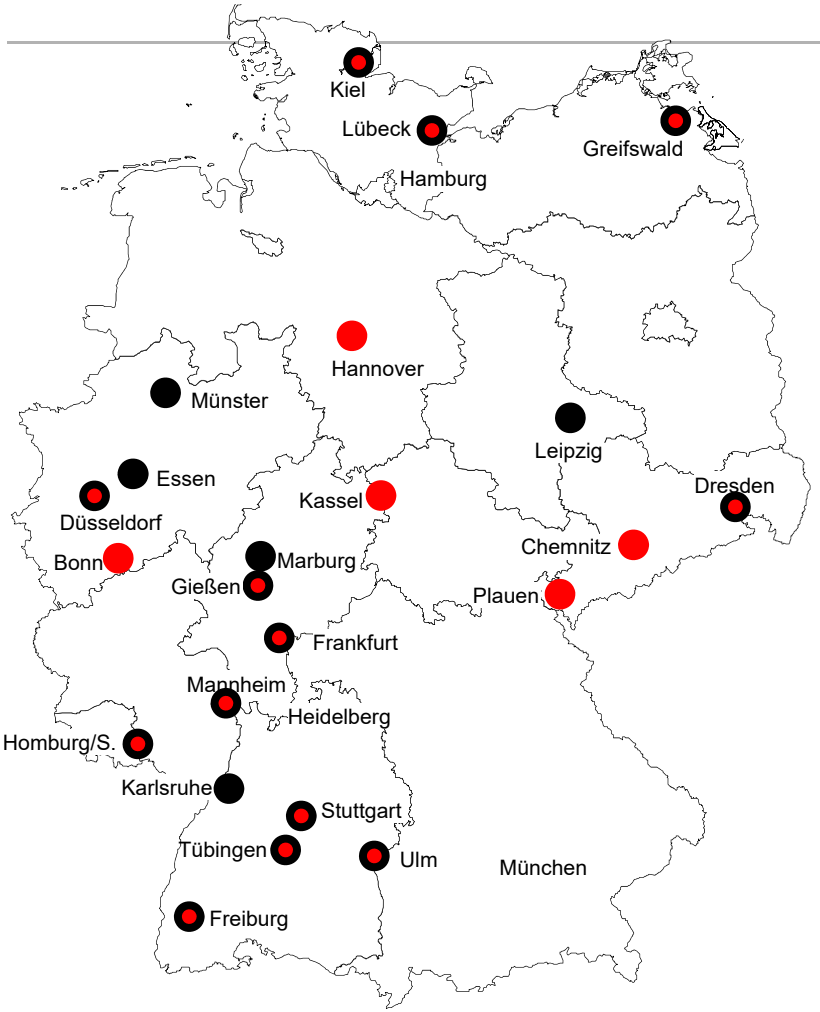


- Collection Center
- Clinical trial center
- Clinical trial and collection center

Status as of 21 January 2021

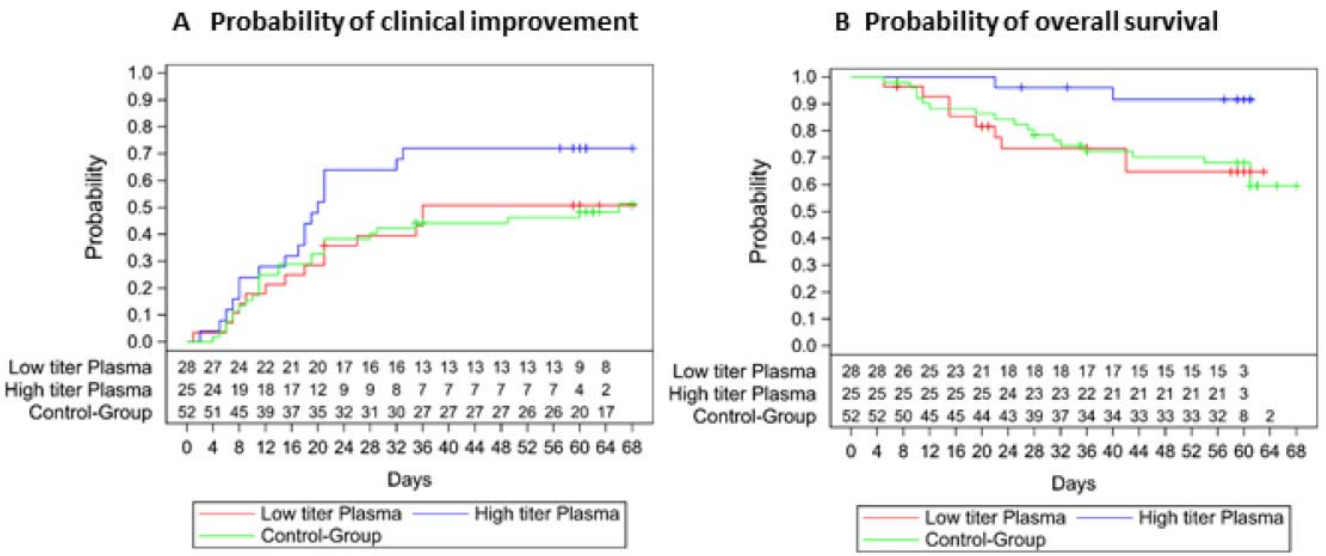
- Enrollment completed
- Results pending

JCI The Journal of Clinical Investigation

Results of the CAPSID randomized trial for high-dose convalescent plasma in severe COVID-19 patients

Sixten Körper, … , Erhard Seifried, Hubert Schrezenmeier

J Clin Invest. 2021. https://doi.org/10.1172/JCI152264.



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Convalescent plasma authorization status in Germany

In Germany blood components are classified as medicinal products according to the German Drug Act (AMG). Thus convalescent plasma will require a marketing authorization based on clinical evidence for safety and efficacy.

As CCP represents an unproven therapy, the German national competent authority “Paul-Ehrlich-Institute” encouraged the conduct of well-controlled clinical trials to rigorously evaluate the safety and efficacy of convalescent plasma.

In parallel, the German regional federal state authorities (the Länder) facilitated access to convalescent plasma for the treatment of COVID-19 disease through an emergency marketing authorization process in April allowing compassionate use.

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IND status granted to nationwide multicentre trial CAPSID by Paul-Ehrlich-Institute (PEI) on April 08.2020

A randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19 (CAPSID)

Eudra-CT 2020-001310-38

Sponsor: German Red Cross Blood Donation Service Baden-Württemberg-Hessen;
Prof. Dr. Hubert Schrezenmeier (Ulm), Prof. Dr. Erhard Seifried (Frankfurt/M)

Since not all expected COVID-19 patients in Germany could be recruited into the randomized CAPSID trial, there was the urgent request by hospitals to also make CCP available on basis of a compassionate use program

The Dresden COVID-19 convalescent plasma program - From donor to product

Universitätsklinikum Carl Gustav Carus
DIE DRESDNER.

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CCP donor pre- screening
CCP donor registry

- 4 weeks symptom free
- SARS-CoV-2 IgG >5
- No medication
- Informed consent
- Optional SARS-CoV-2 neutralizing antibody capacity (>1:320)

CCP donor eligibility

time point 0

- Questionnaire
- Informed consent
- SARS-CoV-2 PCR neg
- IDM negative
- SARS-CoV-2 IgG
- Anti HLA-/HNA in ♀and immunized ♂
- Optional SARS-CoV-2 Neutralizing antibody

CCP donation

+ 24h

- Questionnaire
- Informed consent
- SARS-CoV-2 PCR neg
- IDM negative
- SARS-CoV-2 IgG
- Anti HLA-/HNA in ♀and immunized ♂
- SARS-CoV-2 Neutralizing antibody
- 750 ml donation

CCP pathogen reduction

+ 48h

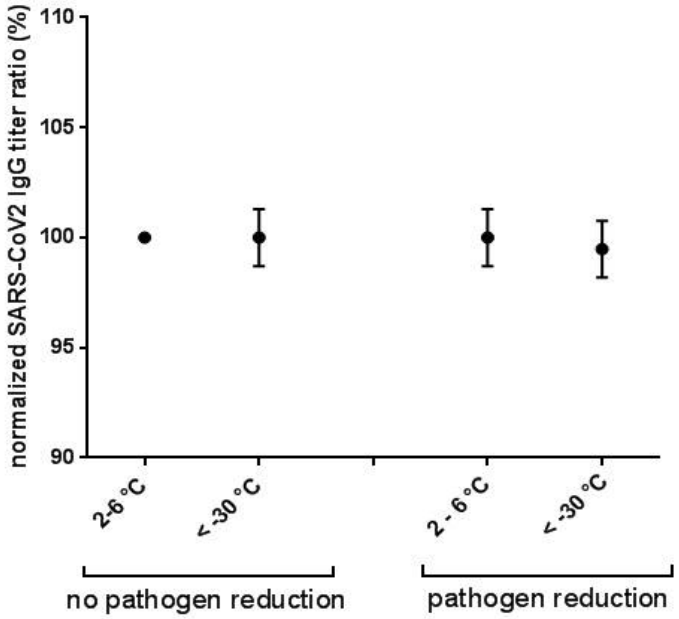
- 650 ml for pathogen inactivation
- 3 bags with ~210 ml
- Back up samples 3x 4ml pre- and post
- Shock freezing

CCP release

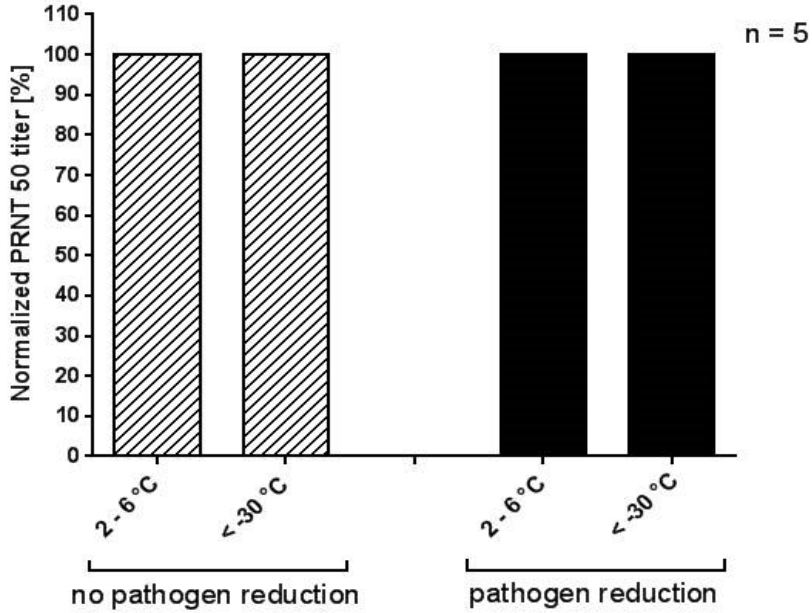
- Labeling after laboratory assessment and conformance with specification
- 3 bags for 1 patient
- Usage information states unproven benefit and informs about potential ADE
- Hemovigilance
- Monitoring of outcome

Pathogen reduction and or cryopreservation does not alter the content and neutralizing capazity of CCP

a)

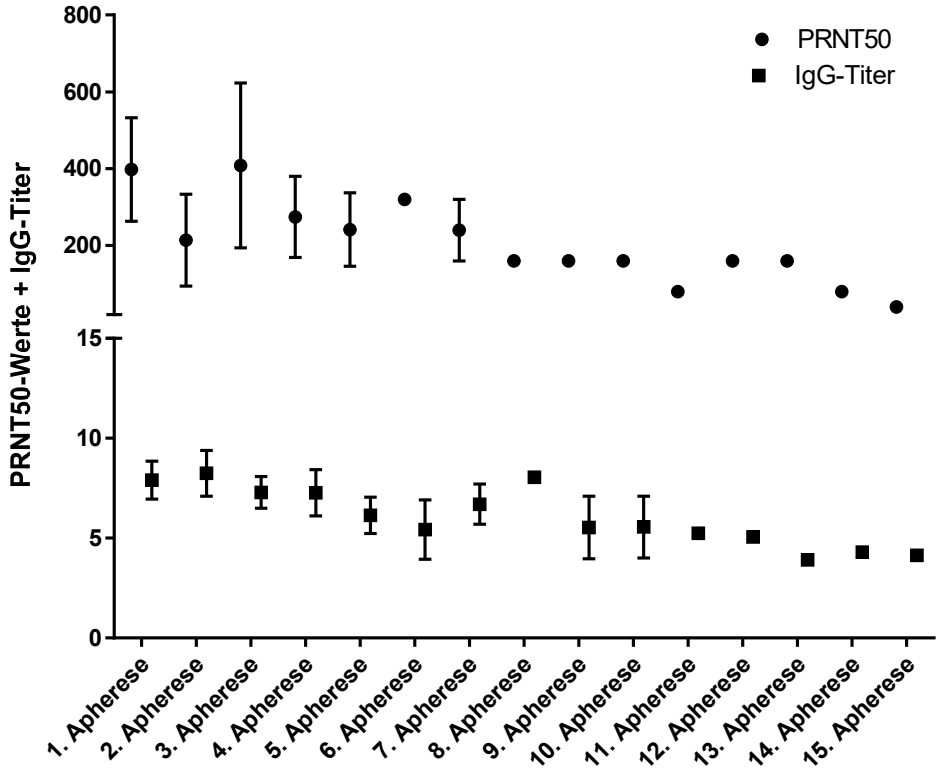


b)



Tonn T. et al. The Lancet Microbe; 2020

Plasmapheresis does not alter the donor´s SARS-CoV-2 IgG titre and neutralising antibody capacity



Potential benefit of convalescent plasma transfusions in immunocompromised patients with COVID-19

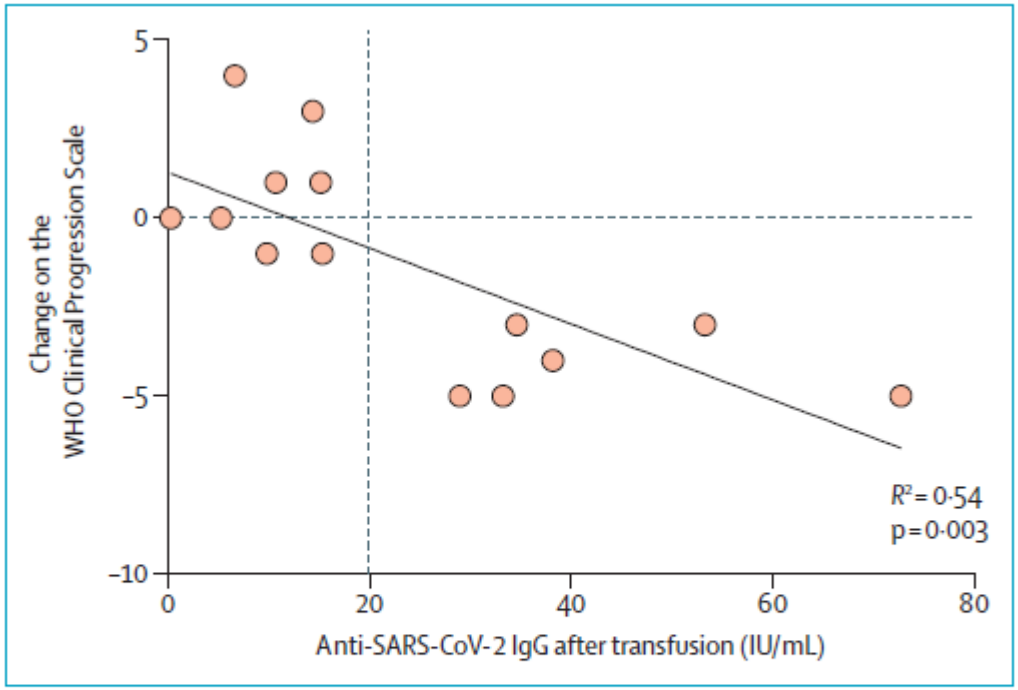


Figure: **Correlation between anti-SARS-CoV-2 IgG titres 24–48 h after the last transfusion and improvement in clinical status in patients with COVID-19 (n=14)**
Datapoints represent each patient. Clinical improvement was defined as an improvement of 1 point or more on the 10-point WHO Clinical Progression Scale for COVID-19 5 days after the last transfusion and the clinical status before transfusion.

Rodionov et al.
Lancet Microbe in press

Relationship between the ABO Blood Group and the COVID-19 Susceptibility

medRxiv preprint doi: https://doi.org/10.1101/2020.03.11.20031096
Jiao Zhao, et al.

The results showed that blood group A
was associated with a higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O was associated with a lower risk for the infection compared with non-O blood groups.

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Rationale for the use of Covid – 19 convalescent plasma as of march 2021

- Randomised clinical trials suggest a therapeutic benefit for high titre Covid-19 Covid-19 convalescent plasma when given early after infection.

- Immunocompromised patients with persistent Covid-19 infections may profit from high titer Covid-19 convalescent plasma. Randomised clinical trials are pending.

- University Hospital Dresden: Patients who are immunocomprised due to stem cell transplantation, cancer radio-/chemotherapy and who did not mount a SARS-CoV-2 IgG response have been treated with high titre Covid-19 convalescent plasma. 20 IE/ml Anti-SARS-CoV-2 IgG titres in the patients serum at day 5 post infusion are seen as therapeutic level.

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