Don par aphérèse, incluant la plasmathérapie contre le COVID-19

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Journée ARL, 12.10.21

TRANSFUSION INTERREGIONALE CRS
INTERREGIONALE BLUTSPENDE SRK

Plan de présentation

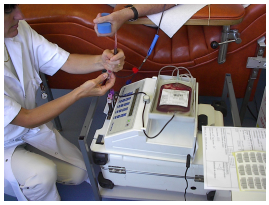
1ère partie – Don par aphérèse

- Différents types de produits sanguins labiles
- Spécificités du don de sang complet
- Spécificités du don par aphérèse (plasma, plaquettes)
- Qualification biologique des dons (QBD) et inactivation des pathogènes
- Indications transfusionnelles

2ème partie – Plasmathérapie contre la maladie COVID-19

- Introduction – qu'avons-nous appris jusqu'à présent?
- Quel bénéfice pour les patients immunosupprimés?
- Différents types de plasma enrichi en anticorps anti-SARS-CoV2
- Thérapie expérimentale sur une base individuelle – notre expérience chuvienne
- Conclusions et perspectives

Les différents types de produits sanguins labiles



Sang complet

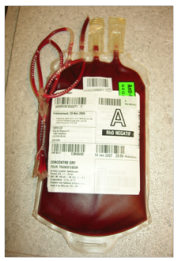
Don par aphérèse

Concentré érythrocytaire (CE)

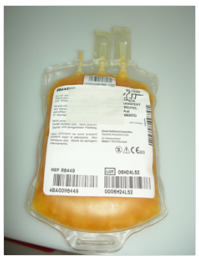
Plasma frais congelé (PFC)

Concentré plaquettaire (CP)

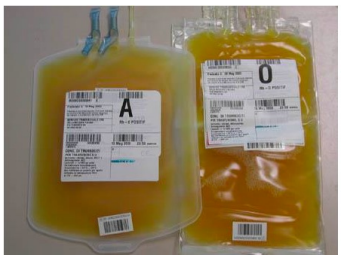
Les différents types de produits sanguins labiles



Concentré érythrocytaire (CE)
- Volume 275 +/- 75 ml
- Hct 60%, Hb 40 gr
- Conservation à 2-6°C pdt 42j



Plasma frais congelé (PFC) inactivé
- Volume 200 ml
- Conservation à -25°C pdt 24 mois



Concentré plaquettaire (CP) inactivé
- Volume 200-330 ml
- >2.4x10E11 plaquettes (5 UI)
- Conservation à 20-24°C pdt 5-7j sous agitation

Le don de sang total ou complet

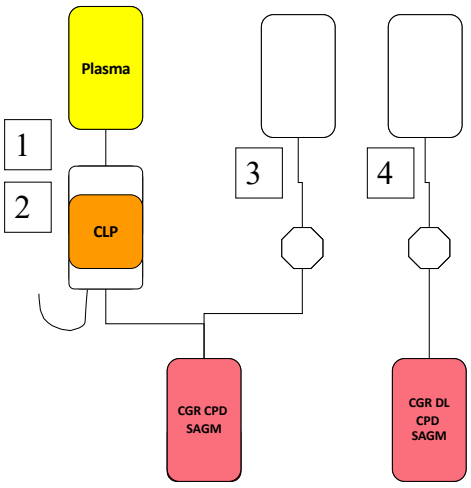
Prélèvement de sang veineux recueilli aseptiquement dans un dispositif clos autorisé, à usage unique, contenant un volume approprié de solution anticoagulante et de conservation, stérile et apyrogène

- De 18 à 70 ans révolus (➔ 75 ans si donneur régulier)
- Poids ≥ 50 kg
- Taux d'hémoglobine: 125 g/l (♀) et 135 g/l (♂)
- Délai entre 2 dons: 10 à 12 semaines
- Maximum 3 dons/an (♀) et 4 dons/an (♂)

- Durée du don en général <10-12 min
- Prélèvement d'env 450 ml de sang (< 15% du VST)
- Perte d'env 1gr d'hémoglobine et 200 mg de fer (adsorption digestive 1-2 mg/j)
- Perte négligeable en plaquettes
- Soustraction de 250 ml de plasma (15-20 g de protéines dont 12 g d'albumine)

https://www.blutspende.ch/fr/informations-pour-les-donneurs/autres-types-de-don

Processus de préparation par filtration du CGR



1) Centrifugation

2) Séparation du plasma, couche leucoplaquettaire (CLP) et du concentré de globules rouges (CGR)

3) Ajout de la solution additive SAG-M

4) Filtration du concentré de globules rouges (CGR) ➔ étape de déleucocytation

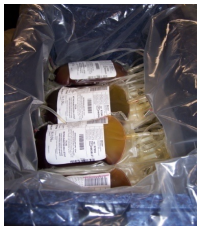
CPD = citrate phosphate dextrose

SAG-M = saline adénine glucose mannitol

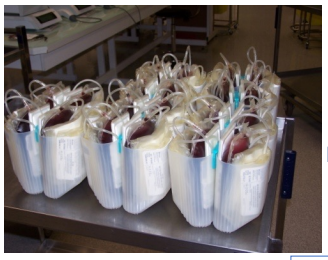
Processus de préparation par filtration du CGR

EFS
ÉTABLISSEMENT FRANÇAIS DU SANG -ALSACE

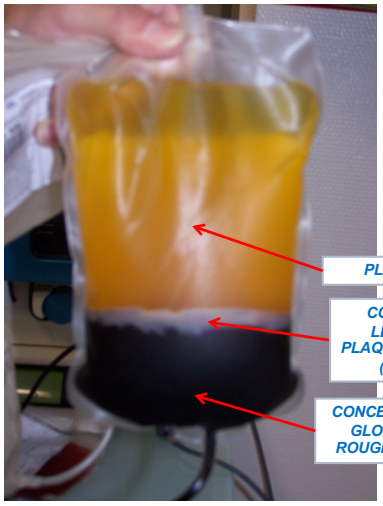
permet la séparation des 3 constituants principaux



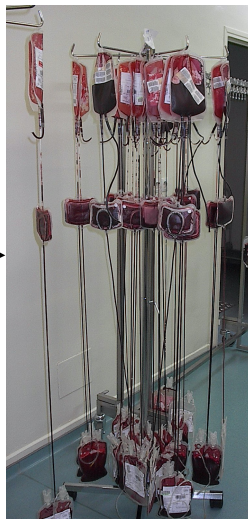
Retour de collecte

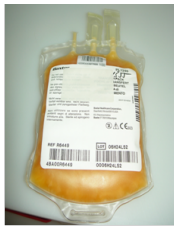


Centrifugation

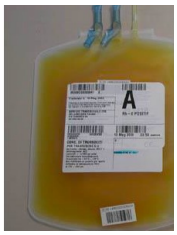


Processus de préparation par filtration du CGR

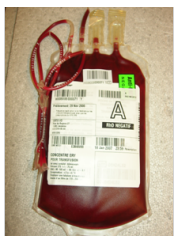




PFC



CP

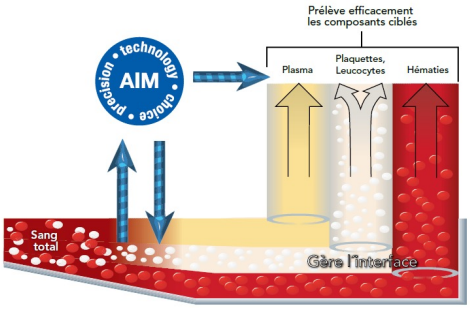


CE

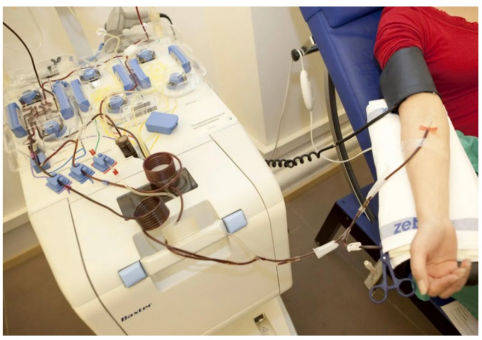
Le don par aphérèse

Prélèvement réalisé avec un séparateur de cellules qui permet au cours d'une circulation extracorporelle d'obtenir un ou plusieurs types de produits sanguins labiles, chacun répondant aux critères-qualité selon les prescriptions de Transfusion Suisse

- Don d'aphérèse simple ou combinée
- Plaquettes ou plasma ou plaquettes/plasma



Le don de plasma thérapeutique

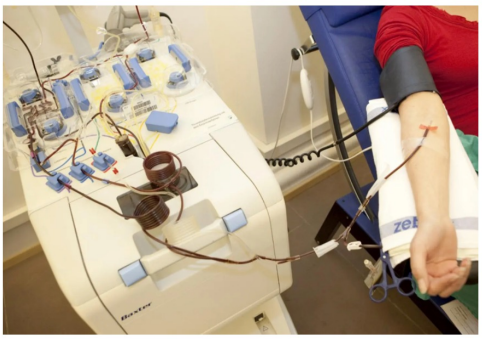


- De 18 à 65 ans révolus
- Poids ≥ 50 kg
- Délai entre 2 dons: de 2 à 4 semaines
- Le taux de protéines totales est ≥ 60 g/l
  - Si inférieur à 60 g/l = contre-indication au don
- Critères de sélection supplémentaires
  - Qualité abord veineux
  - Vigilance sur les risques hémodynamiques (poids, VST, TA, tolérance des dons antérieurs)
  - Vigilance sur les effets 2° du citrate (ACTD de malaise, trouble du métabolisme phosphocalcique, tétanie)
- Prélèvement donneurs hommes (prévention TRALI)

- Durée du don environ 40 min
- Prélèvement d'env 650 ml de plasma (max 750 ml et 16% VST)
- Transfert hydrique du secteur extra-vasculaire vers intravasculaire (40 à100 ml/h). Importance de l'hydratation pré-don
- Soustraction de 50 g de protéines dont 30 g d'albumine
- Potentiel effet hypocalcémiant du citrate

https://www.blutspende.ch/fr/informations-pour-les-donneurs/autres-types-de-don

Le don de plaquettes



- De 18 à 65 ans révolus
- Poids ≥ 50 kg
- Délai entre 2 dons: 4 à 6 semaines (max 12x/an)
- Numération plaquettaire ≥ 150 G/l
  - Si inférieur à <150 G/l = contre-indication au don

- Critères de sélection supplémentaires
  - Qualité abord veineux
  - Vigilance sur les risques hémodynamiques (poids, VST, TA, tolérance des dons antérieurs)
  - Vigilance sur les effets 2° du citrate (ACTD de malaise, trouble du métabolisme phosphocalcique, tétanie)

- Durée du don environ 60 à 90 min
- Prélèvement d'env 500-650 ml de plaquettes (max 750 ml/séance et 16% VST)
- Potentiel effet hypocalcémiant du citrate

- Rejet du donneur si prise d'anti-aggrégants (aspirine, AINS) au cours des 5 jours précédant la thrombocytaphérèse ou allergie aigue

https://www.blutspende.ch/fr/informations-pour-les-donneurs/autres-types-de-don

Concentrés plaquettaires (CP): 2 méthodes de production

Concentré plaquettaire de sang complet

Concentré plaquettaire d'aphérèse

1 concentré plaquettaire >2.4 x 10^{11} plaquettes

Mélange de 5 donneurs (de sang complet): moins de plasma d'un seul donneur

Aphérèse à partir d'un seul donneur: typage HLA et HPA possible (état réfractaire aux transfusions de plaquettes)

Examens virologiques

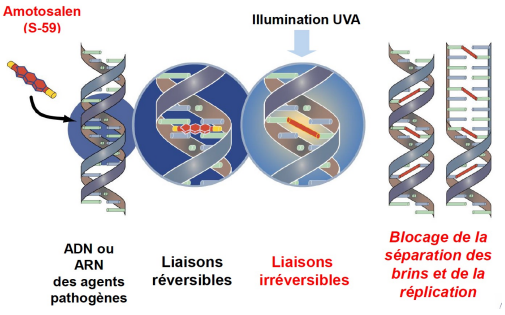
1) Obligatoire
- HIV ➔ sérologie anti-HIV (4e génération avec Ag P24), PCR HIV
- Hépatite B ➔ sérologie (Ag HBs, anti-HBc) et PCR HBV
- Hépatite C ➔ sérologie (anti-HCV) et PCR HCV
- Hépatite E ➔ PCR HEV
- Syphilis TPHA

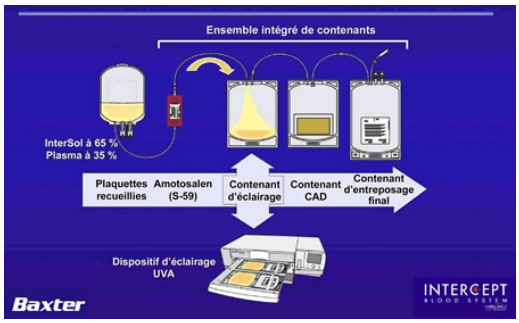
- PCR HAV et parvovirus B19 (demandé par le fractionneur pour le plasma frais congelé)

2) **Si exposition à risque**
- Sérologie de paludisme et de Chagas, virus du Nil occidental

3) **Anti-CMV** sur demande pour transfusion intra-utérine

Inactivation des pathogènes par amotosalen et UV-A (dès janv 2011)





Principe: ajout de l'amotosalen/Intercept et irradiation UV-A = intercalation de molécules d'amotosalen dans les brins d'acides nucléiques sous l'action d'une illumination UVA. Elimination secondaire de l'amotosalem

- Protection possible contre les pathogènes émergents ou non dépistés (virus, bactéries, protozoaires)
- Inactivation moins efficace des virus non-enveloppés (HAV, parvovirus B19 et HEV)
- Efficacité sur les lymphocytes donneur => prévention GvHD post transfusion (plus besoin d'irradier les CP)

Indications cliniques pour la transfusion de CP ou de PFC

Transfusion prophylactique de plaquettes
- Lors de thrombopénies centrales (ex. chimiothérapie thrombopéniante, aplasie médullaire)
- But: prévenir la survenue d'une hémorragie c/o un patient thrombopénique

Transfusion thérapeutique/curative de plaquettes
- Lors de saignement actif avec thrombopénie ou thrombopathie ou choc hémorragique
- But: corriger une hémorragie

Transfusion de plasma
- Coagulation de dilution lors d'une transfusion massive (PTM)
- Trouble global de l'hémostase et saignement
- Echanges plasmatiques en cas de Purpura Thrombotique Thrombopénique (PTT)

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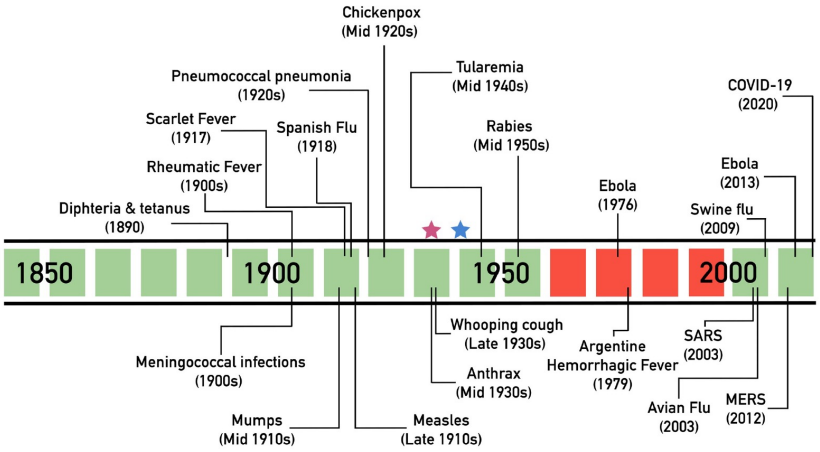
- Conclusions et perspectives

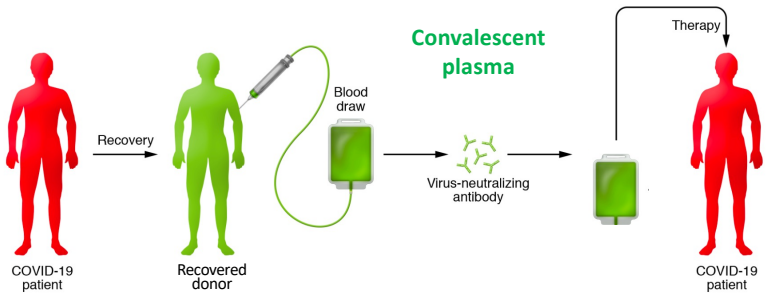
Historical concepts



Convalescent plasma collected from patients who have recovered from an infection, has been used to treat various infectious diseases since the early 20th century, although its benefit has not been consistently studied in randomized clinical trials

Montelongo-Jauregui et al., PLoS Pathogens, 2020; https://doi.org/10.1371/journal.ppat.1008735

Schematic use of convalescent plasma for COVID-19 therapy



Convalescent plasma is a passive antibody transfer therapy

Plasma from donors who have recovered from COVID-19 contains antibodies to SARS-CoV-2 that may help suppress the virus and modify the inflammatory response

Adapted from Casadevall A. and Pirofski LA, J Clin Invest, 2020; 130(4): 1545-1548

What have we learned so far ?

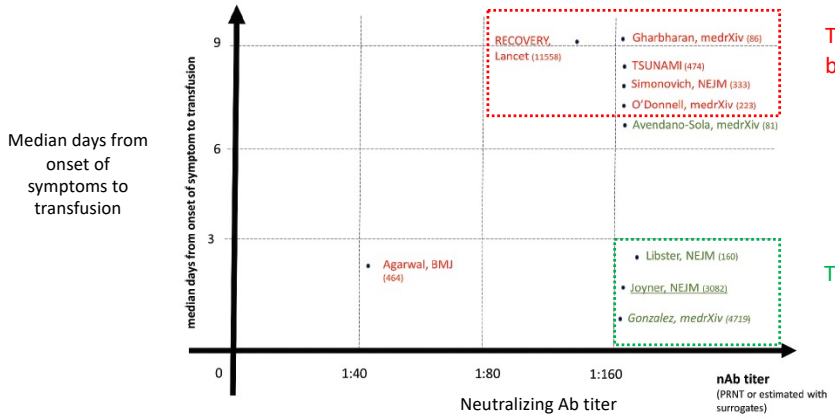


Figure 1. Graphical summary of COVID19 convalescent plasma (CCP) randomized controlled trials (RCT), propensity-score matched trials (italics), and matched controlled trials (underlined characters) for which nAb titer and days from onset of symptoms to transfusion were disclosed, and having placebo or best supportive care as a comparator. The green characters show trials reporting clinical benefits, while the red characters show trials which failed to evidence clinical benefit.

Focosi D and Franchini M, Expert review of vaccines, 2021; https://doi.org/10.1080/14760584.2021.1932475

What have we learned so far ?

JAMA | Original Investigation

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

Perrine Janiaud, PhD; Cathrine Axfors, MD, PhD; Andreas M. Schmitt, MD; Viktoria Gloy, PhD; Fahim Ebrahimi, MD, MSc; Matthias Hepprich, MD; Emily R. Smith, ScD, MPH; Noah A. Haber, ScD; Nina Khanna, MD; David Moher, PhD; Steven N. Goodman, MD, PhD; John P. A. Ioannidis, MD, DSc; Lars G. Hemkens, MD, MPH

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.

No association with a decrease in all-cause mortality

It is becoming clear that we need to:

- Use plasma with sufficient antibody level
- Administer convalescent plasma are the right time
- Identify the subgroups of patients who may benefit

Janiaud P et al., JAMA, 2021; https://doi:10.1001/jama.2021.2747

Mayo Clinic Proceedings

REVIEW | ARTICLES IN PRESS

The Effect of Convalescent Plasma Therapy on COVID-19 Patient Mortality: Systematic Review and Meta-analysis

Stephen A. Klassen, PhD † • Jonathon W. Senefeld, PhD † • Patrick W. Johnson, BSc • ...
Nigel S. Paneth, MD • Arturo Casadevall, MD, PhD † • Michael J. Joyner, MD Show all authors •

Article Highlights

- There remains a lack of consensus on convalescent plasma use in hospitalized patients with COVID-19.
- Meta-analyses of randomized clinical trials and matched-control data demonstrated that COVID-19 patients transfused with convalescent plasma exhibited a lower mortality rate compared to patients receiving standard treatments.
- Additional analyses showed that early transfusion (within 3 days of hospital admission) of high-titer plasma is associated with lower mortality.
- These data provide evidence favoring the efficacy of human convalescent plasma as a therapeutic agent in hospitalized COVID-19 patients.

Association with a lower mortality rate

Klassen SA et al., 2021; https://doi.org/10.1016/j.mayocp.2021.02.008

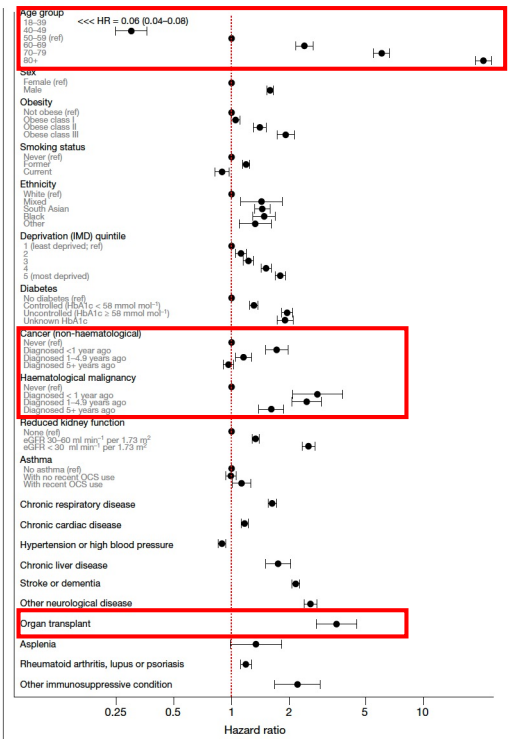
Subgroups of patients that may best benefit

Article

Factors associated with COVID-19-related death using OpenSAFELY

Fig. 3 | Estimated hazard ratios for each patient characteristic from a multivariable Cox model. Hazard ratios are shown on a log scale. Error bars represent the limits of the 95% confidence interval for the hazard ratio. IMD, index of multiple deprivation; obese class I, BMI 30–34.9; obese class II, BMI 35–39.9; obese class III, BMI ≥ 40; OCS, oral corticosteroid; ref, reference group. All hazard ratios are adjusted for all other factors listed other than ethnicity. Ethnicity estimates are from a separate model among those individuals for whom complete ethnicity data were available, and are fully adjusted for other covariates. Total $n = 17,278,392$ for the non-ethnicity models, and 12,718,279 for the ethnicity model.

Comorbidity	Hazard Ratio for death Full adjusted
Solid cancer < 1y	1.72
Hematological malignancy < 1y	2.8
Hematological malignancy 2y – 5y	2.46
Organ transplant	3.53



Willamson et al., Nature, 584;430, 2020, https://doi.org/10.1038/s41586-020-2521-4

JAMA Oncology | Original Investigation

Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19

Michael A. Thompson, MD, PhD; Jeffrey P. Henderson, MD, PhD; Pankil K. Shah, MD, MSPH; Samuel M. Rubinstein, MD; Michael J. Joyner, MD; Toni K. Choueiri, MD; Daniel B. Flora, MD, PharmD; Elizabeth A. Griffiths, MD; Anthony P. Gulati, MD; Clara Hwang, MD; Vadim S. Koshkin, MD; Esperanza B. Papadopoulos, MD; Elizabeth V. Robilotti, MD, MPH; Christopher T. Su, MD, MPH; Elizabeth M. Wulff-Burchfield, MD; Zhuoer Xie, MD, MS; Peter Paul Yu, MD; Sanjay Mishra, MS, PhD; Jonathon W. Senefeld, PhD; Dimpy P. Shah, MD, PhD; Jeremy L. Warner, MD, MS; for the COVID-19 and Cancer Consortium

- Retrospective study, 143 patients with hematological malignancies
- Moderate to severe COVID-19
- Treated with CCP and compared to 823 untreated controls

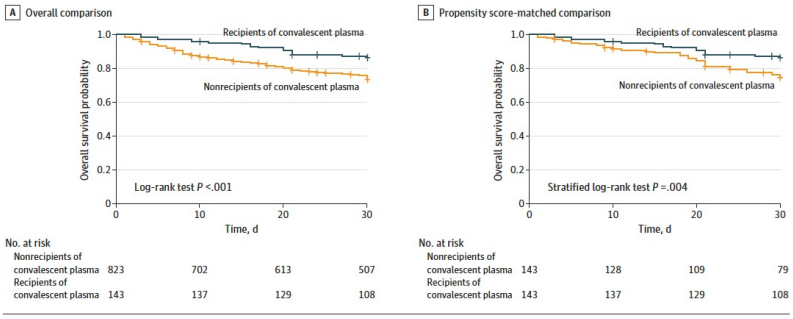
Key Points

Question Is convalescent plasma therapy associated with improved outcomes of hospitalized patients with COVID-19 and hematologic cancer?

Findings In this cohort study of 966 patients with hematologic cancer and COVID-19, after adjustment for potential confounding factors, convalescent plasma treatment was associated with a significantly improved 30-day mortality in the 143 individuals who received it. This association remained significant after propensity score matching.

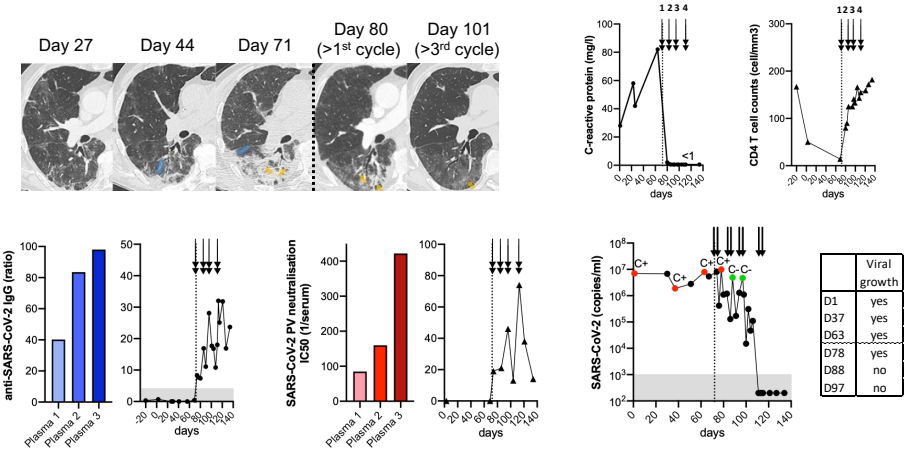
Meaning These findings suggest a potential survival benefit in the administration of convalescent plasma to patients with hematologic cancers and COVID-19.

Figure. Overall Survival Rates Among Recipients vs Nonrecipients of Convalescent Plasma



Thompson et al., JAMA Oncol, 7(8):1167-1175, 2021

Successful convalescent plasma treatment in chronic SARS-CoV-2 infection

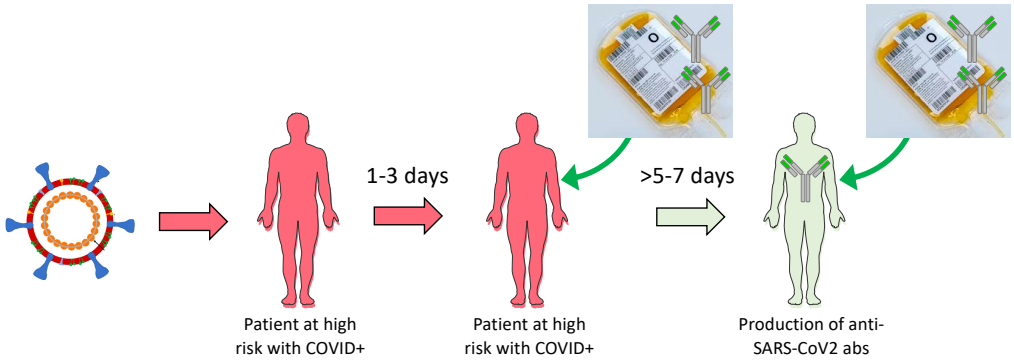


- Successful treatment of a severely immunocompromised patient with prolonged SARS-CoV-2 disease by four cycles of convalescent plasma transfusion
- Cumulative increase in anti-SARS-CoV-2 neutralizing antibodies following each plasma transfusion was associated with progressive and finally complete viral clearance

Zimmerli et al., Front Immunol, 12:613502, 2021 https://www.frontiersin.org/articles/10.3389/fimmu.2021.613502/full

frontiers in Immunology

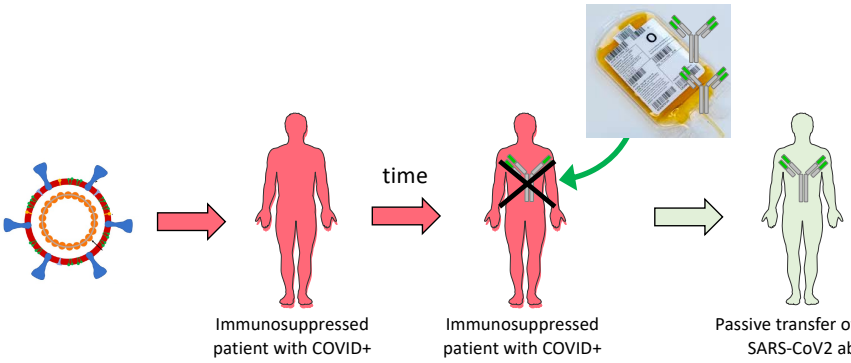
Administration of CP at the right time with high antibody titers



- Convalescent plasma appears ineffective for most immunocompetent patients with COVID-19 pneumonia. This may in part be explained by the fact that **many of them already produce anti-SARS-CoV2 antibodies**
- Yet, the INFANT-COVID study supports the notion that there may be a clinical benefit when **high-titer convalescent plasma are given early (<72 hours after symptom onset) in a selected high-risk cohort of patients**

Simonovich et al., N Eng J Med, Nov, 2020 Libster R. et al., N Eng J Med, 2021; 384(7):610-618

Subgroups of patients who may best benefit of convalescent plasma

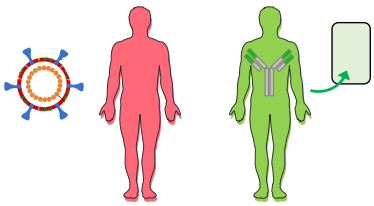


- Several studies have provided evidence that convalescent plasma with anti–SARS-CoV-2 antibodies appears to be a promising approach in the context **of immunosuppressed patients, unable to mount a specific humoral response to SARS-CoV-2**

Hueso et al., Blood, 136(20):2290, 2020 Tremblay et al., Cancer Medicine, 9:8571, 2020 Thompson et al., JAMA Oncol, 7(8):1167-1175, 2021

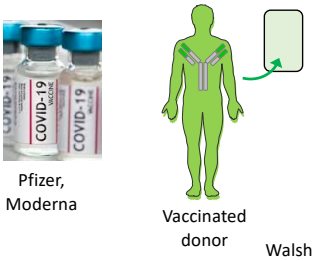
Plasma with enriched antibodies against SARS-CoV2

1. Plasma post COVID = CP

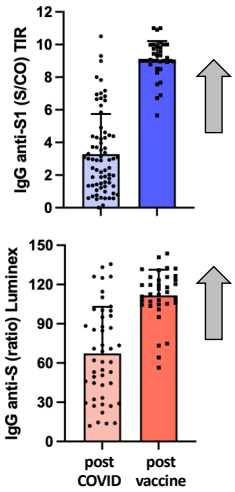


- Heterogeneous responses
- Polyclonal humoral response
- Decay (< 6 mo)
- Variants ?
- **Difficulties for plasma supply with high antibody titers**

2. Plasma post vaccination = VP



- Strong homogeneous responses
- Oligoclonal response (S protein)
- Decay (>6 mo)
- Variants ?
- **Plasmapheresis performed > two weeks after 2nd vaccination**



Unpublished data

Walsh et al., N Engl J Med, Oct 2020 Jackson et al., N Engl J Med, Aug 2020

La plasmathérapie basée sur la vaccination anti-SARS-CoV2, représente-t-elle une source alternative de plasma enrichi en anti-SARS-CoV2 ?

Quels résultats thérapeutiques peuvent être attendus chez les patients immunodéficients traités par plasmathérapie vaccinale par rapport au plasma convalescent ?

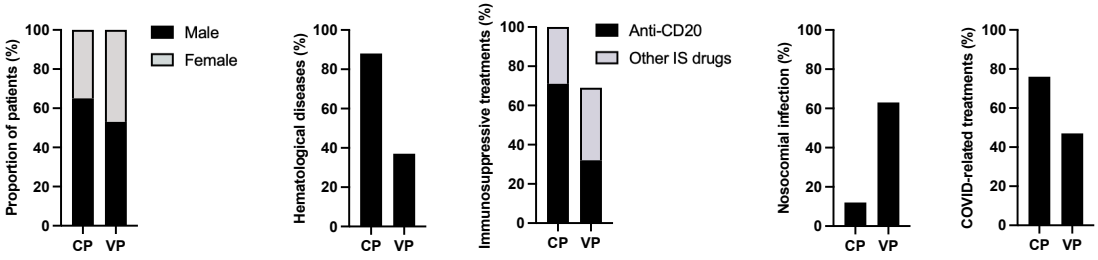
CHUV: Thérapie expérimentale dans le cadre individual

Study design:

- **Immunosuppressed patients:** hematological malignancies treated with rituximab or other immunosuppressive drugs (< 2 yrs), autoimmune disease, organ transplant, or other high-risk factors/nosocomial infection (<72h)

- CP = 17 patients who received convalescent plasma (Nov 2020 to March 2021)
- VP = 19 patients who received vaccine-based plasma (March 2021 to July 2021)
- 6 patients received 2 to 4 treatments, sequentially

- Mild to moderate or severe COVID-19 disease, only 4 patients vaccinated (2 completely)



Gachoud, Rufer et al., unpublished data

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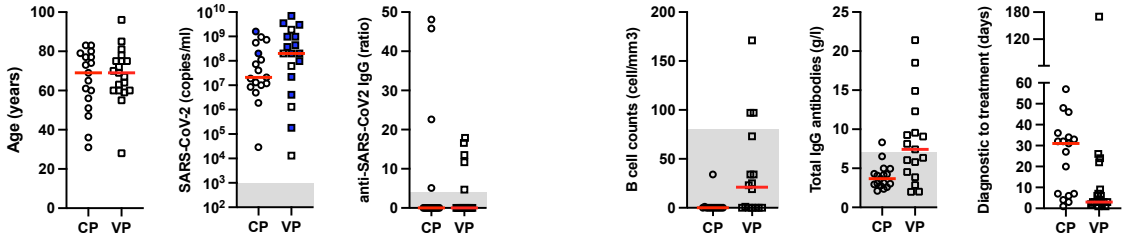
- Mostly high viral loads and negative anti-SARS-CoV2 IgG serology
- B cell lymphopenic and hypogammaglobulinemia

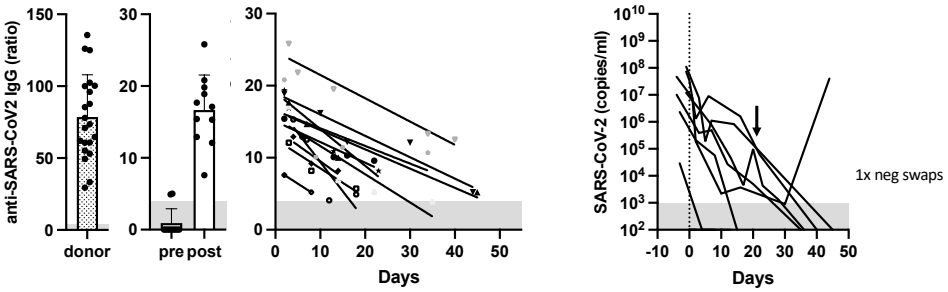


Gachoud, Rufer et al., unpublished data

Preferential decline in anti-S IgG titers in patients with Rituximab

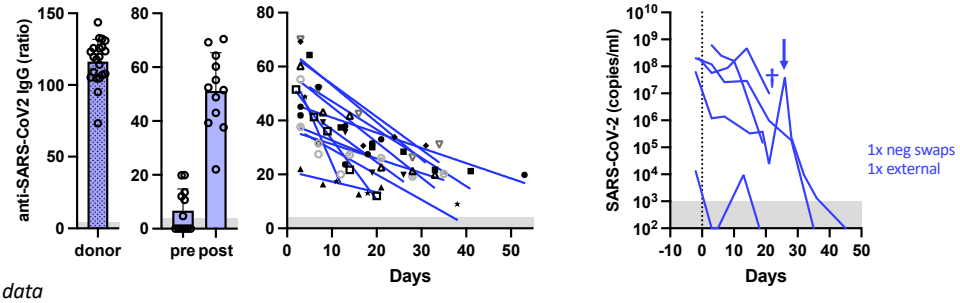
Convalescent plasma

Post COVID
D1: 2x200ml
D2: 2x200ml



Vaccine-based plasma

Post vaccin
D1: 2x200ml

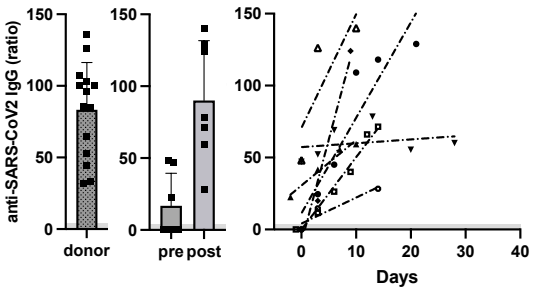


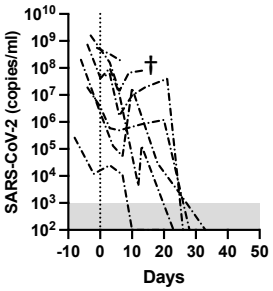
Gachoud, Rufer et al., unpublished data

Antibody-enriched plasma also represents a bridging therapy

Convalescent plasma

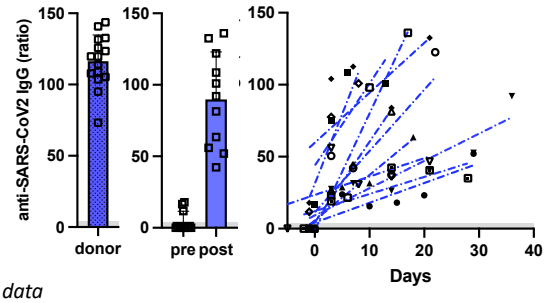
Post COVID
D1: 2x200ml
D2: 2x200ml

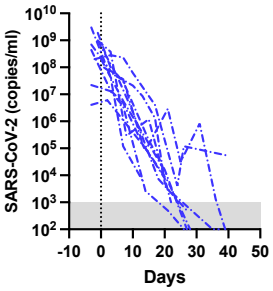




Vaccine-based plasma

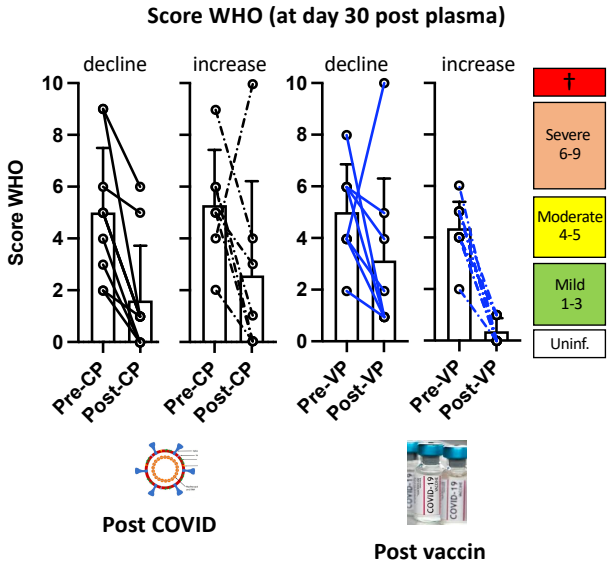
Post vaccin
D1: 2x200ml





Gachoud, Rufer et al., unpublished data

Similar rates of clinical recovery occur in both types of plasma

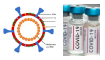


- 29/36 (80%) patients survived
- 2/36 died from COVID-19
- 5/36 died from 1° related disease

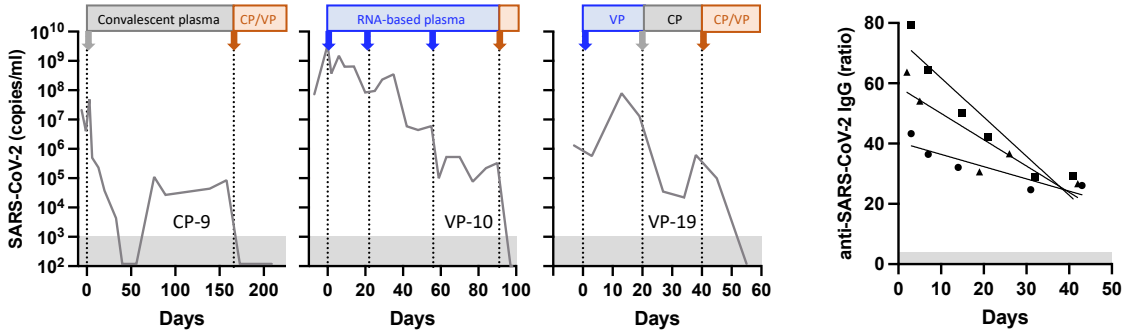
Gachoud, Rufer et al., unpublished data

Plasma transfusion from convalescent/vaccinated donors

Three patients received an additional plasma transfusion from convalescent/vaccinated donors, allowing complete viral clearance



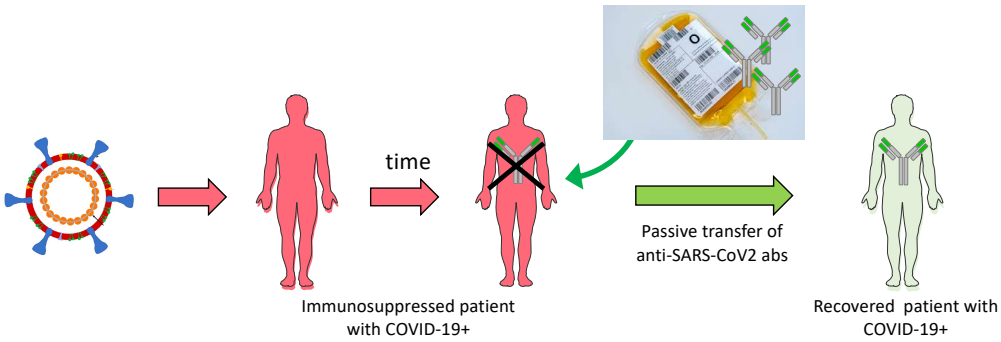
Plasma
COVID+vaccin



Gachoud, Rufer et al., unpublished data

Conclusions -1

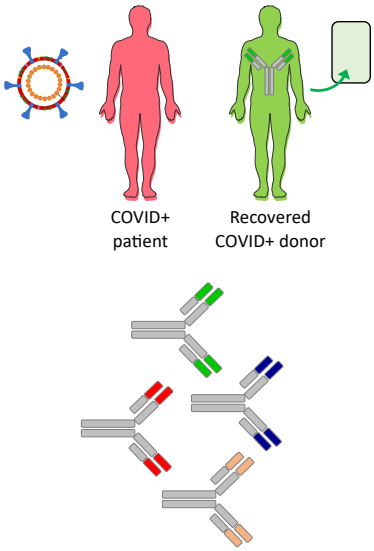
- Treat **the right patients**:
  - It is likely that some forms of immunosuppression will respond better than others (bridging) (anti-CD20 > other hemato-oncological treatment > autoimmun recipient)
- At **the right time** = as early as possible, before severe disease
- Use **high antibody titers**: convalescent plasma versus vaccine-based plasma
- **Follow the response**: re-treat if necessary, CAVE emergence of variants



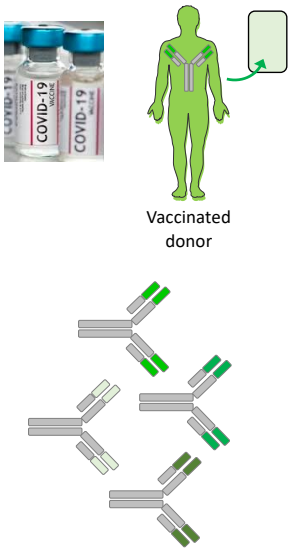
Gachoud, Rufer et al., unpublished data

Conclusions -2

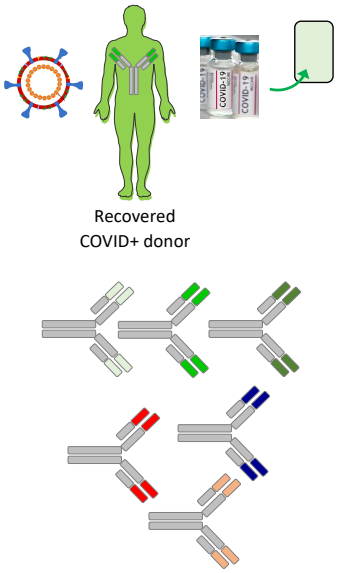
1. Convalescent plasma (post COVID)



2. Plasma post vaccination

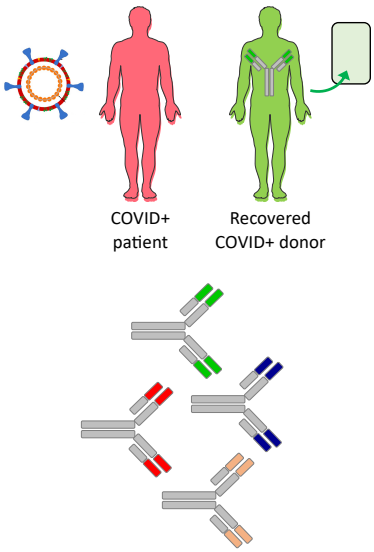


3. Plasma post COVID + vaccination

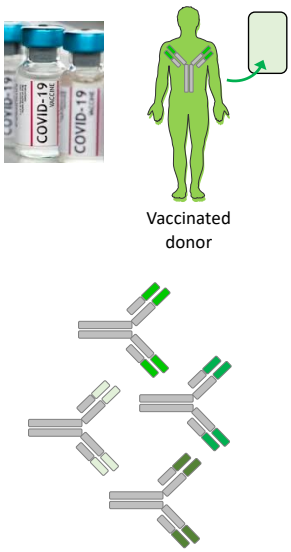


Conclusions -2

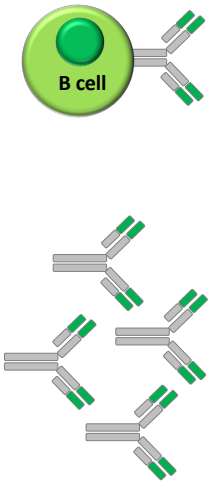
1. Convalescent plasma (post COVID)



2. Plasma post vaccination



4. Monoclonal antibodies (COVID)



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