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A look-back at convalescent plasma to treat COVID-19

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Editorial

The transfer of immunity from a protected to an infected host dates back to the end of the XIXth century, on both experimental and clinical grounds. Perhaps the pioneer large scale experience has achieved during the so-called Spanish flu, a disease which killed almost twice to five times more people (depending on the model used) than the preceding WWI. After that first experience, nearly all severe or serious infectious outbreaks involving a viral pathogen have been considered eligible for convalescent plasma collection from donors who have recovered from the infection [reviewed in: [1,2]; this therapy, however, was accompanied by all-time questions on the dose, the regimen, the amount of protective antibodies, the potential for deleterious effects, and the most appropriate stage of eligibility of recipients [3,4]. The question, in other words, remains as to how to protect against what: from the infection itself or from the severity of the infection?

Convalescent plasma treatment, i.e. passive polyclonal antibody administration to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology, as reviewed by Mair-Jenkins J et al. in their 2015 meta-analysis [5]. Indeed, a number of convalescent plasma studies, unfortunately none adequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish Influenza A (H1N1) infections in 1915–1917, the more recent Influenza A (H1N1)pdm09 infections in 2009/2010 as well SARS-CoV infections in 2003. On the contrary, convalescent plasma was found to provide no benefit for the treatment of Ebola disease [6] while being beneficial in the treatment of another hemorrhagic fever i.e. the Argentinian hemorrhagic fever [7].

Very early after the SARS-CoV-2 infection appeared to be potentially severe and lethal in a number of patients, most presenting with frailties, proposals were made to assess convalescent plasma therapy, either in compassionate situations or in randomized controlled trials (RCTs) [8–10]. Two paramount questions were to be addressed prior to promoting such a treatment: first, to assess whether the recovering person was capable to raise sustainable amounts of antibodies to be collected by

plasmapheresis; and secondly, whether antibodies were indeed neutralizing and not facilitating (such as in certain viral infections, the most exemplary being Dengue viruses, against the other three serotypes) [3,11].

At a speed never seen so far, robust data accumulated regarding the complexity of antibodies made against SARS-CoV-2 moieties (the virus signature track) or by COVID-19 suffering patients, not necessarily overlapping. Indeed, while COVID-19 healers were proven to raise significant amounts of antibodies that do not vanish immediately and last for weeks and likely months [12,13], pathogenic antibodies were also made in parallel. These can bind to macrophages and cause acute lung injury [14], damage vascular endothelium leading to endotheliopathy [15] and possibly coagulopathy [16], and dampen antiviral natural defense when directed to type I interferons [17]. It has been shown that—not unlikely as several other infections, such as HIV and others—the SARS-CoV-2 virus alters the germinal center and forces extra-follicular antibody making [18,19]. In spite of this, recent evidence indicates that robust antibody protection persists for months [20,21], and, if any, enhancing or facilitating antibodies were of moderate concentration.

Collection of convalescent plasma preceded accumulation of scientific evidence that antibodies were neutralizing and not enhancing, and in a quantity large enough to mediate protection, demonstrating that an unprecedented race was engaged against the pandemic, barely allowing time to discuss ethical issues [22,23], with the objective to learn as much as possible to justify the strongly wished vaccine approach.

Less than a single year after the initial reports of the severity of the disease, knowledge has accumulated regarding the potential of convalescent plasma: encouraging data were presented after 3 months of inclusion in a large series of recipients by Joyner et al. [24]. Next, Li et al. [25] concluded that: “Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment did not significantly improve the time to clinical improvement within 28 days, although the trial was terminated early and may have been underpowered to detect a clinically important difference”. In contrast, Liu et al. found that their retrospective, propensity score-matched

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case-controlled study assessed the effectiveness of convalescent plasma therapy with less oxygen requirements on day 14 after transfusion and less worsened cases in plasma recipients compared to propensity score-matched controls [26]. Salazar et al. reported a significant reduction ($P = 0.047$) in mortality within 28 days, specifically in patients transfused within 72 h of admission with plasma with an anti-spike protein receptor binding domain titer of $\geq 1:1350$, and suggested that that treatment of COVID-19 with high anti-receptor binding domain IgG titer convalescent plasma is efficacious in early-disease patients [27]. Agarwal et al., however, found that convalescent plasma was not associated with a reduction of progression to disease or all cause of mortality [28]. In aggregate, Joyner et al., having compiled (nearly) all submitted data—not necessarily peer-reviewed as many are loaded on the MedRxiv site—concluded in favor of a protective effect of convalescent plasma [30]. More recently, convalescent plasma was found to be not superior to placebo in a randomized trial involving hospitalized patients with COVID-19 pneumonia [29]. Apparent discrepancies in conclusions may well be the result of certain inconsistency in defining patient groups (severity, time-course of infection, and outcomes), as was observed in other main trials addressing controversies in blood transfusion; the same concerns were for e.g. raised in this Journal à propos the age of blood [31]. These types of inconsistencies are, in general, pondered in metanalyses. It remained to confirm that transfusion of convalescent plasma was safe, which Joyner reviewed in 5000 transfused COVID-19 patients [30]. Nguyen et al. reviewed, in detail, the adverse reactions in 427 patients having received convalescent plasma and did not report increased risks compared to anticipated side effects [32]. Of note, the observed reaction rate was 12.9 %, among which 82 % (mainly fever, hypoxia or both) were attributed to the underlying disease.

Interestingly, convalescent plasma therapy has proven to be beneficial in B-cell depleted patients having protracted COVID-19 [33], with an acknowledged limit inherent to uncontrolled observations [34]. Compassionate plasma therapy was applied early in the disease course [35–37]. As many more RCTs or compassionate programs are run in major healthcare facilities or within international consortiums, regulatory bodies—such as the FDA—also made more precise recommendations [38].

Very recently, investigators have reported (in a not-yet peer-reviewed format) positive results regarding the very early (within 72 h of mild COVID-19 symptoms) transfusion of convalescent plasma in patients over 75 years old [39]. In this randomized study, convalescent plasma transfusion was associated with significant reduction in the occurrence of severe respiratory disease. These findings, reminiscent of recently reported findings with an anti-SARS-CoV-2 monoclonal treatment [40] as well as much older findings with convalescent plasma treatment of the Argentinian hemorrhagic fever [41], highlight the importance of early intervention when considering passive immunotherapy to treat infectious diseases. As we now move into the COVID-19 vaccination era, passive immunotherapy may become an important early therapeutic intervention for those poorly responding to vaccination (such as patients with acquired immunodeficiency, and possibly the elderly).

In conclusion, convalescent plasma therapy remains a solid option to treat COVID patients, though this option falls into a portfolio of many other therapeutic approaches and does not provide complete cure. The treatment schedule is likely to be refined to sort out the target populations and the most appropriate time frame, and also when to collect plasma from convalescent donors [42]. With a broader perspective, it is interesting to note that once more (after e.g. the Ebola virus saga) plasma therapy competes with vaccine development, the former being not completely disregarded when the latter comes into reality as antibody-enriched plasma may well be obtained from vaccinated persons, to prepare purified, neutralizing antibodies as also recommended by the FDA [43,44]. Two sets of conclusions can be temporarily drawn at this time. First, this pandemic has revealed how fragile the combination

of healthcare and economy, forcing to state decisions that altered autonomy of populations and individual freedom. The swiftness of incremental health care measures to handle actual patients and to protect the rest of the population is barely compatible with the necessary in-depth ethical analysis of all situations and consequences. Secondly, there is an urgent need to set up—in forthcoming preparedness plans for the next pandemic (as this seems to be inevitable)—clearer outcomes to measure, in order to allow for the best-fitted clinical trials. Methods and ethics are more than ever paramount to accompany the vortex of medical and scientific achievements under pressure such as seen in this SARS-CoV-2 crisis.

Declaration of Competing Interest

The authors report no declarations of interest.

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References

- [1] Garraud O, Heshmati F, Pozzetto B, Lefrere F, Girot R, Saillol A, et al. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. *Transfus Clin Biol* 2016;23:39–44.
- [2] Wong HK, Lee CK. Pivotal role of convalescent plasma in managing emerging infectious diseases. *Vox Sang* 2020;115:545–7.
- [3] Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest* 2020;130:1545–8.
- [4] Garraud O. Passive immunotherapy with convalescent plasma against COVID-19? What about the evidence base and clinical trials? *Transfus Apher Sci* 2020;59: 102858.
- [5] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015;211:80–90.
- [6] van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of convalescent plasma for ebola virus disease in Guinea. *New Eng J Med* 2016;374:33–42.
- [7] Ruggiero HA, Pérez Isquierdo F, Milani HA, Barri A, Val A, Maglio F, et al. Traitement de la fièvre hémorragique argentine par le plasma de convalescent : 4,433 cas [Treatment of Argentine hemorrhagic fever with convalescent's plasma. 4433 cases]. *Presse Med* 1987;55:2239–342.
- [8] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020;323:1582–9.
- [9] Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* 2020;130:2757–65.
- [10] Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A* 2020;117:9490–6.
- [11] Lee WS, Wheatley AK, Kent SJ, DeKovsky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol* 2020;5:1185–91.
- [12] Chen Y, Zuiani A, Fischinger S, Muller J, Atyeo C, Travers M, et al. Quick COVID-19 healers sustain anti-SARS-CoV-2 antibody production. *Cell* 2020. <https://doi.org/10.1016/j.cell.2020.10.051>. S0092-8674(20)31458-6.
- [13] Atyeo C, Fischinger S, Zohar T, Slein MD, Burke J, Loos C, et al. Distinct early serological signatures track with SARS-CoV-2 survival. *Immunity* 2020;53:524–32. e4.
- [14] Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* 2019;4. e123158.
- [15] Rauch A, Dupont A, Goutay J, Caplan M, Staessens S, Moussa M, et al. Lille COVID Research Network (LICORNE); Members of the LICORNE Scientific Committee. Endotheliopathy is induced by plasma from critically ill patients and associated with organ failure in severe COVID-19. *Circulation* 2020;142:1881–4.
- [16] Zuo Y, Estes SK, Ali RA, Gandhi AA, Yalavarthi S, Shi H, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. *Sci Transl Med* 2020;12:eabd3876.
- [17] Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020;370. eabd4585.
- [18] Kaneko N, Kuo HH, Boucau J, Farmer JR, Allard-Chamard H, Mahajan VS, et al. Loss of Bcl-6-expressing t follicular helper cells and germinal centers in COVID-19. *Cell* 2020;183:143–57. e13.
- [19] Woodruff MC, Ramonell RP, Nguyen DC, Cashman KS, Saini AS, Haddad NS, et al. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nat Immunol* 2020;21:1506–16.

- [20] Wajnberg A, Amanat F, Firpo A, Altman DR, Bailey MJ, Mansour M, et al. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. *Science* 2020. eabd7728.
- [21] Iyer AS, Jones FK, Nodoushani A, Kelly M, Becker M, Slater D, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. *Sci Immunol* 2020;5. eabe0367.
- [22] Garraud O. COVID-19, transfusion, and publishing ethics. *Transfus Clin Biol* 2020; 27:201–2.
- [23] Barroga E, Matanguihan GJ. Fundamental shifts in research, ethics and peer review in the era of the COVID-19 pandemic. *J Korean Med Sci* 2020;35:e395.
- [24] Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv [Preprint]* 2020;08(12):20169359.
- [25] Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA* 2020;324:460–70.
- [26] Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Firpo-BConvalescent plasma treatment of severe COVID-19: a propensity score-matched control study. *Nat Med* 2020;26:1708–13.
- [27] Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Significantly decreased mortality in a large cohort of coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike protein IgG. *Am J Pathol* 2020. S0002-9440(20)30489-2.
- [28] Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020;371. m3939. Erratum in: *BMJ* 2020;371:m4232.
- [29] Simonovich VA, Burgos Pratz LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, et al. For the PlasmaR study group. A randomized trial of convalescent plasma in Covid-19 pneumonia. *N Engl J Med* 2020. <https://doi.org/10.1056/NEJMoa2031304>.
- [30] Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020;130:4791–7.
- [31] Garraud O. Clinical trials in transfusion medicine and hemotherapy: worth moving forward in evaluating 'fresh' versus 'old' blood cell components? *Transfus Apher Sci* 2017;56:98–9.
- [32] Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020;130:4791–7.
- [33] Nguyen FT, van den Akker T, Lally K, et al. Transfusion reactions associated with COVID-19 convalescent plasma therapy for SARS-CoV-2. *Transfusion* 2020;1–16. <https://doi.org/10.1111/trf.16177>.
- [34] Hueso T, Pouderoux C, Péré H, Beaumont AL, Raillon LA, Ader F, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood* 2020;136:2290–5.
- [35] Murphy MF, Dzik S. COVID-19, plasma, and hypogammaglobulinemia. *Blood* 2020;136:2245–6.
- [36] Sabando Vélez BE, Plaza Meneses C, Felix M, Vanegas E, Mata VL, Romero Castillo H, et al. A practical approach for the compassionate use of convalescent plasma in patients with severe COVID-19 in developing countries. *J Infect Dev Ctries* 2020;14:737–41.
- [37] Maor Y, Cohen D, Paran N, Israely T, Ezra V, Axelrod O, et al. Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma. *EClinicalMedicine* 2020;26:100525.
- [38] Vlachogianni G, Hassapoulou-Matamis H, Politis C, Fylaki E, Mentis A. A case of COVID-19 convalescent plasma donation in Greece: directed donation for compassionate use in the donor's critically ill father. *Transfus Clin Biol* 2020;27: 269–70.
- [39] FDA, 2020. <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>.
- [40] Libster R, Pérez Matrc G, Wappner D, et al. Prevention of severe COVID-19 in the elderly by early high titer plasma. *MedRxiv* 2020. <https://doi.org/10.1101/2020.11.20.20234013doi>. posted November 13th.
- [41] Enria DA, Maiztegui JI. Antiviral treatment of Argentine hemorrhagic fever. *Antiviral Res* 1994;23:23–31.
- [42] Tiberghien P, de Lamballerie X, Morel P, Gallian P, Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how? *Vox Sang* 2020;115:488–94.
- [43] Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med* 2020. *NEJMoa2029849*.
- [44] FDA, 2020. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19>.