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

Running title: COVID-19 convalescent plasma

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## Abstract

Plasma provided by COVID-19 convalescent patients may provide therapeutic relief as the number CODID-19 cases escalate steeply world-wide. Prior findings in various viral respiratory diseases including SARS-CoV related pneumonia suggest that convalescent plasma can reduce mortality, although formal proof of efficacy is still lacking. By reducing viral spread early on, such an approach may possibly downplay subsequent immunopathology. Identifying, collecting, qualifying and preparing plasma from convalescent patients with adequate SARS-CoV-2 neutralizing Ab titers in an

acute crisis setting may be challenging, although well within the remit of most blood establishments. Careful clinical evaluation should allow to quickly establish whether such passive immunotherapy, administered at early phases of the disease in patients at high risk of deleterious evolution may reduce the frequency of patient deterioration, and thereby COVID-19 mortality.

**Keywords**: COVID-19, convalescent plasma, plasma, infectious disease, antibody

## COVID-19 disease

The coronavirus disease 2019 (COVID-19) viral pneumonia is now a worldwide pandemic caused by the Severe acute respiratory virus coronavirus 2 (SARS-CoV-2)[1]. The number of cases, and associated mortality has increased dramatically since the first cases in Wuhan, China in December 2019[2]. As of March 21th, this virus had affected at least 275 469 people worldwide and caused more than 11 420 deaths[3]. In France, at the same date, 12 632 cases were reported with 450 deaths. The global number of cases, and related deaths are increasing steadily, with the notable exception of China that exhibits a flattening incidence curve since mid-February[3].

To date, no specific treatment has been proven to be effective for COVID-19[4]. Treatment is currently mainly supportive, with in particular mechanical ventilation for the critically ill patients (6.1% in a series of 1099 cases in China[2]). Novel therapeutic approaches are in acute need. In this context, the therapeutic potential associated with convalescent plasma needs to be explored[5,6].

## Convalescent plasma to treat viral diseases

Convalescent plasma treatment, i.e. passive polyclonal antibody (Ab) administration to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology[7]. Indeed, a number of studies, unfortunately all inadequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish Influenza A (H1N1) infections in 1915-1917[8], the more recent Influenza A (H1N1) infections in 2009/2010[9], and more importantly here, SARS-CoV infections in 2003[10]. A systematic review and exploratory meta-analysis performed in 2014 identified 32 studies of SARS coronavirus infection and severe influenza[7]. These studies involved 699 treated patients and 568 untreated “controls” (and 60 patients with unknown status). The review revealed evidence for a consistent reduction in mortality upon plasma therapy. Furthermore, exploratory *post hoc* meta-analysis showed a significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45; with limited heterogeneity: $I^2 = 0\%$)[7].

Convalescent plasma for prophylaxis rather than for treatment of viral respiratory diseases may be considered as well[6]. Such plasma may also be pooled and fractionated into hyper immune IgG and has been used with success to treat severe influenza A (H1N1) infection[117]. Although of obvious interest, these approaches for COVID-19 are not within the scope of this review, as the former does not address treatment, and the latter requires complex manufacturing steps and therefore not operational immediately.

## Convalescent plasma to treat SARS-CoV infected patients

In addition to being both highly pathogenic coronavirus with lung tropism, SARS-CoV-2 and SARS-CoV have been recently found to bind to the same entry receptor (ACE2) with similar affinity[12]. Furthermore, SARS-CoV polyclonal Ab inhibit SARS-CoV-2 spike glycoprotein (S) - mediated entry into cells. To reduce the risk of confusion with SARS-CoV-2, SARS-CoV will be indicated as SARS-CoV (1) throughout this manuscript.

SARS-CoV (1) convalescent plasma has been shown to contain neutralizing Ab against the involved virus[13].Furthermore, neutralizing Ab elicited by primary infection of SARS-CoV (1) can protect mice from re-infection[14]. Very recently, similar findings have been reported in monkeys regarding SARS-CoV-2[15]. Importantly, passive intra-peritoneal transfer of such SARS-CoV(1) Ab to naïve mice can prevent SARS-CoV(1) replication in the respiratory tract[14].

The above mentioned review identified 8 observational studies at moderate to high risk of bias that reported improved mortality after SARS-CoV (1) – infected patients received various amount of convalescent plasma[7]. Notably, a small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p=0,049)[16]. Each patient received 200 to 400 ml of plasma. Also, a case series including 80 treated patients reported an overall mortality rate of 12,5% in severe deteriorating SARS-CoV (1) - infected patients while the overall SARS-related mortality rate in Hong-Kong was 17% during the SARS epidemic in 2003[10]. The mean volume of plasma infused was 279 + 127 ml (range 160-640 ml). Interestingly, a subgroup analysis found that those treated with a PCR positive but seronegative for SARS-CoV-1 has a significantly better outcome (i.e. discharge by day 22 vs after day 22 or death) than those who were seropositive at the time of plasma infusion (61% vs 21%, $p<0.001$). Similarly, those receiving convalescent plasma before (versus after) 14 days after onset of symptoms were found to have a better outcome. In multivariate analysis, the time of convalescent plasma was reported to stay significant.

Overall, these findings favor an early administration during the infectious course, at a time where pathology may be driven mainly by viral replication. Lastly, and to the best of our knowledge, at least one study evaluating convalescent plasma to treat SARS-CoV-2 infected patients is underway in China[17].

## Convalescent plasma adverse events

None of the studies analyzed in the 2015 systematic review reported serious adverse events, although reporting of such events was most certainly not comprehensive. In a convalescent plasma trial for Ebola disease we contributed to in 2015, no serious adverse events were reported in 99 patients (minor adverse events were observed 8% of patients, mostly an increase in temperature (5%) and/or itching or skin rash (4%))[18]. Notably, 2 case reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been reported in a patient with Ebola disease[19] and patient with MERS-CoV[20]. In both cases, transfused plasma were found free of anti-HLA or anti-HNA Ab.

## Ab-mediated immunopathology in CoV diseases

Although these last observations of TRALI appear isolated, the issue of potential toxicity associated with convalescent plasma needs to be addressed carefully. SARS-CoV-2 infected patients, as well as SARS-CoV (1) and MERS-CoV patients exhibit acute lung injury (ALI), that may evolve into acute respiratory disease syndrome (ARDS) and death. Such ALI is driven by acute inflammation through mechanisms that remain elusive.

Experimental studies as well as observations in humans suggest that at least initially in the course of SARS-CoV(1) - associated disease, the immune response, notably Ab-mediated, may aggravate ALI by skewing inflammation-resolving responses[21]. Such an Ab-dependent enhancement (ADE) has been suspected in a large variety of diseases[22]. However, with the notable exception of secondary dengue as well as dengue and respiratory syncytial virus (RSV) vaccinations, observations were made in the majority of cases *in vitro* or in animal models and limited evidence from epidemiological series or pathophysiology studies in humans have been reported so far. Heterotopic and/or non (i.e. insufficiently) - neutralizing Ab have been suggested to be contributive. The potential role of such Ab in elderly patients, previously exposed to a variety of coronavirus, is unknown but may contribute to the severity of COVID-19 in this population.

Experimental MERS-CoV data in rabbits suggest that failing to develop neutralizing Ab (or waning titers at distance of infection) may be a risk factor for severe lung disease upon re-exposure to MERS-CoV[23]. From a mechanistic perspective, non-neutralizing Ab may favor a more efficient viral uptake into the

target cell in Fc-gamma or complement-mediated binding leading to enhanced replication and pathogenicity[24]. Furthermore, and as reported with inactivated RSV vaccination, a Th2-type immunopathologic responses upon rechallenge has been described in a mouse model following vaccination with an inactivated SARS-CoV(1) vaccine[25].

## Early vs late Ab responses in CoV diseases

Peak in viral load in SARS patients has been reported to coincide with the first appearance of an Ab response[26]. *In vitro*, higher concentration of Ab collected from SARS-CoV(1) -infected patients (i.e. non-convalescent) facilitated SARS-CoV(1) infection and induced higher levels of virus-induced apoptosis[27]. Importantly, this phenomenon occurred via anti-spike (S) Ab that mediated ADE, but not via anti-nucleocapsid (N) Ab[21,28]. A possibly relevant observation is that temporal changes in S-specific and N-specific neutralizing Ab responses may differ significantly in patients who have either recovered from or succumbed to SARS-CoV(1) infection[29]. In comparison to patients who subsequently died, recovered patients had a delayed but sustained increase in (serum) neutralizing Ab titers with an increasing contribution of anti N Ab (not observed in patients that subsequently died). Increasing Ab affinity is most probably occurring as well. Lastly, long-term persistence of robust Ab (and cytotoxic T cell responses) has been reported in patients infected with SARS CoV-1 (1)[30]. Interestingly, very recent data in COVID-19 patients indicates seroconversion occurring after 6-12 days, but not followed by rapid decline in viral load[31]. This later finding is compatible with a suboptimal endogenous early Ab-response with regard to SARS-CoV-2 replication.

Taken together, these findings suggest that the absence of reported serious adverse effects associated with convalescent plasma may be, at least in partly, in relation with a different quality of Ab in convalescent patients versus earlier during the acute phase of the disease. An appropriate assessment of the Ab response in convalescent patients with a requirement for the presence of an anti-SARS-Cov-2 neutralizing Ab titer at an adequate level in the collected plasma will be an important prerequisite. Furthermore, one may hypothesis that early administration of convalescent plasma containing polyclonal neutralizing Abs may inhibit viral entry and replication (as recently suggested in vitro[12]) and consequently blunt an early pro-inflammatory pathogenic endogenous Ab response. In all cases, a close monitoring of treated patients with convalescent plasma to verify for any unintended side effects, in particular evidence of inflammatory flare-up, will be necessary.

## Plasma collection in COVID-19 convalescent patients

Convalescent donors may be identified through various means, including national disease specific cohorts when those exists, hospitals taking care of such patient, practitioners treating outpatients or

specific social messaging. In convalescent clinically diagnosed SARS-CoV(1) patients 81.2% (311 of 383 patients) were tested positive for serum SARS-CoV(1) IgG[32]. Misdiagnosed disease among the seronegative patients was not excluded in this study. SARS-CoV(1) IgG and neutralizing Ab have been found to peak at 4 months and then began diminishing, reaching undetectable levels in 25.6% (IgG) and 16.1% (neutralizing Ab) of 56 patients at 36 months of follow-up[33]. Another study in 19 recovered SARS-CoV(1) patients showed a serum mean neutralizing activity of 96% (S.D: ≈3%) at 3 months, thereafter declining to 70% (SD: ≈20%) at 12 months and 48% (SD: ≈25%) at 36 months, at which point 17/19 exhibited persisting neutralizing activity. Control blood donors had a neutralizing activity of 1,7% (s.d. 0.6%)[34]. Lastly, a geometric mean neutralizing titer of 1/60 (from 1/12 to 1/512) was measured in 87 SARS-CoV(1) convalescent sera collected between d35 and d180 after the onset of disease[13], with no significant variation between d35 and d180.

Furthermore, the titers in convalescent patients have been found to correlate with the initial viral load and were independently associated with severity of the viral illness both in H1N1 and MERS-CoV patients[35,36]. Lasting seroconversion in a cohort of 42 MERS-CoV infected patients was found in 0/3 asymptomatic patients, 3/5 symptomatic patients without pneumonia, 15/16 with pneumonia without respiratory failure and 9/9 with pneumonia having progressed to respiratory failure[36]. To what extent these findings are relevant to SARS-CoV-2 convalescent patients is to be established. Nevertheless, focusing recruitment efforts on COVID-19 convalescent patients having experienced significant clinical symptoms may be relevant.

Convalescent patients eligible for plasma donation should be invited to undergo plasma apheresis, pending general eligibility such as (in France) an age between 18 and 65 years old and weight not less than 50 kg. We recommend plasma collection not earlier than 14 to 28 days after symptoms resolution. In most countries, eligibility criteria call for such a delay between COVID-19 disease cessation and blood donation to ensure the absence of infectiousness. Furthermore, and as mentioned earlier, such spacing may favor Ab with increased affinity and therefore hopefully an optimized convalescent plasma.

The convalescent donors should undergo standard pre-donation assessment to insure compliance with current regulations regarding plasma donation in the involved jurisdiction (in France:[37]) including standard microbiological assessment, as well as anti-HLA Ab detection in women with children.. Furthermore, and importantly, an appropriate anti-SARS-Cov-2 neutralizing Ab activity titer should be verified. Based on prior SARS-CoV (1) studies[13], we suggest a titer of >= 1/40 as assessed by cytopathic effect - based virus neutralizing tests (described in[38]). If found to be inadequate, the collected plasma may be oriented towards standard transfusion use, for example in trauma patients.

Prior experience with H1N1 convalescent donors highlight a number of practical limitations in convalescent plasma collection programs to be kept in mind when planning large-scale collection[39]. The response rate to telephone and other means of recruitment may be low. Furthermore, further obstacles may preclude successful apheresis donations, among which insufficient neutralizing Ab titers, failure to meet blood donation eligibility criteria, failed laboratory tests, insufficient neutralization Ab titers, and inability to make the apheresis appointment. For those who do not wish to undergo plasma apheresis or in a setting with limited access to plasma apheresis, a whole blood donation may be considered however with drawbacks such the low plasma volume collected and the inability to repeat donations in short time intervals.

The apheresis procedure is to be performed per standard procedures. In particular, the volume of collected plasma may be adapted to gender, height and weight. A mean of approximately 600 ml of plasma may undergo pathogen reduction treatment. At least two pathogen reduction technologies have has been found to adequately inactivate MERS-CoV in blood products[40,41]. Although formally untested as of now, one can reasonably assume approaching efficacy regarding SARS-CoV-2 in plasma. After an earlier report reporting a slight reduction in Ebola virus IgG and neutralizing activity in a convalescent plasma after Intercept pathogen reduction[42], a recently published larger study found that Intercept treatment did not significantly reduce Ebola virus IgG titers or neutralizing activity[43].

Presence of infectious viremia in convalescent patients is not expected, despite a recent report of positive RT-PCR recurrence on repeat throat swabs in in 4 asymptomatic patients 5 to 13 days after hospital discharge[44]. In addition to being an isolated observation as of now, establishing whether viral RNA detected by PCR in such a setting is associated with infectious virus remains to be established. Furthermore, current knowledge regarding viremia kinetics is not in favor of viremia occurring in convalescent, i.e. asymptomatic, patients. Lastly, previous studies with coronavirus or influenza infection convalescent plasma do not report adverse events suggestive of discernable “re”infection in patients acutely infected at time of transfusion. To verify these findings, we recommend that the absence of SARS-CoV-2 RNA in the collected plasma be checked before infusion, perhaps only early on.

As mentioned earlier, convalescent donor’s candidate for plasma donation should undergo eligibility screening just like any other donor, including eligibility criteria pertaining to prior COVID-19 disease. Such donors will therefore be eligible for standard blood donation. This consideration may result in questioning additional safety measures such as verifying the absence of viral RNA and/or pathogen reduction if not performed usually on blood products in the given jurisdiction. In France, plasma for

transfusion currently undergoes pathogen reduction or quarantine for at least 2 months until a renewed microbiological assessment at time of subsequent plasma donation.

Once treated and qualified, plasma should be cryopreserved (in 200 to 250 ml units) and made available for clinical use. Current regulation in France authorizes a plasma donation up to every 2 weeks, shorter intervals are authorized elsewhere. We suggest that consenting donors undergo 3 donations with 2 week intervals between each donation at least. In case of acute shortage of convalescent plasma associated with encouraging initial clinical results, exemptions for some of plasma donation eligibility criteria's, may be considered and requested to competent authority. In France, such criteria could include age =< 65, weight < 50 kg, travel-related ineligibilities, or donation interval no less than 15 days.

## Evaluating the safety and efficacy of COVID-19 convalescent plasma

Adequately assessing safety and efficacy of such an approach is essential. As mentioned earlier, all prior studies involving convalescent plasma for the treatment of viral diseases with lung tropism are poorly controlled[7]. A randomized trial, assessing safety and efficacy upfront, would be the most scientifically-sound approach, and is therefore the preferred option. Setting up such trials in transient acute infectious epidemics settings is quite a challenge[45]. A case-control study would be less satisfactory, but may still be a reasonable option if the controls are closely comparable to the cases for all known and unknown factors impacting the study endpoint. In that respect, adequate control patients may be eligible patients but for whom ABO compatible plasma is unavailable. However, adjustments may be necessary to take into account potential center, date, recipient/donor ABO groups[46], and consenting/non–consenting related effects.

Whatever the format of the study, we suggest that convalescent plasma be administered early in the course of the disease in patients at high risk of subsequent deterioration (i.e. age above 70 or dependence on oxygen with a baseline oxygen saturation of less than 94%). As discussed earlier, administration before SARS-CoV-2 seroconversion may be critical. Early treatment should be favored. Based on the most recent data available[31], initiating treatment no later than day 5 may be the most appropriate. The main study outcome in such patient population should be survival whereas secondary outcomes could be the absence of clinical deterioration (i.e. no need to transfer to an intensive care unit) and shortening of hospitalization. We suggest the transfusion at day 5 of two plasma units of 200 to 250 ml each in patients weighing between 50 and 80 kg, volume to be adjusted for patients weighing outside this range. Infusion should be at a slow rate and under close monitoring, notably to identify and treat circulatory overload occurrence or other transfusion-related immediate side effects. Close monitoring should obviously be maintained after transfusion to detect any further

unintended side effects, in particular evidence of increased inflammatory in the lungs or systemically. A repeat infusion of 2 units 24 to 48 hours later may be considered after verifying adequate tolerance in a first group of treated patients.

## Conclusion

COVID-19 requires urgent development of successful curative treatment modalities. Convalescent plasma may be one of them. Making such plasma available and rigorous clinical evaluation of such an approach is a priority in a number of jurisdictions. In Europe, a coordinated and complementary approach involving a large number of blood establishments and clinical teams is actively promoted by the European Blood Alliance[47].

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