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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 XIX<sup>th</sup> 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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