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Convalescent Plasma in Covid-19: Possible Mechanisms of Action

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Key Words

Coronavirus, COVID-19, SARS-Cov-2, convalescent plasma, cytokines, intravenous immunoglobulins, neutralizing antibodies, ACE-2 receptor.

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Highlights

- Coronavirus disease 19 (COVID-19) is an emerging viral threat with major repercussions for public health.

- There is not specific treatment for COVID-19.

- Convalescent plasma (CP) emerges as the first option of management for hospitalized patients with COVID-19.

- Transference of neutralizing antibodies helps to control COVID-19 infection and modulates inflammatory response

- Other plasma components may enhance the antiviral and anti-inflammatory properties of CP.

Abbreviations

2019-nCoV: 2019 novel coronavirus.

ACE-2: Angiotensin converting enzyme-2.

ADE: Antibody-dependent enhancement.

BAFF: B cell–activating factor.

BCR: B-cell receptor.

COVID-19: Coronavirus disease 2019.

CP: Convalescent plasma.

DCs: Dendritic cells.

HIV: Human immunodeficiency virus.

ICU: Intensive care unit.

IgG: Immunoglobulin G.

IgM: Immunoglobulin M.

IVIg: Intravenous immunoglobulin

MERS: Middle East respiratory syndrome.

MERS-CoV: MERS coronavirus.

NAbs: Neutralizing antibodies.

NAT: Nucleic acid test.

S1-RBD: Spike1-receptor binding protein

SARS: Severe acute respiratory syndrome coronavirus.

SARS-CoV: SARS coronavirus.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible of the coronavirus disease 2019 (COVID-19) pandemic. Therapeutic options including antimalarials, antivirals, antibiotics and vaccines are under study. Meanwhile the current pandemic has called attention over old therapeutic tools to treat infectious diseases. Convalescent plasma (CP) constitutes the first option in the current situation, since it has been successfully used in other coronaviruses outbreaks. Herein, we discuss the possible mechanisms of action of CP and their repercussion in COVID-19 pathogenesis, including direct neutralization of the virus, control of an overactive immune system (i.e., cytokine storm, Th1/Th17 ratio, complement activation) and immunomodulation of a hypercoagulable state. All these benefits of PC are expected to be better achieved if used in non-critically hospitalized patients, in the hope of reducing morbidity and mortality.

1. Introduction

Viruses of the *Coronaviridae* have a positive-sense, single strand, RNA structure with 26 to 32 kilobases length [1]. Coronaviruses have been recognized in numerous avian hosts and in several mammals, such bats, camels, mice, cats, dogs and more recently in scaly anteaters [2–4]. Most of Coronaviruses are pathogenic to humans but they produce mild symptoms or asymptomatic infections. However, in the last two decades two lethal viruses have emerged within this family: the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) [5], and the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) [6]. These are characterized by severe fever (85%), non-productive cough (69%), myalgia (49%) and dyspnea (42%), with a high frequency of admission to intensive care unit (ICU) [5,7].

In December 2019, a new member of the Coronaviridae family associated with severe pneumonia was detected in Wuhan, China [8]. Patients showed similar clinical findings to SARS-CoV and MERS-CoV given by high fever, dyspnea, and chest radiographs revealing invasive multilobed lesions [9,10]. The virus was initially termed as 2019 novel coronavirus (2019-nCoV) [8], and it is currently known as SARS-CoV-2 producing the coronavirus disease 2019 (COVID-19). The origin of the virus is unknown, however, a recent study showed that the virus shares 88% identity with bat-derived SARS-like coronaviruses named bat-SL-CoVZC45 and bat-SL-CoVZXC21, suggesting that bats are the most likely reservoir [4]. Interestingly, phylogenetic analysis revealed that SARS-CoV and MERS-CoV were close to COVID-19 in about 79% and 50%, respectively. Recently, it has been discussed that the similar sequence of the virus with human proteins could be deleterious and associated

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with autoimmune phenomena [11,12]. Although the current situation argues for prompt vaccination strategies, it has been suggested that it would be safer to test cross-reactivity of different viral antigens with those in humans to reduce the probability of autoimmune reactions (i.e., molecular mimicry), especially in individuals with genetic background for autoimmunity [11,13].

Currently, treatment of disease is challenging and the lack of clinical evidence with antiviral agents is the rule. Therapeutic schemes with Lopinavir/Ritonavir failed to prove reduction in overall mortality [14]. A recent randomized controlled trial with Hydroxychloroquine, showed reduction in body temperature and cough remission in the intervention group compared with controls [15]. However, the small sample size and the short period of follow up, preclude conclusions about its efficacy. Other study suggested that Azithromycin plus Hydroxychloroquine may reduce viral load, nonetheless, the clinical response associated with this approach was not evaluated and remains to be defined [16]. This combination was recently associated to worse outcomes when Hydroxychloroquine was administrated at high doses (QTc elongation and higher rates of lethality) [17]. Thus, there is not an effective nor safe medication for the management of COVID-19.

Given the lack of evidence for treatment of COVID-19 and vaccines, classical and historical interventions have remerged as options for the control of disease. That is the case of convalescent plasma (CP), a strategy of passive immunization that has been used in prevention and management of infectious diseases since early 20th century [18]. The CP is obtained using apheresis in survivors with prior infections caused by pathogens of interest in whom antibodies against the causal agent of disease are developed. The major target

is to neutralize the pathogen for its eradication [19]. Given its rapid obtaining, CP has been considered as an emergency intervention in several pandemics, including the Spanish flu, SARS-CoV, West Nile virus, and more recently, Ebola virus [20–24]. CP early administered after symptoms onset showed a reduction in mortality compared with placebo or no therapy in severe acute respiratory infections of viral etiology like influenza and SARS-CoV, however, a similar response in Ebola disease was not observed [20,25].

During apheresis, in addition to neutralizing antibodies (NAbs), other proteins such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins and other undefined proteins are obtained from donors [26]. In this sense, transfusion of CP to infected patients may provide further benefits such as immunomodulation via amelioration of severe inflammatory response [27]. The latter is the case of COVID-19 in which an over-activation of the immune system may come with systemic hyper-inflammation or "cytokine storm" driven by IL-1β, IL-2, IL-6, IL-17, IL-8, TNF and CCL2. This inflammatory reaction may perpetuate pulmonary damage entailing fibrosis and reduction of pulmonary capacity [28,29]. Herein, we propose the likely beneficial mechanisms of administering CP to patients with COVID-19 and provide a summary of evidence of this strategy in the current pandemic. At the time of writing this article there were 44 clinical trials registered at www.clinicaltrials.gov, including ours (NCT04332835, NCT04332380), in which the role of CP in COVID-19 will be evaluated.

2. Production and composition

2.1. Historical perspective

The principle of CP infusion was established in 1880 when it was shown that immunity against diphtheria relied on existing antibodies in blood from animals intentionally immunized with non-lethal doses of toxins, that could be transferred to animals suffering from active infections [30,31]. Then, it was recognized that immune plasma not only neutralizes the pathogen, but also provides passive immunomodulatory properties that allow the recipient to control the excessive inflammatory cascade induced by several infectious agents or sepsis [26,31]. In the early 1950s, purification and concentration of immunoglobulins from healthy donors or recovered patients, provided an option to treat serious infectious diseases as well as immune conditions including primary immunodeficiencies, allergies, and autoimmune diseases [30,32,33].

Several convalescent blood products such as intravenous immunoglobulins (IVIg) and polyclonal or monoclonal antibodies have been developed to treat infectious conditions [18]. However, in situations of emergency, they are difficult and expensive to produce, and may not yield an appropriate infectious control. Thus, the use of CP has been widely used in different outbreaks as the first therapeutic option given the lack of effective medications or vaccines and often as last chance or experimental treatment [26].

From the Spanish influenza to the current pandemic caused by COVID-19, it has been observed that the use of CP significantly reduces case fatality rates. That is the case of Influenza A (H1N1) pdm09, Spanish Influenza A (H1N1) and SARS-CoV infections in which the use of CP was associated to reduction in fatality rates, mortality (Table 1) [5,34–45], and mild adverse events (Table 2) [25,46–49]. Furthermore, the use of CP in other coronaviruses such as SARS-CoV, reduced days of hospital stay in critically ill patients [42,50]. In relation to

the use of mechanical ventilation, in Influenza A (H1N1) pdm09, and avian influenza A (H5N1), administration of CP reduced the duration of invasive ventilation [47,51]. In addition, it has been described that the use of CP in SARS-CoV and avian influenza A (H5N1) decreased the viral load in the respiratory tract [46,49]. Currently, CP used in patients with COVID-19 demonstrated to reduce viral load and improve clinical condition [38,39]. However, it is necessary to conduct randomize controlled trials to confirm the usefulness of this intervention, including hospitalized patients with mild symptoms and those in ICU.

The safety of the use of CP is another issue that has been historically relevant in epidemics. Currently, evidence exists of the safety of CP in situations of emergency (Table 2). In epidemics of Influenza A (H1N1), SARS-CoV and MERS-CoV, studies did not find any adverse event associated to CP administration. In the case of Ebola, CP administration was associated with mild adverse reactions such as nausea, skin erythema, and fever [25]. In COVID-19, reports have shown that administration of CP is safe, and it was not associated with major adverse events. Thus, due to tolerability and potential efficacy CP is good candidate to be evaluated as a therapeutic option to control the current pandemic.

2.2. Acquisition and plasma composition

The convalescent donors must undergo standard pre-donation assessment to ensure compliance with current regulations regarding plasma donation [52]. Currently, convalescent donors between 18 and 65 are considered as subjects

without infectious symptomatology and a negative test for COVID-19 after 14 days of recovery. These tests must be repeated 48 hours later and at the moment of donation [39,52]. Donors from endemic areas for tropical diseases (e.g., malaria) should be excluded. In addition to molecular tests, it is critical to recognize the emotional situation, to explore susceptibilities, and guarantee not exploitation of donors [53].

Apheresis is the recommended procedure to obtain plasma. This procedure is based on a continuous centrifugation of blood from donor to allow a selective collection plasma. The efficiency of this technique is around 400 mL to 800 mL from a single apheresis donation. This amount of plasma could be storage in units of 200 mL or 250 mL, and frozen within 24 hours of collection to be used in further transfusions [54].

As CP production requires high quality standards, it must be free of any infection, so tests for human immunodeficiency virus (HIV), hepatitis B, hepatitis C, syphilis, human T-cell lymphotropic virus 1 and 2, and *Trypanosoma cruzi* (if living in an endemic area) should be carried out [52,55]. In this sense, the nucleic acid test (NAT) for HIV and hepatitis viruses is mandatory to guarantee the safety of recipients [56]. Other protocols suggest the inactivation of pathogens with riboflavin or psoralen plus exposure to ultraviolet light to improve safety of CP [57].

There is not a standard transfusion dose of CP. In different studies for coronaviruses the administration of CP range between 200 mL to 500 mL in single or double scheme dosages (Table 1). Currently, the recommendation is to administrate 3 mL/kg per dose in two days [54]. This strategy facilitates the

distribution of plasma units (250 mL per unit) and provide a standard option of delivery in public health strategies.

Composition of CP is variable and include a wide variety of blood derive components. Plasma contains a mixture of inorganic salts, organic compounds, water, and more than 1000 proteins. In the latter we found albumin, immunoglobulins, complement, coagulation and antithrombotic factors among others [58] (Fig. 1A). Interestingly, it is supposed that plasma from healthy donors provides immunomodulatory effects via de infusion of anti-inflammatory cytokines, and antibodies that blockade complement, inflammatory cytokines and autoantibodies [27]. These factors may influence the immunomodulatory effect of CP in patients with COVID-19 (see below for details).

3. Antiviral mechanisms

NAbs are crucial in virus clearance and have been considered essential in protecting against viral diseases. Passive immunity driven by CP can provide these NAbs that restrain the infection. The efficacy of this therapy has been associated with the concentration of NAbs in plasma from recovered donors [25]. In SARS-CoV and MERS was discovered that NAbs bind to spike1-receptor binding protein (S1-RBD), S1-N-terminal domain and S2, thus inhibiting their entry, limiting viral amplification [59]. Moreover, other antibody-mediated pathways such as complement activation, antibody-dependent cellular cytotoxicity and/or phagocytosis may also promote the therapeutic effect of CP.

Tian et al. [60], showed through ELISA and BLI that one SARS-CoV-specific antibody, CR3022, bind with COVID-19 RBD and more importantly this antibody

did not show any competition with angiotensin converting enzyme-2 (ACE-2) for the binding to COVID-19 RBD. The RBD of COVID-19 varies broadly from the SARS-CoV at the C-terminus residues. Although this difference does not enable COVID-19 to bind ACE-2 receptor, does influence the cross-reactivity of NAbs [60].

A pseudotyped-lentiviral-vector-based neutralization assay to measure specific NAbs in plasma from recovered patients with SARS-CoV-2 showed variations in NAbs titers, approximately 30% of patients did not develop high NAbs titers after infection [61]. These variations are associated with age, lymphocyte count, and C reactive protein levels in blood, suggesting that other components from plasma contribute to the recovery of these patients.

In plasma, in addition to NAbs, there are other protective antibodies, including immunoglobulin G (IgG) and immunoglobulin M (IgM). Non-NAbs that bind to the virus, but do not affect its capacity to replicate, might contribute to prophylaxis and/or recovery improvement [54].

SARS-CoV-2 infection induces IgG antibodies production against N protein that can be detected at day 4 after the onset of disease and with seroconversion at day 14 [62]. In SARS infection 89% of the recovered patients, showed IgG-specific and NAbs 2 years post infection [63]. Moreover, the highest concentration of IgM was detected on the ninth day after the onset of disease and class switching to IgG occurred in the second week [64].

Shen et al. [38], showed that recovered donors from COVID-19 infection had SARS-CoV-2–specific antibody titers ranging between 1.800 and 16.200 and NAbs titers were between 80 and 480. The plasma obtained from the donors

and transfused in the recipients on the same day, lead to viral load decreased. After transfusion of CP, the titers of IgG and IgM in the recipients increased in a time-dependent manner. Moreover, presence of NAbs in the recipients played a vital role in the restriction of viral infection. Another study evaluated the kinetics of SARS-CoV-2-specific NAbs development during the course of the disease. The titers of NAbs in patients infected with SARS-CoV-2 were low before day 10 post-disease onset and then increased, with a peak 10 to 15 days after disease onset, remaining stable thereafter in all patients [64].

4. Immunomodulation

4.1. F(ab´)2 mechanisms

Historically, administration of IVIg has been one of the critical interventions in patients with autoimmune diseases as well as in autoinflammatory diseases, transplantation (i.e., chronic graft vs. host disease after marrow transplantation), primary and secondary immunodeficiency, hematologic malignancies among other conditions. Preparation of IVIg includes anti-idiotypic antibodies that blockade autoreactive recipient antibodies [36,65]. This reaction is critical to control autoantibodies in patients with autoimmune diseases. In this sense, a recent report in patients with COVID-19, showed that critically ill patients exhibited positivity for anti-cardiolipin IgA antibodies as well as for anti–β2-glycoprotein I IgA and IgG antibodies [66]. This evidence may suggest that CP-COVID-19 may neutralize this type of autoantibodies reducing the odds of suffering from thrombotic events (i.e., antiphospholipid syndrome-like disease), especially in critically ill patients. In the same line, a recent report of a patient

with Sjögren's syndrome and COVID-19 successfully treated with CP may suggest that this strategy is safe and effective in autoimmune conditions [37].

In addition, some antibodies inhibit complement cascade (i.e., C3a and C5a), and limit the formation of immune complexes (Fig. 1C) [67,68]. Complement-deficient mice with induced SARS-CoV infection showed high viral titers, secretion of inflammatory cytokines and chemokines, and immune cell infiltration within the lung. These results suggest that complement activation largely contribute to systemic inflammation and migration of neutrophils to the lungs, perpetuating tissue damage [69]. Additional studies have shown that IgG transferred by plasma neutralize cytokines such as IL-1β and TNFα [70]. In this sense, passive immunity by infusion of CP-COVID-19 may limit the inflammatory cascade driven by pathogenic antibodies, as well as the cellular damage induced by the complement cascade activation in excessive inflammatory environments.

Antibody-dependent enhancement (ADE) is a mechanism in which the intensity of infection increases in the presence of preexisting poorly NAbs, favoring the replication of virus into macrophages and other cells through interaction with Fc and/or complement receptors [71]. This phenomenon is used by feline coronaviruses, HIV and dengue viruses, use to take advantage of prior anti-viral humoral immune response to effectively infect host target cells [72,73]. *In vitro* assays with human promonocyte cell lines demonstrated that SARS-CoV ADE was primarily mediated by antibodies against spike proteins, significantly increasing the rate of apoptosis in these cells [73]. This is of major interest in regions in which coronaviruses are endemic. Vaccines development should consider this phenomenon in patients with COVID-19, and administration of CP-

COVID-19 in these areas should be conducted with caution since ADE may emerge as a harmful reaction in patients with active infection [74]. If one suspects of this phenomenon following CP-COVID-19 administration, clinicians must promptly notify the health authorities and evaluate the safety according to endemic coronaviruses in the region.

4.2. Fc mechanisms

FcRn is a critical regulator of IgG half-life. This receptor works by preventing degradation and clearance of IgG, by a pinocytotic mechanism that allow antibody circulation within the cell for its posterior excretion [65,75]. The FcRn inhibitor rozanolixizumab showed reduction of IgG concentrations in a phase 1 study [76], and it proved to be critical in IVIg catabolism in common variable immunodeficiency patients [77]. It has been demonstrated that saturation of this receptor by IVIg may account as the most likely mechanism to clear autoantibodies in autoimmune conditions by shortening their lifetime [78–80]. Whether antibodies play a critical role in COVID-19 pathogenesis stills remain to be elucidated, however, the saturation of FcRn may provide an additional immunomodulatory pathway in patients receiving CP.

Fcγ receptors are found in about all immune cells. These receptors are critical factors in modulating or inhibiting activity of immune cells, including lymphocytes [75]. Fcγ receptor activation by IgG induces the upregulation of FCγRIIB which has been associated with inhibitory effects. This was demonstrated in B cells, where the upregulation of FCγRIIB was associated with treatment efficacy for acute rejection after kidney transplantation [81], and was

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a key determinant for IVIg response in patients with Kawasaki disease [82]. It has been suggested that sialylation of this receptor is critical for inhibitory effects in immune cells [83]. However, the study of Th17 cells in autoimmune encephalomyelitis model revealed that this process is dispensable for the immunomodulatory effect of IVIg treatment [84]. Despite these results, CP infusion may help the modulation of immune response *via* Fcγ receptors, and merits attention in the current management of COVID-19.

4.3. Dendritic cells

Dendritic cells (DCs) are key regulators of innate immunity and work as specialized antigen presenting cells. *In vitro* studies have shown that administration of IVIg may abrogate maturation of DCs, as well as a reduction in the production of IL-12. Interestingly, the production of IL-10 was enhanced [85]. In the study conducted by Sharma et al. [86], authors found that IVIg induced the production of IL-33 that subsequently expands IL-4-producing basophils. In this line, other study found that IVIg could promote the production of IL-4 and IL-13 which correlated with levels of IL-33 [87]. A Th2 cytokine-mediated downregulation of FcγRIIa and IFN-γR2 was suggested to be the most likely mechanisms for this phenomenon. Recently, it was found that IVIg activates β-catenin in an IgG-sialylation independent manner, which is critical for reducing inflammation [88].

Down regulation of HLA-II and costimulation molecules such CD86, CD80, and CD40 have been reported in DCs after stimulation with IVIg [85]. In patients with systemic lupus erythematosus, which show a high proinflammatory environment, administration of IVIg abrogated IFNα-mediated maturation

[89,90]. All together, data suggest that infusion of plasma from recovered COVID-19 donors may enhance anti-inflammatory properties of DCs, which could be critical in phases of excessive inflammatory stimuli in patients with COVID-19.

4.4. T cells

Despite the ability of enhancing Th2 *via* IL-33 in DCs [87], it has been described that IVIg modulates the balance between CD4+/CD8+ T cells, as well as promoting proliferation and survival of Tregs. Treatment with IVIg seems to reduce antigenic presentation of T cells *via* the modulation and inhibition of DCs. This process was independent of FcγRIIB [91], and other reports showed that reduced activation of T cells was independent of IgG sialylation, monocytes or B cells [92].

In addition, patients treated with IVIg showed a reduction in Th1 cells and low levels of IFNγ and TNFα with the increase of Th2 cytokines such as IL-4 and IL-10 [93]. Clinically, it has been demonstrated that patients with Influenza A (H1N1) treated with CP exhibited a reduction of IL-6 and TNFα [94], with an increase of IL-10 [46]. This support the notion of an anti-inflammatory effect of CP in subjects with acute viral infections.

Cytotoxicity is also regulated by administration of IVIg. In the study of Klehmet et al. [95], authors found that patients with chronic inflammatory demyelinating polyneuropathy treated with IVIg, showed reduction in CD8+ T cells with high levels of CD4+ T effector memory and T central memory cells. In another study, IVIg proved to reduce the activation of CD8+ T cells associated with a T-cell

receptor blockade, thus reducing the interaction between effector and target cells [96]. In subjects with Kawasaki disease, a high proportion of CD8$^+$ was associated with resistance to IVIg, thus suggesting that these cells could be considered a predictive factor for IVIg response [97].

Recent studies have shown that IVIg reduces the proliferation of Th17 cells, as well as decreases the production of IL-17A, IL-17F, IL-21, and CCL20 [98,99]. In other study, IVIg appeared to modulate the Th17/Treg ratio which is associated with recurrent pregnancy loss [100]. It is plausible that CP may act in a similar way in patients with COVID-19 [28,29] (Fig. 1C).

4.5. B cells

B cells are critical in adaptive immunity *via* production of antibodies and cytokines. In patients with demyelinating polyneuropathy, administration of IVIg was associated with overexpression of FcγRIIB receptors on B cells [101,102]. IVIg abrogated TLR-9-dependent B cell responses. This was associated with IVIg inhibitions of NF-κB signaling pathway, reduction of CD25 and CD40 expression, and reduction of IL-6 and IL-10 production by B cells. This process seems to be regulated by SH2 domain–containing phosphatase 1 [103].

Proliferation and survival of B cells is mediated by the B cell–activating factor (BAFF). In the study conducted by Le Pottier et al. [104], authors found that IVIg contained NAbs for BAFF. This could explain the reduction in proliferation, as well as the increased rates of apoptosis of B cells. Regarding the latter process, it was found that anti-Fas (anti-CD95) antibodies, present in IVIg preparations, induced apoptosis in B cells [105].

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In DCs, downregulation of costimulatory molecules following administration of IVIg has been observed. This is similar to B cells which exhibited a reduction in antigen-presentation activity secondary to IgG internalization, in concordance with a reduced IL-2 production by T cells [106]. Moreover, IVIg administration modulates B-cell receptor (BCR) signaling. In the study of Séïté et al. [107], authors found that interaction between BCR and CD22 resulted in a down-regulation of tyrosine phosphorylation of Lyn and the B-cell linker proteins which resulted in a sustained activation of Erk 1/2 and arrest of the cell cycle at the G/1 phase.

These mechanisms may account for immunomodulation of the inflammatory response in COVID-19 secondary to CP administration. As showed above, recent reports suggest the production of antiphospholipid antibodies in patients with COVID-19 together with an antiphospholipid-like syndrome [66], and the regulation of this cascade could be critical to avoid deleterious outcomes in these group of patients (i.e., thrombosis, disseminated intravascular coagulopathy).

4.6. Other immune cells

The major immunological factor suspected to be associated with inflammation and lung damage in COVID-19 is the activation of macrophages. It has been suggested that patients with COVID-19 may suffer from a macrophage activation syndrome-like disease associated to innate immune migration to lung tissues [28]. In this context, the inhibition of this immunological pathway may help to control excessive cytokine production and prevent pulmonary damage

(i.e., fibrosis). This was recently supported by the study of Blanco-Melo et al. [108] who described an up regulation of chemokines for innate immune cells in ferrets as well as in patients with COVID-19. Interestingly, results suggest that this scenario mainly occurred in the first 7 days post infection, whereas at day 14th, other cytokines such as IL-6 and IL-1 persisted activated [108]. These data have critical therapeutic consequences.

In the study conducted by Kozicky et al. [109], authors found that macrophages treated with IVIg showed an increased production of IL-10, with a reduction in IL-12/23p40, thus suggesting the promotion of an anti-inflammatory macrophage profile. Although there is no evidence of macrophage pulmonary migration inhibition by IVIg, a study on induced peripheral neurotoxicity showed that this treatment reduced nerve macrophage infiltration in rats [110]. This observatios deserves attention in those patients treated with CP-COVID-19 since they may account for the positive results encountered in critically ill patients with COVID-19 [38,39]. In this line, we argue for CP-COVID-19 administration in early stages of diseases to prevent innate immune cells migration and avoid lung damage.

5. Conclusions

CP is a safe and potentially effective strategy for the treatment of emerging and re-emerging pathogens, especially in those scenarios without proved antiviral agents or vaccines. IVIg and CP shared similar mechanisms of action. The potential antiviral and immunomodulatory effects of CP are currently evaluated

in COVID-19. According to the physiopathology of COVID-19 severe patients should be privileged over critical ones reduce mortality and improve outcomes.

Acknowledgements

References

[1] Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol 2016;24:490–502. https://doi.org/10.1016/j.tim.2016.03.003.

[2] Cavanagh D. Coronavirus avian infectious bronchitis virus. Vet Res 2007;38:281–97. https://doi.org/10.1051/vetres:2006055.

[3] Ismail MM, Tang AY, Saif YM. Pathogenicity of turkey coronavirus in turkeys and chickens. Avian Dis 2003;47:515–22. https://doi.org/10.1637/5917.

[4] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–74. https://doi.org/10.1016/S0140-6736(20)30251-8.

[5] Nie Q-H, Luo X-D, Hui W-L. Advances in clinical diagnosis and treatment of severe acute respiratory syndrome. World J Gastroenterol 2003;9:1139–43. https://doi.org/10.3748/wjg.v9.i6.1139.

[6] Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in

Saudi Arabia. N Engl J Med 2012;367:1814–20.
https://doi.org/10.1056/NEJMoa1211721.

[7]   Phua J, Weng L, Ling L, Egi M, Lim C-M, Divatia JV, et al. Intensive care
        management of coronavirus disease 2019 (COVID-19): challenges and
        recommendations. Lancet Respir Med 2020.
        https://doi.org/10.1016/S2213-2600(20)30161-2.

[8]   Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel
        Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med
        2020;382:727–33. https://doi.org/10.1056/NEJMoa2001017.

[9]   Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial
        cluster of pneumonia associated with the 2019 novel coronavirus
        indicating person-to-person transmission: a study of a family cluster.
        Lancet 2020;395:514–23. https://doi.org/10.1016/S0140-6736(20)30154-
        9.

[10]   Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of
        patients infected with 2019 novel coronavirus in Wuhan, China. Lancet
        2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[11]   Shoenfeld Y. Corona (COVID-19) time musings: Our involvement in
        COVID-19 pathogenesis, diagnosis, treatment and vaccine planning.
        Autoimmun Rev 2020:102538.
        https://doi.org/https://doi.org/10.1016/j.autrev.2020.102538.

[12]   Kanduc D, Shoenfeld Y. On the molecular determinants and the
        mechanism of the SARS-CoV-2 attack 2020;Submitted.

[13]   Rojas M, Restrepo-Jiménez P, Monsalve DM, Pacheco Y, Acosta-
        Ampudia Y, Ramírez-Santana C, et al. Molecular mimicry and
        autoimmunity. J Autoimmun 2018;95:100–23.
        https://doi.org/10.1016/j.jaut.2018.10.012.

[14]   Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-
        Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med
        2020:In press. https://doi.org/10.1056/NEJMoa2001282.

[15]   Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of
        hydroxychloroquine in patients with COVID-19: results of a randomized
        clinical trial. MedRxiv 2020. https://doi.org/10.1101/2020.03.22.20040758.

[16]   Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al.
        Hydroxychloroquine and azithromycin as a treatment of COVID-19:
        results of an open-label non-randomized clinical trial. Int J Antimicrob
        Agents 2020:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.

[17]   Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et
        al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive
        Therapy for Patients Hospitalized With Severe Acute Respiratory
        Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical
        Trial. JAMA Netw Open 2020;3:e208857.
        https://doi.org/10.1001/jamanetworkopen.2020.8857.

[18] Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14:152–7. https://doi.org/10.2450/2015.0131-15.

[19] Burnouf T, Seghatchian J. Ebola virus convalescent blood products: where we are now and where we may need to go. Transfus Apher Sci 2014;51:120–5. https://doi.org/10.1016/j.transci.2014.10.003.

[20] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F-M, Lim WS, et al. 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. https://doi.org/10.1093/infdis/jiu396.

[21] Rojas M, Monsalve DM, Pacheco Y, Acosta-Ampudia Y, Ramírez-Santana C, Ansari AA, et al. Ebola virus disease: An emerging and re-emerging viral threat. J Autoimmun 2020;106:102375. https://doi.org/10.1016/j.jaut.2019.102375.

[22] Planitzer CB, Modrof J, Kreil TR. West Nile virus neutralization by US plasma-derived immunoglobulin products. J Infect Dis 2007;196:435–40. https://doi.org/10.1086/519392.

[23] Haley M, Retter AS, Fowler D, Gea-Banacloche J, O'Grady NP. The role for intravenous immunoglobulin in the treatment of West Nile virus encephalitis. Clin Infect Dis 2003;37:e88-90. https://doi.org/10.1086/377172.

[24] Shimoni Z, Niven MJ, Pitlick S, Bulvik S. Treatment of West Nile virus encephalitis with intravenous immunoglobulin. Emerg Infect Dis 2001;7:759. https://doi.org/10.3201/eid0704.010432.

[25] 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. N Engl J Med 2016;374:33–42. https://doi.org/10.1056/NEJMoa1511812.

[26] 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. https://doi.org/https://doi.org/10.1016/j.tracli.2015.12.003.

[27] Lünemann JD, Nimmerjahn F, Dalakas MC. Intravenous immunoglobulin in neurology--mode of action and clinical efficacy. Nat Rev Neurol 2015;11:80–9. https://doi.org/10.1038/nrneurol.2014.253.

[28] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev 2020;In press:102537. https://doi.org/https://doi.org/10.1016/j.autrev.2020.102537.

[29] Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized

patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv 2020. https://doi.org/10.1101/2020.02.10.20021832.

[30] Shahani L, Singh S, Khardori NM. Immunotherapy in clinical medicine: historical perspective and current status. Med Clin North Am 2012;96:421–31, ix. https://doi.org/10.1016/j.mcna.2012.04.001.

[31] Shakir EM, Cheung DS, Grayson MH. Mechanisms of immunotherapy: a historical perspective. Ann Allergy Asthma Immunol 2010;105:340–7; quiz 348, 368. https://doi.org/10.1016/j.anai.2010.09.012.

[32] Sherer Y, Levy Y, Shoenfeld Y. IVIG in autoimmunity and cancer--efficacy versus safety. Expert Opin Drug Saf 2002;1:153–8. https://doi.org/10.1517/14740338.1.2.153.

[33] Katz U, Achiron A, Sherer Y, Shoenfeld Y. Safety of intravenous immunoglobulin (IVIG) therapy. Autoimmun Rev 2007;6:257–9. https://doi.org/10.1016/j.autrev.2006.08.011.

[34] Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea. J Korean Med Sci 2020;35:e149. https://doi.org/10.3346/jkms.2020.35.e149.

[35] Ko J-H, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 2018;23:617–22. https://doi.org/10.3851/IMP3243.

[36] Spalter SH, Kaveri S, Kazatchkine MD. Anti-Idiotypes to Autoantibodies in Therapeutic Preparations of Normal Polyspecific Human IgG (Intravenous Immunoglobulin, IVIg) In: Shoenfeld Y, Kennedy RC, Ferrone Infection and Cancer SBT-I in MA, editors. Idiotypes Med. Autoimmun. Infect. Cancer, Amsterdam: Elsevier; 1997, p. 217–25. https://doi.org/10.1016/B978-044482807-1/50021-1.

[37] Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol 2020. https://doi.org/10.1002/jmv.25882.

[38] 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;In press. https://doi.org/10.1001/jama.2020.4783.

[39] 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. https://doi.org/10.1073/pnas.2004168117.

[40] Soo YOY, Cheng Y, Wong R, Hui DS, Lee CK, Tsang KKS, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10:676–8. https://doi.org/10.1111/j.1469-0691.2004.00956.x.

[41] Cheng Y, Wong R, Soo YOY, Wong WS, Lee CK, Ng MHL, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin

Microbiol Infect Dis 2005;24:44–6. https://doi.org/10.1007/s10096-004-1271-9.

[42] Yeh K-M, Chiueh T-S, Siu LK, Lin J-C, Chan PKS, Peng M-Y, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56:919–22. https://doi.org/10.1093/jac/dki346.

[43] Zhou X, Zhao M, Wang F, Jiang T, Li Y, Nie W, et al. [Epidemiologic features, clinical diagnosis and therapy of first cluster of patients with severe acute respiratory syndrome in Beijing area]. Zhonghua Yi Xue Za Zhi 2003;83:1018–22.

[44] Kong L. Letter to editor. Transfus Apher Sci 2003;29:101. https://doi.org/https://doi.org/10.1016/S1473-0502(03)00109-5.

[45] Wong VWS, Dai D, Wu AKL, Sung JJY. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med J 2003;9:199–201.

[46] Hung IF, To KK, Lee C-K, Lee K-L, Chan K, Yan W-W, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011;52:447–56. https://doi.org/10.1093/cid/ciq106.

[47] Chan KKC, Lee KL, Lam PKN, Law KI, Joynt GM, Yan WW. Hong Kong's experience on the use of extracorporeal membrane oxygenation for the treatment of influenza A (H1N1). Hong Kong Med J 2010;16:447–54.

[48] Yu H, Gao Z, Feng Z, Shu Y, Xiang N, Zhou L, et al. Clinical characteristics of 26 human cases of highly pathogenic avian influenza A (H5N1) virus infection in China. PLoS One 2008;3:e2985. https://doi.org/10.1371/journal.pone.0002985.

[49] Kong LK, Zhou BP. Successful treatment of avian influenza with convalescent plasma. Hong Kong Med J 2006;12:489.

[50] Wong SSY, Yuen K-Y. The management of coronavirus infections with particular reference to SARS. J Antimicrob Chemother 2008;62:437–41. https://doi.org/10.1093/jac/dkn243.

[51] Zhang H, Zeng Y, Lin Z, Chen W, Liang J, Zhang H, et al. [Clinical characteristics and therapeutic experience of case of severe highly pathogenic A/H5N1 avian influenza with bronchopleural fistula]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese J Tuberc Respir Dis 2009;32:356–9.

[52] Tiberghien P, de Lambalerie X, Morel P, Gallian P, Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how. Vox Sang 2020;n/a. https://doi.org/10.1111/vox.12926.

[53] Tissot J-D, Garraud O. Ethics and blood donation: A marriage of convenience. Press Medicale 2016;45:e247-52. https://doi.org/10.1016/j.lpm.2016.06.016.

[54] 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. https://doi.org/10.1172/JCI138745.

[55] Dodd RY, Crowder LA, Haynes JM, Notari EP, Stramer SL, Steele WR. Screening Blood Donors for HIV, HCV, and HBV at the American Red Cross: 10-Year Trends in Prevalence, Incidence, and Residual Risk, 2007 to 2016. Transfus Med Rev 2020. https://doi.org/10.1016/j.tmrv.2020.02.001.

[56] Niazi SK, Bhatti FA, Salamat N, Ghani E, Tayyab M. Impact of nucleic acid amplification test on screening of blood donors in Northern Pakistan. Transfusion 2015;55:1803–11. https://doi.org/10.1111/trf.13017.

[57] Bello-López JM, Delgado-Balbuena L, Rojas-Huidobro D, Rojo-Medina J. Treatment of platelet concentrates and plasma with riboflavin and UV light: Impact in bacterial reduction. Transfus Clin Biol 2018;25:197–203. https://doi.org/10.1016/j.tracli.2018.03.004.

[58] Benjamin RJ, McLaughlin LS. Plasma components: properties, differences, and uses. Transfusion 2012;52 Suppl 1:9S-19S. https://doi.org/10.1111/j.1537-2995.2012.03622.x.

[59] Du L, He Y, Zhou Y, Liu S, Zheng B-J, Jiang S. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol 2009;7:226–36. https://doi.org/10.1038/nrmicro2090.

[60] Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect 2020;9:382–5. https://doi.org/10.1080/22221751.2020.1729069.

[61] Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. MedRxiv 2020:2020.03.30.20047365. https://doi.org/10.1101/2020.03.30.20047365.

[62] Hsueh P-R, Huang L-M, Chen P-J, Kao C-L, Yang P-C. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. Clin Microbiol Infect 2004;10:1062–6. https://doi.org/10.1111/j.1469-0691.2004.01009.x.

[63] Gorse GJ, Donovan MM, Patel GB. Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illnesses. J Med Virol 2020;92:512–7. https://doi.org/10.1002/jmv.25715.

[64] Rokni M, Ghasemi V, Tavakoli Z. Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: Comparison with SARS and MERS. Rev Med Virol 2020. https://doi.org/10.1002/rmv.2107.

[65] Chaigne B, Mouthon L. Mechanisms of action of intravenous immunoglobulin. Transfus Apher Sci 2017;56:45–9. https://doi.org/10.1016/j.transci.2016.12.017.

[66] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med 2020;In press. https://doi.org/10.1056/NEJMc2007575.

[67] Lutz HU, Späth PJ. Anti-inflammatory effect of intravenous immunoglobulin mediated through modulation of complement activation. Clin Rev Allergy Immunol 2005;29:207–12. https://doi.org/10.1385/CRIAI:29:3:207.

[68] Basta M, Van Goor F, Luccioli S, Billings EM, Vortmeyer AO, Baranyi L, et al. F(ab)'2-mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins. Nat Med 2003;9:431–8. https://doi.org/10.1038/nm836.

[69] Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, Leist SR, et al. Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis. MBio 2018;9. https://doi.org/10.1128/mBio.01753-18.

[70] Abe Y, Horiuchi A, Miyake M, Kimura S. Anti-cytokine nature of natural human immunoglobulin: one possible mechanism of the clinical effect of intravenous immunoglobulin therapy. Immunol Rev 1994;139:5–19. https://doi.org/10.1111/j.1600-065x.1994.tb00854.x.

[71] Kulkarni R. Antibody-Dependent Enhancement of Viral Infections BT - Dynamics of Immune Activation in Viral Diseases. In: Bramhachari PV, editor. Dyn. Immune Act. Viral Dis., Singapore: Springer Singapore; 2020, p. 9–41. https://doi.org/10.1007/978-981-15-1045-8_2.

[72] Vatti A, Monsalve DM, Pacheco Y, Chang C, Anaya J-M, Gershwin ME. Original antigenic sin: A comprehensive review. J Autoimmun 2017;83:12–21. https://doi.org/10.1016/j.jaut.2017.04.008.

[73] Wang S-F, Tseng S P, Yen C-H, Yang J-Y, Tsao C-H, Shen C-W, et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochem Biophys Res Commun 2014;451:208–14. https://doi.org/10.1016/j.bbrc.2014.07.090.

[74] Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130:1545–8. https://doi.org/10.1172/JCI138003.

[75] Nimmerjahn F, Ravetch J V. Anti-inflammatory actions of intravenous immunoglobulin. Annu Rev Immunol 2008;26:513–33. https://doi.org/10.1146/annurev.immunol.26.021607.090232.

[76] Kiessling P, Lledo-Garcia R, Watanabe S, Langdon G, Tran D, Bari M, et al. The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study. Sci Transl Med 2017;9. https://doi.org/10.1126/scitranslmed.aan1208.

[77] Litzman J. Influence of FCRN expression on lung decline and intravenous immunoglobulin catabolism in common variable immunodeficiency patients. Clin Exp Immunol 2014;178 Suppl:103–4. https://doi.org/10.1111/cei.12529.

[78] Akilesh S, Petkova S, Sproule TJ, Shaffer DJ, Christianson GJ, Roopenian D. The MHC class I-like Fc receptor promotes humorally mediated autoimmune disease. J Clin Invest 2004;113:1328–33. https://doi.org/10.1172/JCI18838.

[79] Hansen RJ, Balthasar JP. Effects of intravenous immunoglobulin on platelet count and antiplatelet antibody disposition in a rat model of immune thrombocytopenia. Blood 2002;100:2087–93.

[80] Hansen RJ, Balthasar JP. Intravenous immunoglobulin mediates an increase in anti-platelet antibody clearance via the FcRn receptor. Thromb Haemost 2002;88:898–9.

[81] Jin J, Gong J, Lin B, Li Y, He Q. FcγRIIb expression on B cells is associated with treatment efficacy for acute rejection after kidney transplantation. Mol Immunol 2017;85:283–92. https://doi.org/10.1016/j.molimm.2017.03.006.

[82] Shrestha S, Wiener H, Shendre A, Kaslow RA, Wu J, Olson A, et al. Role of activating FcγR gene polymorphisms in Kawasaki disease susceptibility and intravenous immunoglobulin response. Circ Cardiovasc Genet 2012;5:309–16. https://doi.org/10.1161/CIRCGENETICS.111.962464.

[83] Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science (80-) 2006;313:670–3. https://doi.org/10.1126/science.1129594.

[84] Othy S, Topcu S, Saha C, Kothapalli P, Lacroix-Desmazes S, Kasermann F, et al. Sialylation may be dispensable for reciprocal modulation of helper T cells by intravenous immunoglobulin. Eur J Immunol 2014;44:2059–63. https://doi.org/10.1002/eji.201444440.

[85] Bayry J, Lacroix-Desmazes S, Carbonneil C, Misra N, Donkova V, Pashov A, et al. Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. Blood 2003;101:758–65. https://doi.org/10.1182/blood-2002-05-1447.

[86] Sharma M, Schoindre Y, Hegde P, Saha C, Maddur MS, Stephen-Victor E, et al. Intravenous immunoglobulin-induced IL-33 is insufficient to mediate basophil expansion in autoimmune patients. Sci Rep 2014;4:5672. https://doi.org/10.1038/srep05672.

[87] Tjon ASW, van Gent R, Jaadar H, Martin van Hagen P, Mancham S, van der Laan LJW, et al. Intravenous immunoglobulin treatment in humans suppresses dendritic cell function via stimulation of IL-4 and IL-13 production. J Immunol 2014;192:5625–34. https://doi.org/10.4049/jimmunol.1301260.

[88] Karnam A, Rambabu N, Das M, Bou-Jaoudeh M, Delignat S, Käsermann F, et al. Therapeutic normal IgG intravenous immunoglobulin activates Wnt-β-catenin pathway in dendritic cells. Commun Biol 2020;3:96. https://doi.org/10.1038/s42003-020-0825-4.

[89] Bayry J, Lacroix-Desmazes S, Delignat S, Mouthon L, Weill B, Kazatchkine MD, et al. Intravenous immunoglobulin abrogates dendritic

cell differentiation induced by interferon-alpha present in serum from patients with systemic lupus erythematosus. Arthritis Rheum 2003;48:3497–502. https://doi.org/10.1002/art.11346.

[90]   Sharma M, Saha C, Schoindre Y, Gilardin L, Benveniste O, Kaveri S V, et al. Interferon-α inhibition by intravenous immunoglobulin is independent of modulation of the plasmacytoid dendritic cell population in the circulation: comment on the article by Wiedeman et al. Arthritis Rheumatol 2014;66:2308–9. https://doi.org/10.1002/art.38683.

[91]   Aubin E, Lemieux R, Bazin R. Indirect inhibition of in vivo and in vitro T-cell responses by intravenous immunoglobulins due to impaired antigen presentation. Blood 2010;115:1727–34. https://doi.org/10.1182/blood-2009-06-225417.

[92]   Issekutz AC, Rowter D, Miescher S, Käsermann F. Intravenous IgG (IVIG) and subcutaneous IgG (SCIG) preparations have comparable inhibitory effect on T cell activation, which is not dependent on IgG sialylation, monocytes or B cells. Clin Immunol 2015;160:123–32. https://doi.org/10.1016/j.clim.2015.05.003.

[93]   Ahmadi M, Abdolmohammadi-Vahid S, Ghaebi M, Aghebati-Maleki L, Afkham A, Danaii S, et al. Effect of Intravenous immunoglobulin on Th1 and Th2 lymphocytes and improvement of pregnancy outcome in recurrent pregnancy loss (RPL). Biomed Pharmacother 2017;92:1095–102. https://doi.org/10.1016/j.biopha.2017.06.001.

[94]   Hung IFN, To KKW, Lee C-K, Lee K-L, Yan W-W, Chan K, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. Chest 2013;144:464–73. https://doi.org/10.1378/chest.12-2907.

[95]   Klehmet J, Goehler J, Ulm L, Kohler S, Meisel C, Meisel A, et al. Effective treatment with intravenous immunoglobulins reduces autoreactive T-cell response in patients with CIDP. J Neurol Neurosurg Psychiatry 2015;86:686–91. https://doi.org/10.1136/jnnp-2014-307708.

[96]   Trépanier P, Chabot D, Bazin R. Intravenous immunoglobulin modulates the expansion and cytotoxicity of CD8+ T cells. Immunology 2014;141:233–41. https://doi.org/10.1111/imm.12189.

[97]   Ye Q, Gong F-Q, Shang S-Q, Hu J. Intravenous immunoglobulin treatment responsiveness depends on the degree of CD8+ T cell activation in Kawasaki disease. Clin Immunol 2016;171:25–31. https://doi.org/10.1016/j.clim.2016.08.012.

[98]   Maddur MS, Vani J, Hegde P, Lacroix-Desmazes S, Kaveri S V, Bayry J. Inhibition of differentiation, amplification, and function of human TH17 cells by intravenous immunoglobulin. J Allergy Clin Immunol 2011;127:823–7. https://doi.org/10.1016/j.jaci.2010.12.1102.

[99]   Maddur MS, Kaveri S V, Bayry J. Comparison of different IVIg preparations on IL-17 production by human Th17 cells. Autoimmun Rev

2011;10:809–10. https://doi.org/10.1016/j.autrev.2011.02.007.

[100] Kim DJ, Lee SK, Kim JY, Na BJ, Hur SE, Lee M, et al. Intravenous immunoglobulin G modulates peripheral blood Th17 and Foxp3(+) regulatory T cells in pregnant women with recurrent pregnancy loss. Am J Reprod Immunol 2014;71:441–50. https://doi.org/10.1111/aji.12208.

[101] Tackenberg B, Jelcic I, Baerenwaldt A, Oertel WH, Sommer N, Nimmerjahn F, et al. Impaired inhibitory Fcgamma receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc Natl Acad Sci U S A 2009;106:4788–92. https://doi.org/10.1073/pnas.0807319106.

[102] Nikolova KA, Tchorbanov AI, Djoumerska-Alexieva IK, Nikolova M, Vassilev TL. Intravenous immunoglobulin up-regulates the expression of the inhibitory FcgammaIIB receptor on B cells. Immunol Cell Biol 2009;87:529–33. https://doi.org/10.1038/icb.2009.30.

[103] Séité J-F, Guerrier T, Cornec D, Jamin C, Youinou P, Hillion S. TLR9 responses of B cells are repressed by intravenous immunoglobulin through the recruitment of phosphatase. J Autoimmun 2011;37:190–7. https://doi.org/10.1016/j.jaut.2011.05.014.

[104] Le Pottier L, Bendaoud B, Dueymes M, Daridon C, Youinou P, Shoenfeld Y, et al. BAFF, a new target for intravenous immunoglobulin in autoimmunity and cancer. J Clin Immunol 2007;27:257–65. https://doi.org/10.1007/s10875-007-9082-2.

[105] Prasad NK, Papoff G, Zeuner A, Bonnin E, Kazatchkine MD, Ruberti G, et al. Therapeutic preparations of normal polyspecific IgG (IVIg) induce apoptosis in human lymphocytes and monocytes: a novel mechanism of action of IVIg involving the Fas apoptotic pathway. J Immunol 1998;161:3781–90.

[106] Paquin Proulx D, Aubin E, Lemieux R, Bazin R. Inhibition of B cell-mediated antigen presentation by intravenous immunoglobulins (IVIg). Clin Immunol 2010;135:422–9. https://doi.org/10.1016/j.clim.2010.01.001.

[107] Séïté J-F, Cornec D, Renaudineau Y, Youinou P, Mageed RA, Hillion S. IVIg modulates BCR signaling through CD22 and promotes apoptosis in mature human B lymphocytes. Blood 2010;116:1698–704. https://doi.org/10.1182/blood-2009-12-261461.

[108] Blanco-Melo D, Nilsson-Payant BE, Chun Liu W, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;In press. https://doi.org/10.1016/j.cell.2020.04.026.

[109] Kozicky LK, Zhao ZY, Menzies SC, Fidanza M, Reid GSD, Wilhelmsen K, et al. Intravenous immunoglobulin skews macrophages to an anti-inflammatory, IL-10-producing activation state. J Leukoc Biol 2015;98:983–94. https://doi.org/10.1189/jlb.3VMA0315-078R.

[110] Meregalli C, Marjanovic I, Scali C, Monza L, Spinoni N, Galliani C, et al. High-dose intravenous immunoglobulins reduce nerve macrophage

infiltration and the severity of bortezomib-induced peripheral neurotoxicity in rats. J Neuroinflammation 2018;15:232. https://doi.org/10.1186/s12974-018-1270-x.

Figure 1. Schematic representation of convalescent plasma components and its mechanisms of action. **A.** Main convalescent plasma components. **B.** Antiviral effects of NAbs. IgG and IgM are the main isotypes, although IgA may be also important, particularly in mucosal viral infections. Other non-NAbs may exert a protective effect. The humoral immune response is mainly directed towards spike (S) protein. **C.** Anti-inflammatory effects of CP include network of autoantibodies, and control of an overactive immune system (i.e., cytokine storm, Th1/Th17 ratio, complement activation and regulation of a hypercoagulable state) (see text for details).

Tabl

Author	Country	Study design	Viral Etiology	Diagnosis	individual included	Non-CP treatment	Previous clinical state CP	Dose protocol CP	Intervention	Outcomes	Mortality
Shen *et al.* (2020) [38]	China	Case series	COVID-19	RT-PCR	Intervention: 5	All patients received antiviral management during treatment.	Clinical deterioration	CP from the same donor	CP 200-250 ml two consecutive transfusions CP 200 ml single dose	Improvement in viral load and increase in antibodies	0% intervention group
Duan *et al*. (2020) [39]	China	Clinical trial	COVID-19	RT-PCR	Intervention: 19	Ribavirin, Cefoperazone, Levoflaxacin, Methylprednisolone, Interferon, Peramivir, Caspofungin.	Clinical deterioration	CP from the same donor	CP 200 ml single dose	Viral load improvement and lung imaging	Reduction of viral load and improvement in lung images
Ye *et al*. (2020) [37]	China	Case series	COVID-19	RT-PCR	Intervention: 6	Not reported	Clinical deterioration	Unknown	CP 200-250 ml two consecutive transfusions	Reduction of viral load and increase of SARS-CoV-2 IgG and IgM antibodies	0% intervention group
Anh et al. (2020) [34]	South Korea	Case report	COVID-19	RT-PCR	Intervention: 2	Lopinavir, Ritonavir, hydroxychloroquine and empirical antibiotics	Clinical deterioration	Unknown	Unknown	Reduction of viral load and increase of SARS-CoV-2 IgG and IgM antibodies	0% intervention group
Soo *et al* (2004) [40]	China	Retrospective comparison of cases	SARS-CoV	CDC Case Definition	Intervention: 19 control: 21	Intervention Group: Ribavirin, 3 doses Methylprednisolone (1·5g). Control group: Ribavirin, 4 or more doses of Methylprednisolone (1·5g).	Clinical deterioration	Unknown	CP 200-400 ml days 11 and 42 after the onset of symptoms	Mortality, length of hospital stay, adverse events	23% reduction (p = 0.03)
Cheng *et al* (2005) [41]	China	Case series	SARS-CoV	CDC case definition and serology	Intervention: 80	Unknown	Clinical deterioration	Unknown	CP 279 ml per day 14	Mortality, length of hospital stay,	12.5% intervention group.
Nie *et al*. (2003) [5]	China	Case series	SARS-CoV	Unknown	Intervention: 40	Unknown	Unknown	Unknown	CP unknown dose	Mortality	0% intervention group
Yeh *et al* (2005) [42]	Taiwan	Case series	SARS-CoV	serology	Intervention: 3	Ribavirin, Moxifloxacin, Methylprednisolone	Clinical deterioration	Unknown	CP unknown dose on day 11 of symptom onset	Mortality, antibodies, viral load, adverse events	0% intervention group
Zhou *et al*. (2003) [43]	China	Case series	SARS-CoV	CDC case definition	Intervention: 1 control: 28	All patients received	Vulnerable	Unknown	CP 50 ml single dose on	Mortality,	7% reduction

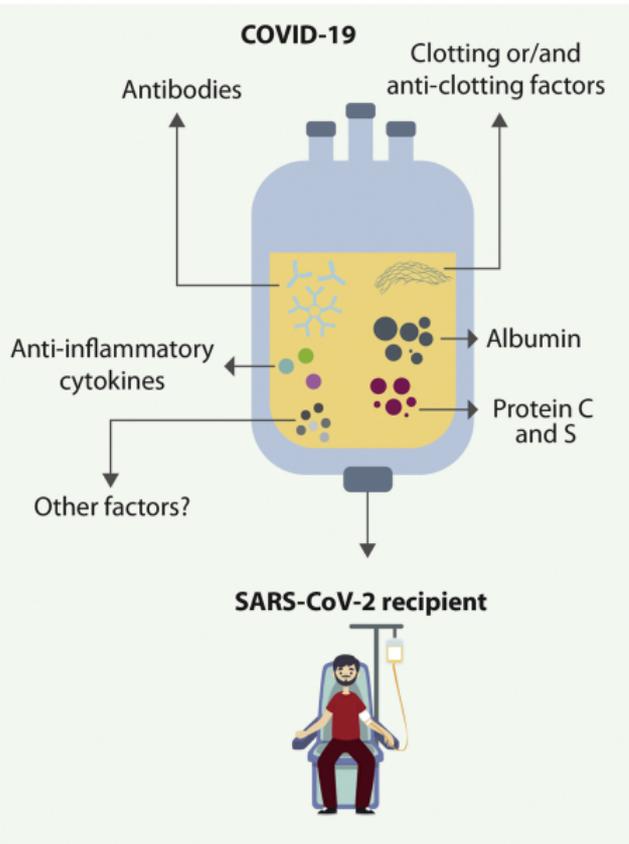|											
						Levofloxacin, Steroids, Mechanical ventilation.	older adults		symptom onset	hospital stay	
Kong (2003) [44]	China (Hong Kong)	Case report	SARS-CoV	Clinical Diagnosis	Intervention: 1	Antivirals, Steroids, Ventilation	Clinical deterioration	CP from the same donor	CP 250 ml 2 doses day 7 of the onset of symptoms	Mortality	0% intervention group
Wong *et al* (2003) [45]	China (Hong Kong)	Case report	SARS-CoV	WHO case definition	Intervention: 1	Ribavirin, Oseltamivir, Cefotaxime, Levofloxacin	Clinical deterioration	CP from the same donor	200 ml CP on day 14 of symptom onset	Mortality	0% intervention group
Ko et al. (2018) [35]	South Korea	Case series	MERS-CoV	RT-PCR	Intervention: 3	Steroids	Clinical deterioration	Unknown	CP unspecified dose	Antibody titers	0% intervention group

ARDS: Acute respiratory distress syndrome; CDC: Centers for disease control and prevention; COVID-19: Coronavirus disease 2019; CP: Convalescent plasma; CPAP: Continuous positive airway pressure; ICU: Intensive care unit; MERS: Middle east respiratory syndrome coronavirus; ml: Millilitres; NA: Not available; RT PCR: Real-time polymerase chain reaction; SARS-CoV: Severe acute respiratory syndrome coronavirus; USA: United States of America; WHO: World health organization. Taken and modified from [20].

Table 2. Associated adverse events to convalescent plasma in different epidemics.
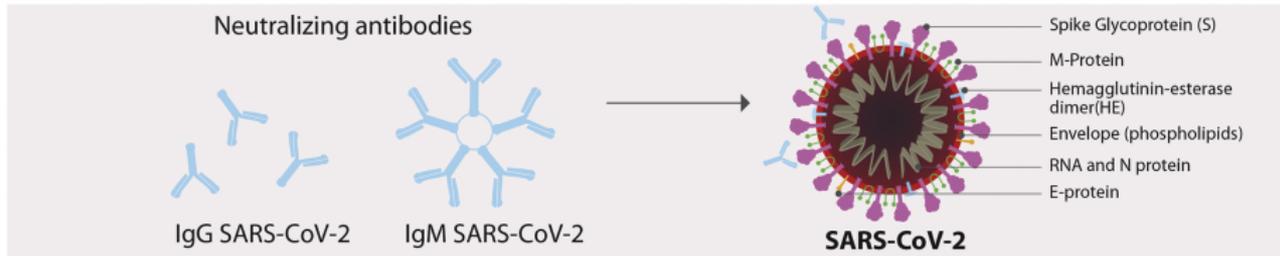
Author	Country	Viral Etiology	Adverse Events
Shen *et al.* (2020) [38]	China	COVID-19	None
Duan et al. (2020) [39]	China	COVID-19	Self-limited facial erythema in 2/10 patients. No major adverse events.
Ye *et al.* (2020) [37]	China	COVID-19	None
Anh *et al.* (2020) [34]	South Korea	COVID-19	None
Soo *et al* (2004) [40]	China	SARS-CoV	None
Cheng *et al* (2005) [41]	China	SARS-CoV	None
Nie *et al.* (2003) [5]	China	SARS-CoV	None
Yeh *et al* (2005) [42]	Taiwan	SARS-CoV	None
Zhou *et al.* (2003) [43]	China	SARS-CoV	None
Kong *et al.* (2003) [44]	China	SARS-CoV	None
Wong *et al* (2003) [45]	China	SARS-CoV	None
Ko et al. (2018) [35]	South Korea	MERS-CoV	None
Van Griensven *et al.* (2016) [25]	Guinea	Ebola	Nausea, skin erythema, fever. No major adverse events.
Hung *et al.* (2011) [46]	China	Influenza A(H1N1)	None
Chan *et al.* (2010) [47]	China	Influenza A(H1N1)	None
Yu *et al.* (2008) [48]	China	Influenza A(H5N1)	None
Kong *et al.* (2006) [49]	China	Influenza A(H5N1)	None

COVID-19: Coronavirus disease 2019; MERS-CoV: Middle East respiratory syndrome coronavirus; SARS-CoV: Severe acute respiratory syndrome coronavirus.

A. CONVALESCENT PLASMA

COVID-19

Antibodies

Clotting or/and anti-clotting factors

Anti-inflammatory cytokines

Albumin

Protein C and S

Other factors?

SARS-CoV-2 recipient

B. ANTIVIRAL EFFECTS

Neutralizing antibodies

IgG SARS-CoV-2

IgM SARS-CoV-2

SARS-CoV-2

Spike Glycoprotein (S)
M-Protein
Hemagglutinin-esterase dimer (HE)
Envelope (phospholipids)
RNA and N protein
E-protein

C. IMMUNOMODULATORY EFFECTS

Pro-inflammatory cytokines

Complement
C3a   C5a

Autoantibodies

HLA-II ↓   Endocytosis ↓
CD80/CD86 ↓
IL-12 ↓   IL-1RA ↑
IL-10 ↑   IL-4 ↑

Neutralization of cytokines, complement, and autoantibodies

Innate immunity

Th1   IL-6 ↓

Th2   IL-4 ↑   IL-5 ↑

Th17   IL-17A ↓   IL-17F ↓   IL-21 ↓

Treg ↑   IL-10 ↑

B cell   FcγRIIB ↓   Proliferation ↓   Apoptosis ↑

Adaptive immunity

Figure 1