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Convalescent Plasma: Therapeutic Hope or Hopeless Strategy in the SARS-CoV-2 Pandemic

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ABSTRACT

As the world faces the current SARS-CoV-2 pandemic, extensive efforts have been applied to identify effective therapeutic agents. Convalescent plasma collected from recovered patients has been a therapeutic modality employed for over a hundred years for various infectious pathogens. Specifically, it has been used in the treatment of many viral infections with varying degrees of clinical efficacy. As we consider the use of convalescent plasma in the battle against this new strain of coronavirus, it is prudent to review what is known from past experiences. Accordingly, the aim of this review is to examine in detail studies of convalescent plasma used during previous viral outbreaks and pandemics with particular focus on hemorrhagic fevers, influenza, and other coronaviruses. The concluding sections of this review address the potential use of convalescent plasma during the present-day SARS-CoV-2 pandemic, not only insofar as its clinical benefit but also the steps required to make convalescent plasma treatments readily available for an exponentially growing patient population. By the end, the authors hope to address the extent to which convalescent plasma represents a realistic therapeutic approach, or a distraction from other potentially useful treatments.

Contents

A New Pandemic

December 31, 2019 marked the day the World Health Organization (WHO) first became aware of an infectious outbreak in the Hubei province in China, an outbreak that would quickly change the lives of people around the world [1]. Shortly thereafter, the causative agent was determined to be a member of the coronavirus family, now referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) pandemic. In the time between January 30, 2020 and March 11, 2020 the outbreak went from being classified as a Public Health Emergency of International Concern to a full-fledged global pandemic. At the time of this writing, over 1.4 million people have been afflicted by the virus worldwide and more than 80,000 people have died (https://coronavirus.jhu.edu/map.html [2]). Healthcare systems everywhere are preparing (and, increasingly, scrambling) to care for the exponentially growing number of patients presenting to hospitals. With the lack of any observable natural immunity in the population to this virus, and no established treatments or vaccines, management to date has been

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mainly supportive. That being said, researchers and clinicians are investigating and implementing a variety of therapeutics including retroviral medications such as Lopinavir /Ritonavir and Remdesivir [3]; combination of hydroxychloroquine and azithromycin [4]; and the anti-malarial drug chloroquine [5]. Attention has also been given to the prospect of utilizing plasma from convalescent donors to treat patients with severe COVID-19 infection [6,7].

Passive antibody transfer dates back to the 1890's when antibodies were first used to protect against bacterial toxins before the introduction of antimicrobials [8]. Subsequently, passive antibody administration has been used to treat those infected with various microorganisms including bacteria, fungi, and viruses. Modern formulations of intravenous immunoglobulin (IVIG), pooled from thousands of healthy donors, is still used to prevent viral infections in certain patient populations [9,10]. As such, it is logical to consider the use of passive antibody transfer to treat patients in the current pandemic. Could plasma collected from COVID-19 convalescent patients be efficacious in treating patients still battling the infection, or as a prophylactic approach to prevent this disease? In this review we attempt to address this question along with presenting historical accounts of the use of convalescent plasma in the management and treatment of viral infections, focusing on outbreaks in the twentieth and twenty-first centuries. We shall start by examining the use of convalescent plasma in other viral diseases and ultimately direct our attention to coronaviruses. By the end, the authors hope to address whether convalescent plasma is a realistic therapeutic approach to address the SARS-CoV-2 pandemic.

Ebola

The 2013-2016 West African Ebola virus disease (EVD) outbreak provided a recent opportunity to evaluate the use of convalescent plasma. Despite a noticeable lack of prospective, randomized control trials, several nonrandomized trials emerged offering some evidence upon which to build. One described 84 patients from Guinea who received convalescent plasma (two consecutive transfusions, 200-250 mL/transfusion) within 2 days of diagnosis and compared them to a cohort of 418 controls treated at the same facility [11]. No significant improvement in mortality was noted in the treatment group compared to the control; however, both groups had high mortality. Even before day 3, 17% of patients in both cohorts had died, and after day 3, 31% of the plasma-treated patients and 38% of the control patients died. The study's main limitation was that the control group was a historical cohort of patients; as such, many unaccounted confounding variables could have impacted mortality. Viral load was also not directly measured but rather PCR cycle threshold was used as a surrogate. Another key limitation was that at the time of transfusion, the anti-Ebola virus (EBOV) antibody and neutralizing antibody titers were not known. Subsequently, the same group published a follow-up letter to the editor with results of antibody testing [12]. Interestingly, patients receiving plasma with high doses of anti-EBOV IgG antibodies exhibited a correlation with larger decreases in viral loads. In terms of neutralizing antibodies, the majority (75%) of plasma donors had low titers (1:10-1:40) and only a minority (5%) had high titers (1:160). These serological results bring the relevance of neutralizing antibody to the forefront and raise the important question of whether high levels of neutralizing antibody affect clinical efficacy.

The second nonrandomized study was out of Sierra Leone and compared clinical outcomes in 44 subjects treated with convalescent whole blood to 25 non-treated patients [13]. They showed an improvement in fatality in patients receiving convalescent whole blood compared to the control group (27.9% vs 44%, respectively) with a 2.3 odds ratio of survival for those receiving treatment. Although this study was not randomized, had a small n, and used whole blood as opposed to plasma, the results, unlike the previous study, suggest efficacy of convalescent blood products. The remaining Ebola-related publications are limited to case series that provide anecdotal efficacy of convalescent plasma in patients receiving at least one other investigational therapy, precluding definitive interpretation of the effects of convalescent plasma as a monotherapy [14,15]. Notwithstanding the lack of overwhelming evidence, the WHO has recommended the investigation of convalescent plasma in the treatment of EVD and provided specific protocol guidelines [16]. This provision will hopefully propagate continued investigation, and recently, a prospective phase 1 trial was designed to assess the safety of pathogen reduced convalescent plasma in the treatment of EVD [17].

Influenza: Convalescent Plasma

Convalescent plasma has also been used in the setting of influenza, which is relevant to its application against coronavirus. Data on the use of convalescent plasma in the treatment of influenza dates back the 1918 H1N1 pandemic. A meta-analysis of several related studies published between 1918 and 1925 revealed decreased case-fatality rate in the treated group vs the nontreated controls (16% vs. 37%, respectively) [18]; there was also a difference in case-fatality rate noted in patients who received convalescent plasma early compared to those who were transfused later in their disease course (19% vs 59%, respectively). None of the included studies were blinded or randomized and most contained heterogeneous and sometimes archaic treatment methods.

The randomized control trials that have been performed examining the efficacy of convalescent plasma concern influenza infection. Based on the promising results of their randomized, phase 2 trial, which investigated the utility of convalescent plasma versus standard of care in patients with severe influenza A or B [19], Biegel and colleagues proceeded to carry out a prospective, randomized, double-blind phase 3 trial that sought to compare the clinical efficacy of convalescent plasma with high titer (≥1:80) anti-influenza A antibodies against convalescent plasma with low titer (≤1:10) anti-influenza A titers in patients with severe disease [20]. Patients were followed for 28 days with a primary end point being clinical status on day 7 as defined by a six-point ordinal scale. Ninety-two patients received high-titer plasma while 48 received low titer plasma. No benefit in high titer plasma over low titer plasma was found. In fact, the study was terminated early when it was determined that even if the planned full 150 participants were recruited, the high-titer group would still show no improvement in clinical status over low titer plasma. Of note, 34% of the subjects experienced serious adverse events including acute respiratory distress syndrome (ARDS) and allergic transfusion reactions, which highlight the potential hazards of convalescent plasma. Given the results and possible adverse reactions, the group concluded that the data did not warrant the treatment of influenza A with convalescent plasma.

Although this study had more patients than most published convalescent plasma studies, the overall number of patients included was only 138. Furthermore, they did not have a control group without plasma transfusion, as the investigators believed that a no-plasma control group would have affected the blinding because a saline infusion solution has a distinct appearance from plasma. The aforementioned phase 2 trial did assess high-titer plasma versus standard of care, and like the phase 3 trial, there was no significant benefit in plasma over standard treatment in terms of the primary endpoint. That being said, both the phase 2 and 3 trials indicated benefits in secondary endpoints, particularly in duration of mechanical ventilation and in intensive care. Lastly, the phase 3 trial used hemagglutination inhibition titers as inclusion criteria for use of plasma. Some studies would contend that neutralizing antibody titers or anti-neuraminidase titers are more appropriate markers to measure [21]. Despite some of these limitations, this study represents the type of investigative design needed to properly evaluate the use of convalescent plasma.

During the influenza A (H1N1) pandemic of 2009, a prospective cohort study of adults with severe infection, requiring intensive care, was conducted [22]. In this study patients were offered convalescent plasma treatment and clinical outcomes were compared between those who

accepted treatment and those who declined. In all, 93 patients were recruited of which 20 patients received convalescent plasma and were matched to the non-treatment control group. The group that received the convalescent plasma experienced significantly lower mortality than the control group (20.0% vs 54.8%, respectively), which remained significant in multivariate analysis. In addition to lower mortality, the treatment group saw significantly lower viral loads as well as lower cytokine levels post treatment. Even though this was not a randomized trial, it was prospective in nature with well-matched experimental and control groups and findings held up in multivariate models. When combining these findings with those from retrospective observational studies from the same period [23], the use of convalescent plasma would seem to at least show potential in the setting of H1N1.

The 2006 avian influenza A/H5N1 outbreak and the 2015 outbreak influenza A (H7N9) mostly yielded case reports and cases series [24-27]. Like the case reports from the Ebola experience, these reports suffer from the same limitations, including co-administration of other antivirals and treatments, particularly oseltamivir. Interestingly though, the investigator of one of these reports made a point to compare the viral sequences from the convalescent plasma donor and the patient and found >99% homology [25]. This comparison addresses an important point for consideration when selecting convalescent donors, especially when there are multiple strains of influenza virus known to be in circulation.

Influenza: Hyperimmune IV Immunoglobulin

Convalescent plasma can be fractionated into hyperimmune IV immunoglobulin (H-IVIG), a concentrated formulation with enriched levels of pathogen-specific antibodies. In regard to quality, the few studies that examine H-IVIG arguably supply some of the best designed studies of passive antibody transfer in human subjects. One such study was a multicenter, prospective, double-blind randomized control trial in the setting of the 2009 influenza A (H1N1) pandemic [28]. H-IVIG was manufactured from convalescent plasma from a total of 276 donors, all of whom had neutralizing antibody titers of > 1:40; and patients who received H-IVIG (n=17) had similar baseline demographics to and were compared to patients who received standard IVIG (n=18). The group that received H-IVIG had significantly lower viral loads on day 5 and 7 post infusion than the IVIG arm. Multivariate analysis revealed that treatment with H-IVIG was the only variable that reduced mortality (0% vs. 40%, experimental vs control group, respectively) when administered within 5 days of symptom onset.

Though this was a well-designed study, it is not without its limitations. The authors note that the fractionation process took approximately 6 months, and as such, the first wave of the pandemic was missed. By the time the study was carried out (2010-2011), the pandemic started to dissipate, which negatively affected enrollment. Consequently, after exclusion criteria were applied, only 35 patients were included, limiting the power of the study. The generalizability of results is also limited, as the exclusion of late presentation precludes extrapolating data to a more critically ill subset of patients; and only donors with neutralizing antibody titers >1:40 were included. Thus, whether lower titer donors would offer any benefit remains unknown.

More recently in 2019, a multinational group, 45 institutions in all, published a randomized, double-blind, placebo-controlled trial investigating the safety and efficacy of H-IVIG in a cohort of adult patients over 5 influenza seasons [29]. Patients with symptom onset within 7 days of randomization and a National Early Warning score of at least 2 were randomized to either treatment group—standard of care and 500 mL of H-IVIG—or control group—saline placebo; study participants and investigators were blinded to treatment. The primary end point was a clinical outcome as defined by 6-category ordinal scale at day 7, which was used to estimate odds ratio. After excluding patients that did not receive randomized treatments, 308 were included in analysis with 156 randomized to H-IVIG and 152 receiving placebo. Of the 308 patients, 224 had influenza A serotypes and 84 had influenza B serotypes. The overall results showed that when administered with antiviral therapy, the addition of H-IVIG did not demonstrate clinical improvement over placebo. The odds ratio of clinical improvement was 1.25 (95% CI: 0.79-1.97, $P = .33$). Death, serious adverse events, or grade 3 or 4 adverse events were 30% in each group. Notably, a pre-specified subgroup comparison of outcomes in influenza A and influenza B ran counter to the investigators' hypothesis. They found that the subgroup of patients with influenza A derived no benefit from treatment even though they achieved high titers of hemagglutinating antibody following infusion of H-IVIG. In contrast, the subgroup of patients with influenza B had improved clinical benefit at day 7 but achieved lower titers of antibody in response to infusion of H-IVIG. Post-study analysis found that the antibodies to influenza B had higher affinity. Yet, the data for influenza B are based on a small subset (n=84) of the total cohort (n = 308) and therefore have wide confidence intervals. Nevertheless, if H-IVIG were to demonstrate benefit in well-designed trials of SARS-CoV-2, H-IVIG may prove useful with regard to ease of administration compared with convalescent plasma. For example, H-IVIG volumes are generally small, simplifying distribution, and preparations could be administered via injection in outpatient settings as opposed to transfusion of plasma, which involves larger volumes delivered intravenously in a hospital type setting [30].

Coronavirus: SARS-CoV and MERS

The use of convalescent plasma in the treatment of coronaviruses is not new. Convalescent plasma was studied in the treatment of SARS during the 2003 SARS-associated coronavirus 1 (SARS-CoV-1) outbreak originating in Hong Kong. Although the data are mainly limited to case reports [31-33] and case series [34], there are several retrospective, non-randomized studies that offer more substance.

Soo and colleagues compared 19 patients receiving convalescent plasma to 21 patients treated with pulsed methylprednisolone [35]. More subjects who received convalescent plasma were discharged by day 22 of hospitalization compared to the subjects in the steroid group (74% vs 19%, respectively). Mortality was also lower in the convalescent plasma group, which had no deaths, whereas, five subjects in the steroid group died. The steroid group also had more co-comorbidities, but statistical significance between groups remained even after controlling for co-existing conditions. Nonetheless, this was a retrospective, non-randomized trial and similarly to some of the aforementioned Ebola studies, anti-SARS-CoV-1 antibodies contained within the convalescent plasma were not standardized; therefore, the degree to which antibody titer or type of antibodies present affect outcomes is unknown. The authors also questioned whether the poorer outcomes in the steroid group could have been due to the detrimental effects of steroids. This theory is thought-provoking considering the current anecdotal observation that steroids may exacerbate disease in COVID-19 infection.

Cheng et al. examined the use of convalescent plasma from a different angle. They retrospectively reviewed 80 patients with SARS infection who had been given convalescent plasma (median volume 279.3 mL) and compared those who had been transfused before day 14 following the onset of symptoms to those who received plasma after day 14 [36]. The results showed that the group that received convalescent plasma earlier had better outcomes (defined as discharge by day 22 vs. death by day 22 or later discharge) than the patients who received plasma later. Limitations were similar to the previous study: retrospective nature, non-randomization, and non-standardized antibody titers in the convalescent plasma. Additionally, there was not a non-transfused control group for comparison. Notwithstanding the shortage of high-quality evidence and the moderate to high biases in the SARS-CoV-1 study designs, a meta-analysis of 8 of these studies demonstrated a benefit in mortality following convalescent plasma transfusion [37].

Another coronavirus responsible for human infection is the Middle East respiratory syndrome coronavirus (MERS-CoV). The 2015 MERS-CoV outbreak in South Korea resulted in a few case reports and series that failed to show clinical improvement with the administration of convalescent plasma [38,39]. However, one study found that donor plasma containing higher titers of MERS-CoV neutralizing antibody resulted in seroconversion of the recipient post-transfusion whereas seroconversion was not noted when plasma with a low titer of neutralizing antibody was transfused [40]. Granted, data presented therein was only based on 3 patients and a total of 4 convalescent plasma transfusions, so definitive conclusions cannot be drawn. Nonetheless, the study again raises the valid consideration of quality of convalescent plasma and the role neutralizing antibody titers might play.

Viral Hemorrhagic Fevers

In addition to Ebola, convalescent plasma has been evaluated in the treatment of other viral hemorrhagic fevers including Bolivian hemorrhagic fever [41], Lassa fever [42], and the Argentine hemorrhagic fever [43]. These studies were either small and/or suffered from poor design with numerous, non-controlled confounding factors. Of potential interest, one Lassa fever study was a controlled trial in which the investigators demonstrated improved mortality in patients who received convalescent plasma prior to day 10 of illness onset compared to those who received plasma after day 10 (9% vs 72%, respectively) [42]. However, there are some caveats to this report. This was a retrospective analysis that included cases spanning years starting in 1970, and variations in management that may have changed over the course of the years were not detailed. Mortality of patients with Lassa fever who did not receive convalescent plasma was 27%, which is significantly better than those who received plasma after day 10. This could indicate a myriad of confounding factors including but not limited to: plasma after day 10 may have been detrimental, the group that received plasma later was sicker at baseline, or variation in medical management between patients.

Coronavirus: SARS-CoV-2

Given the past experiences outlined above and the current threat of SARS-CoV-2, experts have proposed the potential clinical benefit of convalescent plasma in the management of COVID-19 infected patients [1,3,7,30,44]. To date though, only three case series of convalescent plasma in the setting of COVID-19 has been published from January to April of 2020 (See Table 1 for summary of reports) [45-47].

In their cases series, Shen et al. feature 5 critically ill patients, all of whom received convalescent plasma containing SARS-Cov-2 antibodies (titer >1:1000) and neutralizing antibody (titer >1:40) between day 10 and 22 of admission [45]. Following transfusion, 4/5 patients experienced increases in viral antibody titers, decreases in SARS-Cov-2 viral loads, and normalization of temperature and resolution of acute respiratory distress syndrome. Duan and colleagues, present a series of 10 severely ill COVID-19 who all received one 200 mL transfusion of convalescent plasma with high titers of neutralizing antibody (>1:640) at a median of 16.5 days [46]. The primary endpoint in this study was safety, which was demonstrated as all patients tolerated plasma transfusion without severe adverse events. The secondary endpoints included amelioration of clinical symptoms and improvement in laboratory values by day 3 post transfusion. They reported increases in neutralizing antibody titer, oxygen saturation, and lymphocyte count; and decreases in C-reactive protein, SARS-Cov-2 viral load, and lung lesions on radiological examination. Lastly, Zhang et al. describe 4 critically ill patients who were transfused between 200 and 2400 mL of convalescent plasma ranging from day 11 to day 18 of admission [47]. All 4 patients were considered recovered from the COVID-19 infection; however, recovery/discharge ranged anywhere from approximately 1 week to 1 month post initial transfusion so the temporal relationship between convalescent plasma and clinical improvement is difficult to reconcile. The definition of recovery is arguable given one patient was discharged on supplemental oxygen and another patient required continued critical care for multi-organ failure, granted the SARS-Cov-2 viral load had decreased and lung lesions resolved on imaging.

Though these reports provide some preliminary data suggesting benefit of convalescent plasma, conclusions should be drawn with

Table 1
Summary of 3 cases series examining the use of convalescent plasma in the setting of SARS-CoV-2.

Study (year)	Number of patients (age range in years)	Patient characteristics	Volume of CP transfused (average day from admission)	CP antibody profile	Summary of outcomes observed post-transfusion (ratio of patients demonstrating outcome)
Shen et al [45] (2020)	5 (36-73)	- qRT-PCR confirmed COVID-19 infection - severe PNA - Pao_2/Fio_2 <300 mmHG - mechanically ventilated	400 mL (18.2)	SARS-CoV-2–specific antibody titer > 1:1000 neutralizing antibody titer > 1: 40	-Increase in Pao_2/Fio_2 within 12 days -Decrease in viral loads within 12 days -Increase in SARS-CoV-2–specific and neutralizing antibody titers -Resolution of ARDS within 12 days (4/5) - Mechanical ventilation weaned within 14 days (3/5) -Discharged between days 51-55 (3/5) -Remained mechanically ventilated (2/5)
Duan et al [46] (2020)	10 (34 -78)	- qRT-PCR confirmed COVID-19 infection - 2/4 of the following: 1) ≥18 years 2) respiratory distress 3) O_2 saturation <93% at rest 4) Pao_2/Fio_2 <300 mmHg	200 mL (16.5)	Neutralization antibody titer >1:640	-Clinical symptoms were significantly within 3 days -Increase in O_2 saturation within 3 days -Trend in increased lymphocyte counts -Trend in decreased C-reactive protein -Imaging showed varying degrees of absorption of lung lesions within 7 days -Undetectable viral load (7/10)
Zhang et al [47] (2020)	4 (31-73)	- Confirmed COVID-19 infection (3/4 RT-PCR positive) - Respiratory failure requiring mechanical ventilation (2 required ECMO)	200-2400 mL (15.25)	Not measured	-Negative qRT-PCR -Imaging showed absorption, or partial absorption, of lung lesions -Discharged between days 18-43(3/4) -Remained hospitalized with multiorgan failure (1/4)

Table 2
Study limitations of 3 case series examining the use of convalescent plasma in the setting of SARS-CoV-2.

- Limited power—small patient populations (total n = 19)
- Poor generalizability of data—each report was based on a single institution's experience
- Weak study design—only one of the three studies had a control group for comparison but it was a historical control group
- Confounding factors—concurrent treatment with steroids and antivirals
- Timing of treatment—convalescent plasma given relatively late in disease course (>Day 10 in most cases)
- Narrow inclusion criteria—treated patients limited to severely ill and/or critically ill patients

caution as these reports share the same limitations as summarized in Table 2. Most of these limitations also apply to the majority of published reports on the use of convalescent plasma in the treatment of viral infections. The pervasiveness of such limitations in the literature points to the necessity for large scale, multi-center randomized controlled clinical trials.

Worth mentioning, a risk benefit analysis employing a stochastic age-specific susceptible-exposed-infected-removed (SEIR) model based on age, symptomatic/asymptomatic ratio, age-specific severity rates using comorbidity data, and COVID-19 transmission parameters was published in a recent review by Bloch and colleagues [44]. Five hundred stochastic simulations were carried out assuming varying degrees of effectiveness (25%, 50%, 75%) of convalescent plasma treatment and presuming a break-point where the fatality ratio of treatment would need to be greater than the fatality ratio of the disease (i.e., the point at which risk of transfusion related fatalities surpasses COVID-19 related mortality). The model exhibited remarkable benefit of convalescent plasma in the setting of COVID-19 infection even at conservative estimates of 25% effectiveness. In other words, the model indicates the risk of morbidity and mortality of COVID-19 infection coupled with the potential benefit, even if minimal, outweighs the risks of transfusion.

Based on the use of convalescent plasma in the aforementioned epidemics and pandemics and the conceivable benefit for COVID-19 patients, the US Food and Drug Administration (FDA) has approved the use of convalescent plasma to treat severely ill patients with COVID-19 infection [48]. Given that efficacy is far from proven, the FDA is calling for clinical trials to investigate administration of convalescent plasma in the setting of COVID-19. Accordingly, the FDA is urging physicians to submit investigational new drug (IND) applications [49]. Per FDA stipulations, plasma collected from recovered COVID-19 patients must have a negative SARS-CoV-2 test and must be symptom free for 14 days. Donors must also meet the eligibility criteria for standard blood donors set forth by the federal regulation 21 CFR 630.10 and 21 CFR 630.15; and standard testing is to be undertaken set as per regulation 21 CFR 610.40. So far, five clinical trials have begun to investigate convalescent plasma in a variety of COVID-19 settings: [44] as prophylaxis after exposure, in treatment of symptomatic but mild disease to avoid complications and hospitalization, for moderate disease in hospitalized patients to prevent ICU admission and ventilation, as rescue therapy in severe infection in mechanically ventilated patients, and in pediatric patients. For patients who may not meet criteria for these clinical trials, the FDA has also approved protocols for emergency use and expanded access [49].

Pros, Cons, and Final Deliberation

When considering adding convalescent plasma to the current armamentarium in the fight against COVID-19 infection, the pros and cons must be weighed. The pros would include possible clinical efficacy, immediate availability from a large donor pool, relative ease of procuring plasma through current approved methods, and potential cost advantages over some of the more experimental antivirals [50]. Additionally, convalescent plasma may also offer prophylactic benefits, which could keep our healthcare workers on the frontlines healthy as well as prevent self-quarantine after exposure, which risks decreasing an already overstretched workforce [7]. Clinically, some investigators have attempted to assess the prophylactic potential of convalescent plasma [51], but much more work is needed prior to drawing definitive conclusions.

The cons of convalescent plasma include basic administrative and logistical barriers of identifying, consenting, collecting, and testing donors. The efforts of the FDA delineated above should attenuate some of these hindrances. Finding donors with robust humoral response could be a hurdle as well, as not all recovered patients have detectable antibodies in the convalescent stage [39,52]. Additionally, the current lack of widely available and validated SARS-CoV-2 antibody assays, particularly assays detecting neutralizing antibodies, may hamper identification of ideal donors. Concentrating for neutralizing activity may also mitigate potential viral antibody dependent enhancement (ADE), a process in which plasma antibodies exacerbate disease by enhancing viral cell entry and viral replication by various mechanisms, some of which have been described in MERS infectious model [53,54]. Theoretically, ADE could exacerbate COVID-19 infection in patients who receive convalescent plasma from donors who were not tested for SARS-CoV-2 specific neutralizing antibodies. Moreover, the administration of passive antibodies can suppress the recipient's humoral immune system from generating pathogen-specific antibodies thereby leaving an individual susceptible to reinfection [55].

Of course, there is the rare but non-zero risk of transfusion transmitted infections. However, pathogen reduction could improve the safety profile of convalescent plasma. In fact, one study found that psoralen treatment did not substantially reduce the titers of anti-EBOV specific antibodies or their neutralizing effect [56]. These findings are promising as they indicate that convalescent plasma can be safely modified to reduce infectious risk without disrupting possible efficacy. Finally, there are non-infectious hazards of transfusion [57]. These risks include transfusion reactions such as transfusion related acute lung injury, transfusion associated dyspnea, transfusion circulatory overload, and serve allergic reactions with associated bronchospasm, all of which could worsen respiratory disease in COVID-19 patients, especially those who are already on supplemental oxygen and/or intubated.

These pros and cons must be weighed in the context of data presented in the literature, and identifying the literature that presents the strongest evidence is fundamental. Though there are many case reports and case series that espouse the benefits of convalescent plasma, they select for the patients who did well and are confounded by co-administration of other treatment modalities, making it difficult to discern the contribution of the convalescent plasma in the patient's improvement. The nonrandomized and randomized studies presented herein appear to both support and refute the clinical efficacy of convalescent plasma in the setting of viral infections. The nonrandomized trials of convalescent plasma appear to demonstrate benefit, while most of the randomized trials have failed to demonstrate improvement in clinical outcomes. The results from the randomized control trials investigating the use of H-IVIG suggest some clinical efficacy, which may be related to uniformly high titers of antiviral antibodies in the pharmaceutical preparations. Therefore, there may be merit in concentrating future efforts in H-IVIG or concentrated formulations of antiviral antibodies. Whatever the antibody formulation, the need is evident for prospective, randomized trials comparing convalescent plasma to well defined control groups. The current SARS-CoV-2 pandemic offers yet another occasion to execute such high caliber studies, without which the clinical efficacy of convalescent plasma will continue to be in question.

Conflict of interest

The authors have no conflict of interest to disclose in relation to the submitted review.

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