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Convalescent Plasma for Infectious Diseases: Historical Framework and Use in COVID-19

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Abstract
Convalescent plasma has emerged as a promising therapeutic agent for patients with coronavirus disease 2019 (COVID-19), has received emergency use authorization, and is being widely used during the COVID-19 pandemic. Passive antibody therapy via plasma or serum has been successfully used to treat infectious diseases for more than a century. Passive antibody administration is based on the presumption that convalescent plasma or serum contains therapeutic antibodies that can be passively transferred to the plasma recipient. There are numerous examples in which convalescent plasma has been used successfully as post-exposure prophylaxis and treatment of infectious diseases, including previous coronavirus outbreaks. In the context of the COVID-19 pandemic, convalescent plasma was demonstrated to be safe and potentially effective among patients infected with COVID-19. This review provides an overview of the historical uses of convalescent plasma therapy, summarizes current evidence for convalescent plasma use for COVID-19, and highlights future antibody therapies.

Introduction
The first Nobel Prize in Physiology or Medicine in 1901 was awarded to Emil Adolf von Behring “for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths” [1].

Emerging and epidemic infectious disease outbreaks represent a significant threat to global public health [2]. On 31 December 2019, the World Health Organization (WHO) became aware of a cluster of zoonotic viral pneumonia cases linked to a wet animal seafood and wholesale market in Wuhan, China [3]. The new pathogen rapidly spread worldwide, and within 3 months was declared a pandemic by the WHO, on 11 March 2020 [4,5]. The causative agent was a novel strain of coronavirus (CoV) belonging to the same family of viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and was dubbed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6]. The disease caused by SARS-CoV-2 was named coronavirus disease 19 (COVID-19). By November 2020, more than 50 million people had been afflicted worldwide and nearly 1.3 million had died due to SARS-CoV-2 [7].
In response to the pandemic, clinical research has focused on evaluating the effectiveness of open-label COVID-19 therapies [8]. Initial efforts focused on repurposing existing antiviral drugs, with limited success except for remdesivir. Among hospitalized patients with COVID-19, hydroxychloroquine [9], lopinavir/ritonavir [10], and interferon [11] had little or no clinical or mortality benefit. However, dexamethasone therapy was shown to have a mortality benefit among patients receiving respiratory support via supplemental oxygen or mechanical ventilation [12], and remdesivir had a clinical benefit among patients not receiving respiratory support [13]. In light of the lack of definitive treatments for hospitalized patients with COVID-19, current medical management remains largely supportive. Although vaccines are under investigation and two vaccines received Emergency Use Authorization (EUA) in the US and conditional approval in several other countries in late 2020, there are significant barriers to rapid implementation, including regulatory standards, logistic hurdles, and intrinsic properties of product storage (i.e., cold storage) that preclude immediate, rapid distribution and administration en masse [14,15].

In contrast, convalescent plasma therapy is likely a readily implementable [16], safe [17,18], and effective stopgap treatment for COVID-19 [19,20] until the “COVID-19 vaccine cavalry” arrives. Importantly, passive immunity therapies are potential long-term immunization and treatment strategies for patients who are unable to receive a vaccine. In this context, this review briefly describes SARS-CoV-2 and its clinical implications. Subsequently, we discuss the mechanisms of passive immunotherapy and outline the historical precedent for antibody-based therapies. Finally, we conclude with a summary of evidence behind the use of convalescent plasma for treatment of COVID-19.

**SARS-CoV-2 and Clinical Implications**

**SARS-CoV-2**

CoVs are large, enveloped, single-stranded RNA viruses that are usually present in animals or humans [6,21]. With the emergence of SARS-CoV-2, seven CoV species are now known to cause human disease. Four viruses (HKU1, OC43, 229E, and NL63) are prevalent in humans, causing only mild to moderate upper respiratory symptoms, similar to the common cold in immunocompetent recipients [6,21]. The remaining three strains—MERS-CoV, SARS-CoV-1, and the newly discovered SARS-CoV-2—can cause fatal pneumonia and have led to major epidemics and pandemics [6,21].

SARS-CoV-2 has multiple unique characteristics, including being highly transmissible during asymptomatic infection, which has contributed to its rapid and pandemic worldwide spread [22]. The spike proteins of CoVs have a region called the receptor-binding domain (RBD) that is required for entry into human cells [23]. Similar to those of other CoVs, the SARS-CoV-2 RBD is effective at invading cells in the upper respiratory tract (e.g., sinuses). However, SARS-CoV-2 is more efficient than other CoVs at infecting cells in the lower respiratory tract (e.g., lungs). Moreover, SARS-CoV-2 binds to the ACE2 receptor with high affinity and is uniquely equipped for forcing entry into host cells. Relative to SARS-CoV-1, SARS-CoV-2 is 10 to 20 times more likely to bind ACE2 and has an RBD that is particularly close fitting [23]. These unique characteristics of SARS-CoV-2 contribute to the variability of clinical presentations and high mortality rates among patients with COVID-19 [24].

COVID-19 can present with a wide range of clinical manifestations, varying from an asymptomatic carrier state to severe, multi-organ failure requiring intensive care unit level of care [6,21]. The virus is primarily transmitted via respiratory droplets from face-to-face contact and to a lesser extent via aerosols and contaminated surfaces [25]. The mean incubation period of COVID-19 is approximately 5 days, with more than 95% of patients showing symptoms within 11 days of infection [6,21]. Among patients with COVID-19 who require hospitalization, the average interval from symptom onset to hospital admission is 7 days. The median age of hospitalized patients ranges between 47 and 73 years old, and most (~60%) hospitalized patients are male [6,21].

**Convalescent plasma therapy**

Since the 1890s, passive antibody therapy has been successfully used to treat infectious diseases [19]. Prior to the availability of monoclonal antibodies and gamma globulin products, passive immunization therapy relied on use of convalescent or immune blood products (i.e., plasma or serum) collected from recovered donors (or animals) as a therapeutic agent for at-risk or infected patients for the purpose of prophylaxis or treatment of a specific pathogen [26]. Contrary to active immunization therapy (vaccination), which requires an extended time to elicit an immune response and can display a wide range of clinical variability among recipients [26], passive antibody administration involves the transfer of pre-formed antibodies and is the only effective strategy that confers immediate protection in susceptible individuals. Hence, until an effective vaccine becomes widely available, convalescent plasma has the potential to confer immunity among at-risk or infected patients, reducing the societal disease burden during large-scale pandemics [26].

Historically, the use of passive immunotherapy has involved different formulations, including whole blood, pooled human immunoglobulin, convalescent blood products, antibodies harvested from animals such as horses and rabbits, and, more recently, monoclonal or polyclonal antibodies [27]. Plasma collection by apheresis with subsequent convalescent plasma transfusion has been the most widely used passive immunotherapy strategy during prior pandemics [27]. Practically, an individual who has recovered from an infectious disease has a blood product withdrawn via venipuncture, and the blood product is screened for neutralizing antibodies (see below) specific to the causative pathogen. Ideally, high-titer neutralizing antibody convalescent plasma is used for therapy to maximize biologic activity. Convalescent plasma may be transfused to non-infected individuals to provide passive immunity to the recipient or to ameliorate the disease course in infected individuals [27,28].

Convalescent plasma confers immunity or is therapeutically active in patients with disease primarily via neutralizing antibodies.
against a specific infectious agent [29]. Neutralizing antibodies that bind to a pathogen restrict entry of the pathogen into host cells and enhance clearance of the pathogen via antibody-dependent phagocytosis, antibody-dependent cellular toxicity, and/or complement activation [29]. Additional bioactive agents in convalescent plasma may also contribute to the reduction in disease burden, including anti-inflammatory cytokines, pentraxin, natural antibodies, defensins, enosodemes, and other agents [29]. Direct and indirect humoral and cellular immune mechanisms by which convalescent plasma acts against pathogens have been also described [30–32]. Ultimately, the general goals of convalescent plasma therapy are to initiate or augment the humoral immune response, mitigate the potential cytokine storm, improve the disease course, and reduce disease progression [33].

A fundamental principle of convalescent plasma therapy is that to maximize clinical or mortality benefit, the plasma must be given early in the course of the infectious disease [34]. This fundamental principal has been repeatedly recapitulated over the past century, notably including during the meningococcal meningitis epidemic in 1913 and for diphtheria infections in children in 1940.

**Historical Framework of Convalescent Plasma**

**Broad use for infectious diseases**

Convalescent plasma therapy is reported back to the late 1800s, during which time it was the primary means of treating many infectious diseases prior to the development of antimicrobial therapy in the 1930s [19]. In 1890, Emil Adolph von Behring and Shibasaburo Kitasato used immune serum to treat tetanus and diphtheria [35], and it was particularly effective at both preventing and treating diphtheria [35]. The use of immune serum garnered support worldwide and became a revolutionary treatment. In light of these discoveries in immune serum therapy, Emil Adolph von Behring was awarded the first Nobel Prize in Physiology or Medicine in 1901 [35]. Notably, for bacterial diseases, therapy relied on the use of serum from immunized animals, while for viral diseases, physicians relied on human convalescent sera, given that virology was in its infancy and it was not possible to obtain virus for immunization studies. Convalescent blood product therapy became the basis for prevention and treatment of a myriad of infectious diseases during the 20th century, also serving as the foundation for vaccine development. Historical data from convalescent plasma trials for infectious diseases are summarized in **Table 1**.

The Spanish influenza (1918 to 1920), caused by an H1N1 influenza virus of avian origin, was the first reported pandemic for which convalescent blood products were used as therapeutic agents. A meta-analysis of eight studies from the Spanish influenza pandemic evaluated the use of convalescent plasma to treat 1,703 patients and provided evidence that infected patients who received convalescent blood products had 21% lower mortality than patients not treated with convalescent plasma [36]. Interestingly, the greatest clinical and mortality benefits were noted among patients receiving convalescent blood products in early stages of the disease course [36].

During the first half of the 20th century, the therapeutic role of convalescent blood products extended to other viral conditions, such as mumps [37], polio [38], and measles [39], and bacterial infections, including *Haemophilus influenzae B* [40], pneumococcus, and meningococcus [41] infections. Nevertheless, the use of convalescent plasma therapy to treat bacterial infections markedly declined following the discovery of antibiotics in the 1930s and was largely abandoned by the mid-1940s.

In the post-antibiotic era, the interest in antibodies as therapeutic agents for infectious diseases has been notable but has generally been restricted to replacement therapy for patients with immunoglobulin deficiencies [19] or in the context of epidemics or pandemics. During the intervals between infectious disease outbreaks, however, support for convalescent plasma therapy appears to wane, only to wax during an ensuing infectious disease outbreak.

Between 1974 and 1978, a double-blind, randomized clinical trial in patients with Argentine hemorrhagic fever treated with convalescent plasma within 8 days of disease onset revealed a 15.4% lower mortality rate compared to patients who received control plasma lacking neutralizing antibodies to Argentine hemorrhagic fever virus [42]. Comparable results were described in subsequent outbreaks of Argentine hemorrhagic fever [43]. Similarly, during the 2009-2010 H1N1 influenza pandemic, convalescent plasma was used to treat individuals with severe H1N1 infections requiring intensive care [44]. Patients treated with convalescent plasma had reduced respiratory viral burden, reduced serum cytokine responses, and reduced mortality [44]. During the 2013 West African Ebola epidemic, a small nonrandomized study in Sierra Leone revealed significantly longer survival for patients who were treated with convalescent whole blood compared to patients receiving standard treatment [45]. Two patients with Ebola who were transferred to the U.S., were treated with a combination of convalescent plasma and an experimental drug (TKM-100802), and both survived their infections [46]. There is also anecdotal evidence from the H5N1 [47,48] and H7N9 [49] avian flu outbreaks that use of convalescent plasma was effective, with all patients treated with convalescent plasma surviving. Although each viral disease and epidemic is unique, these experiences provide important historical precedents supporting convalescent blood products as “empiric” therapies that should be readily implemented early during a pandemic and disease course for patients.

**Use of convalescent plasma for treatment of CoVs**

Convalescent plasma is not a new therapy in the management of CoVs [50]. During the 21st century, there have been two major epidemics caused by CoVs that were associated with high mortality: the 2003 SARS-CoV-1 epidemic originating in Hong Kong and the 2012 MERS-CoV epidemic, which originated in Saudi Arabia. In both outbreaks, the high mortality and absence of effective therapies engendered the use of convalescent plasma.

The initial studies supporting the use of convalescent plasma for treatment of SARS-CoV-1 were limited to case reports [51,52] and case series [53,54]. Multiple subsequent non-randomized and retrospective studies added more robust evidence to the efficacy
| Disease/outbreak                        | Study description                                                                 | Finding                                                                 |
|----------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Diphtheria (Corynebacterium diphtheria) | Case series of 220 children diagnosed with diphtheria                              | Transfused patients severe diphtheria or mortality rate: 23% (51/220)  |
|                                        | Treatment started on the first 2 days after diagnosis of disease was ~100% successful, whereas by day 6, a steep decline to ~50% was observed. |                                                                          |
| Pneumonia (pneumococcal pneumonia)     | Aggregation of 13 non-randomized studies                                           | Transfused patient overall mortality rate: 21% (374/1815)               |
|                                        | Non-transfused patient overall mortality rate: 31% (518/1689)                      | Mortality reduction associated with convalescent plasma: 10%           |
| Meningitis (meningococcal bacteria and viruses) | Review of several meningitis epidemics where convalescent serum therapy was employed | In the Shreveport, Louisiana, meningitis epidemic (1912):               |
|                                        | • Transfused patient overall mortality rate: 30% (53/176)                         | • Non-transfused patient overall mortality rate: 85% (63/74)            |
|                                        | • Mortality reduction associated with convalescent plasma: 55%                    |                                                                          |
| Chickenpox (varicella-zoster virus)    | Post-exposure prophylaxis case series study of immunocompromised patients exposed to varicella | Transfused patients rate of developing varicella infection: 32% (10/31) |
| Measles (Morbillivirus)                | Post-exposure prophylaxis case series study of patients exposed to measles        | Transfused patients rate of developing measles infection: 10% (10/102) |
| 1918 Influenza pandemic (influenza A H1N1 virus) | Meta-analysis of eight matched-control studies                                   | Transfused patient overall mortality rate: 16% (54/336)               |
|                                        | Non-transfused patient overall mortality rate: 37% (452/1219)                     | Mortality reduction associated with convalescent plasma: 21% [95% CI, 29%-54%] |
|                                        | Patients transfused <4 days of pneumonia complications overall mortality rate: 19% (28/148) |                                                                          |
|                                        | Patients transfused >4 days of pneumonia complications overall mortality rate: 59% (49/83) |                                                                          |
| Argentine hemorrhagic fever (arenavirus) | Double-blind randomized clinical trial                                             | Transfused patient overall mortality rate: 1% (1/91)                  |
|                                        | Non-transfused patient overall mortality rate: 17% (16/97)                       | Mortality reduction associated with convalescent plasma: 16%           |
| 2003 SARS epidemic (SARS-CoV-1)        | Matched-control study                                                             | Transfused patient overall mortality rate: 0% (0/19)                  |
|                                        | Non-transfused patient overall mortality rate: 24% (5/21)                        | Mortality reduction associated with convalescent plasma: 24%           |
| 2009-2010 influenza pandemic (influenza A H1N1 virus) | Matched-control study                                                          | Transfused patient overall mortality rate: 20% (4/20)                |
|                                        | Non-transfused patient overall mortality rate: 55% (40/73)                      | Mortality reduction associated with convalescent plasma: 80% (95% CI, 31% to 94%) |
| 2012-2015 MERS epidemics (MERS-CoV)     | Case series study                                                                | Transfused patient overall mortality rate: 0% (0/3)                   |
| 2013 Ebola epidemic (Ebola virus)      | Matched-control study                                                             | Transfused patient overall mortality rate: 28% (12/43)                |
|                                        | Non-transfused patient overall mortality rate: 44% (11/25)                      | Mortality reduction associated with convalescent blood transfusion: 16% |
| COVID-19 pandemic (SARS-CoV-2)         | Meta-analysis of 17 studies (13 matched-control, four randomized clinical trials) | Transfused patient overall mortality rate: 19% (530/2755)              |
|                                        | Non-transfused patient overall mortality rate: 29% (2106/7217)                   | Mortality reduction associated with convalescent plasma: 51% (CI, 36% to 63%) |
of convalescent plasma for SARS-CoV-1. A study by Soo et al. compared 21 patients treated with steroids (methylprednisolone) to 19 patients receiving convalescent plasma [55]. The number of patients discharged by day 22 of hospitalization was higher for patients treated with convalescent plasma than for those in the steroid group (74% versus 19%, respectively). Additionally, the mortality rate was lower in the convalescent plasma group (0 deaths) than in the steroid group (5 deaths) [55].

The largest investigation of convalescent plasma during the SARS-CoV-1 outbreak involved 80 patients with SARS in Hong Kong [56]. In a retrospective analysis, 80 patients who received convalescent plasma were dichotomized into early and late transfusion groups, using 14 days between the onset of symptoms and the transfusion date as the cut point [56]. Compared to the late transfusion group, the early group had improved prognosis, as evidenced by a higher rate of hospital discharge by day 22 (58% versus 16%). These data suggest that convalescent plasma is an effective treatment for CoV infections and are consistent with the notion that the optimal use of convalescent plasma involves early administration. In addition, patients who were RT-PCR positive and seronegative for CoV at the time of therapy had improved prognosis [56], consistent with the notion that early use, prior to host development of an immune response, was most effective. A meta-analysis including eight observational studies and 214 patients with SARS demonstrated a mortality benefit following transfusion of convalescent plasma [57].

The initial case reports and case series in the MERS epidemic failed to show a clinical benefit for patients who were transfused with convalescent plasma containing uncharacterized neutralizing antibody titers [58]. In line with the notion that neutralizing antibody titers are a marker of convalescent plasma potency, a subsequent study provided evidence that transfusion of convalescent plasma containing a high MERS-CoV neutralizing antibody titer resulted in seroconversion of the recipient post-transfusion. However, seroconversion was not achieved among patients transfused with convalescent plasma containing a low neutralizing antibody titer [59]. These findings highlight a challenge for the therapeutic use of convalescent plasma, namely, that recovered survivors of viral diseases may not produce high-titer neutralizing antibody [60].

Use of Convalescent Plasma for Treatment of COVID-19

Characterization of COVID-19 convalescent plasma

In the current COVID-19 pandemic, blood collection centers from around the world have established programs for recovered survivors to donate COVID-19 convalescent plasma, and regulatory agencies in the U.S. have provided widespread access to convalescent plasma for emergency use in hospitalized patients with COVID-19. Convalescent plasma may be obtained from recovered COVID-19 survivors via apheresis or separated from whole blood collected as a standard blood donation (Fig. 1). Apheresis collection is strongly preferred because it yields more units of convalescent plasma per donation and for a given donor it may be performed more frequently than standard blood donation [61]. There were several barriers to recruitment of potential convalescent plasma donors during the COVID-19 pandemic primarily due to public health interventions to mitigate the spread of COVID-19, including physical distancing, restricted traveling and public transit, and imposed lockdowns [62]. Strategies that have been used to successfully recruit convalescent plasma donors include donor self-identification, based on public awareness following social media campaigns and campaigns through formal media outlets, as well clinician referral of patients who previously tested positive for SARS-CoV-2 infection [63].

Early work from the current CoV pandemic suggests that SARS-CoV-2 elicits a robust immune response with high levels of antibodies, including immunoglobulins (IgM and IgG), for months after the onset of COVID-19, suggesting a relatively large window of time and high probability of successful extraction of high-titer anti-SARS-CoV-2 plasma [64-68]. Subsequent studies have highlighted several nuances in the neutralizing antibody response; levels have been found to be higher following more severe disease [69] and to decrease substantially within the first 90 days after symptom onset in individuals with mild disease [70]. Neutralizing antibody levels can be measured in donors or convalescent plasma units indirectly, using enzyme-linked immunosorbent assays or pseudovirus neutralization assays, or directly, using live SARS-CoV-2 neutralization assays performed under biosafety level 3 conditions. Under the U.S. emergency use authorization for use of convalescent plasma to treat COVID-19 [71] issued on 23 August 2020, convalescent plasma units were dichotomized as low or high antibody titer based on results from a qualitative chemiluminescent immunoassay for detection of IgG against spike protein.

COVID-19 convalescent plasma routinely undergoes standard infectious disease screening for donated blood products but is not routinely tested for SARS-CoV-2, as respiratory viruses are not known to be transmitted by transfusion [72]. ABO and Rhesus blood type are determined to facilitate compatible plasma transfusion.

Safety profile of COVID-19 convalescent plasma

In interim reports from a large U.S. national registry including over 100,000 hospitalized adults with COVID-19, data from the first 5,000, and 20,000 patients transfused with COVID-19 convalescent plasma demonstrated low incidences of transfusion reactions (<1% of patients) [17,18]. These interim reports provide evidence that among hospitalized patients with COVID-19, transfusion of convalescent plasma is safe and carries no excess risk of complications beyond what may be expected from fresh frozen plasma use in critically ill patients [18]. The safety of convalescent plasma treatment for COVID-19 is further supported by data from a randomized clinical trial comparing convalescent plasma transfusion to fresh frozen plasma transfusion [73]. In this trial, events were seen at comparably low rates between the control (7%) and convalescent plasma (4%) arms, suggesting that the safety profile of convalescent plasma transfusion is similar to the known safety profile of fresh frozen plasma transfusion.
Efficacy signals for COVID-19 convalescent plasma

There have been several randomized, controlled trials investigating convalescent plasma treatment in patients hospitalized for severe or life-threatening COVID-19 [74-78]. Four of these trials found a (non-significant) reduction in mortality following treatment with convalescent plasma [74-77] versus control, whereas one trial found no mortality benefit [78,79]. However, in the latter study, by Agarwal et al. [78], a positive effect of convalescent plasma on clinical symptoms and viral clearance was still evident, despite treatment being late in the disease course (median time to treatment = 8 days after symptom onset). Furthermore, reduced mortality from COVID-19 with convalescent plasma treatment has been observed consistently in matched-control studies [68, 80-91]. When pooling data across all randomized trials and controlled studies, convalescent plasma treatment was shown to be associated with a significant reduction in mortality (mortality in convalescent plasma group, 31%; versus mortality in control group, 19%; odds ratio, 0.5; 95% confidence interval (CI), 0.40 to 0.69; \( P < 0.001 \)) [92].

Analyses from the U.S. COVID-19 convalescent plasma expanded access program (EAP) have revealed a dose-dependent response between the neutralizing antibody titer in donor convalescent plasma and COVID-19 mortality, where patients who received convalescent plasma with higher neutralizing antibody titers had lower mortality than patients who received convalescent plasma with lower neutralizing antibody titers (7-day mortality, ~9% versus ~12%) [93]. A smaller cohort study (\( n = 49 \)) by Maor et al. [94] similarly found that a larger proportion of patients who received convalescent plasma containing high levels of virus-specific antibodies improved within 14 days compared to those receiving low-IgG convalescent plasma (~61% versus ~37%). A dose-dependent response between mortality and IgG antibody levels was also apparent in an Argentine randomized control trial of early plasma use in elderly patients [95]. The existence of a dose-response relationship is a particularly strong piece of evidence for plasma efficacy, which directly implicates specific antibodies to SARS-CoV-2 as the active agents in convalescent plasma.

Figure 1. Schematic illustrating the use of convalescent plasma for COVID-19. An individual who was sick with COVID-19 and currently recovered (COVID-19 Survivor) has blood drawn and screened for virus neutralizing antibodies. Following identification of those with high levels of neutralizing antibody, plasma containing these virus neutralizing antibodies can be administered to individuals currently sick with COVID-19. (Adapted from [26].)
Data from the EAP cohort also revealed that patients who were transfused with convalescent plasma within 3 days of COVID-19 diagnosis versus 4 or more days after diagnosis had reduced mortality (7-day mortality, -9% versus -12%) [96]. A single-center, propensity score-matched cohort study including 353 COVID-19 patients also assessed the relationship between the timing of convalescent plasma transfusion and mortality. Salazar et al. [91] found that 60-day mortality was not different between patients transfused with convalescent plasma >72 hours after admission and controls, whereas mortality was significantly decreased in patients who received high-antibody titer convalescent plasma within 72 hours of admission (convalescent plasma, -6% versus control, -11% mortality). In fact, these investigators found that the greatest efficacy of convalescent plasma was associated with administration in the first 44 hours of hospitalization [97]. Overall, these results provide evidence that the mortality benefit of convalescent plasma is most apparent in patients transfused with plasma containing high antibody levels early in the disease course, consistent with historical precedents of convalescent plasma use in prior infectious disease outbreaks [36,56,59].

Framework for the Future

In the context of COVID-19, the available data support the notion that convalescent plasma provides clinical and mortality benefits for hospitalized patients and that the benefit of convalescent plasma is most apparent in patients transfused with plasma containing high anti-SARS-CoV-2 antibody levels early in the disease course. The observed dose-response relationship between antibody levels and mortality suggests that neutralizing antibodies are an active agent in convalescent plasma and that antibody activity is a marker of convalescent plasma potency. Based on the notion that virus-neutralizing antibodies are an effective treatment, monoclonal antibody treatments are being developed and have demonstrated encouraging signs of effectiveness in reducing symptoms and viral load in early studies [98-100]. In line with the development of vaccines subsequent to convalescent plasma in 5000 patients. J Clin Invest 2020;130:4791-7.

Although there are uncertainties and limitations regarding the use of convalescent blood products in the context of any pandemic [27], convalescent blood products should be considered an “empiric” therapy and a first-line defense against novel infectious diseases. Convalescent blood products may continue to be an effective stopgap therapeutic until the vaccine cavalry arrives. Experiences from the COVID-19 pandemic may serve as a model for future responses to outbreaks of novel viral diseases among humans.

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