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CONVALESCENT PLASMA THERAPY- A PROMISING APPROACH TO TREAT COVID 19

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INTRODUCTION

In a rapidly evolving pandemic, therapeutic options must be available quickly as is applicable to the current pandemic threat to the human life named COVID 19.[1] Besides, many other options being tried to treat the disease, apart from use of medicinal agents which at the moment are being used as a blind trial and nothing more than that, use of convalescent plasma transfusions could be of great value in the current pandemic of coronavirus disease (COVID-19), given the lack of specific preventative and therapeutic options. This convalescent plasma therapy is of particular interest when a vaccine or specific therapy is not yet available for emerging viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. Response to emerging and re-emerging infectious diseases throughout history has included rapid scientific collaborations to develop specific vaccines or therapies. To that end, currently, there is a large global trial supported by the World Health Organization (WHO), SOLIDARITY, to investigate existing therapies for COVID-19, including remdesivir, chloroquine and hydroxychloroquine, lopinavir and ritonavir, and lopinavir + ritonavir + interferon-beta. In addition, there is broad interest to leverage convalescent plasma from recovered COVID-19 patients as treatment or for prophylaxis of health care workers and other caregivers. The United States Food and Drug Administration (US FDA) has released guidance for investigation of convalescent plasma in the United States for COVID- 19.[2] Additionally, historic data has reported safety and efficacy of convalescent plasma for use in other infectious diseases, and there is also new data on convalescent plasma use in the current global public health emergency specifically to treat COVID-19. Optimization of known potential benefits of convalescent plasma may improve efficacy to support the medical needs of the widespread impact of COVID-19.

Immune (i.e. "convalescent") plasma refers to plasma that is collected from individuals, following resolution of infection and development of antibodies. Passive antibody therapy, through transfusion of convalescent plasma, may prevent clinical infection or blunt clinical severity in individuals with recent pathogen exposure. Antibody therapy can also be used to treat patients who are already manifesting symptoms of varying severity. However, passive antibody therapy is most effective when administered prophylactically or used early after the onset of symptoms.[3, 4]

COVID-19 disease

The coronavirus disease 2019 (COVID-19) viral pneumonia is now a worldwide pandemic caused by the severe acute respiratory virus coronavirus 2 (SARS-CoV-2).[5] The number of cases and associated mortality has increased dramatically since the first cases in Wuhan, China in December 2019. As of May 20th, this virus had affected at least 4900000 people worldwide and caused more than 330000 deaths. The global number of cases and related deaths are increasing steadily, with the notable exception of China that exhibits a flattening incidence curve since mid-February.

To date, no specific treatment has been proven to be effective for COVID-19. Treatment is currently mainly supportive, with in particular mechanical ventilation for the critically ill patients. Novel therapeutic approaches are in acute need. In this context, the therapeutic potential associated with convalescent plasma needs to be explored.[6, 7]

Clinical use of convalescent plasma

The transfusion of convalescent blood products is not a new clinical tool in emerging infectious disease outbreaks ("Fig.1"). Historically, passive immune therapy has involved convalescent whole blood, convalescent plasma, pooled human immunoglobulin for intravenous or intramuscular administration, high-titer human immunoglobulin, and polyclonal or monoclonal antibodies; however, plasma collected by apheresis is currently the preferred therapy.[8] Use of blood products from recovered patients dates back to the late 1800s.[9]

The Spanish influenza (pandemic of 1918–1920) was the first viral infection for which convalescent blood products were found to be potentially effective during clinical studies.[10] A meta-analysis of 8 studies of the Spanish flu (1703 patients) showed reduced mortality from treatment with convalescent blood products.[11] The possibility of using convalescent plasma for prevention and/or treatment was of interest during the recent West African Ebola outbreak due to the lack of vaccines and therapeutics, highly infectious nature of the virus, and high associated case-fatality rate.[12] Several other emerging infectious diseases, such as West Nile Virus, MERS-CoV, SARS-CoV-1, and H1N1 have also been the target of possible passive immunity with convalescent plasma. Despite a long history of convalescent plasma usage, clinical efficacy has not been studied robustly and conclusions are weak, likely because convalescent plasma was used in critical situations, during massive epidemic/pandemic outbreaks, requiring immediate actions. The effectiveness of this convalescent plasma therapy appears to differ depending on the pathogen and treatment protocols (e.g. timing, volume, and dosing of administration). There have been several publications on convalescent plasma use for SARS-CoV-1 and MERS, including reviews/editorials, observational studies (retrospective, prospective, or case series), and a systematic literature review.[13]

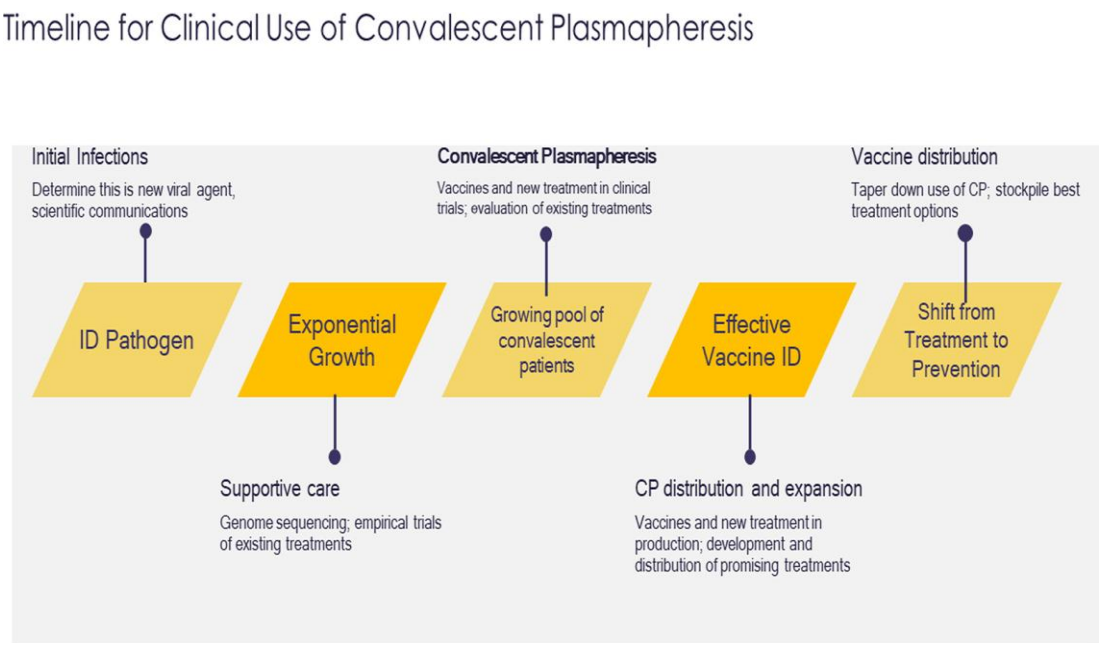

Fig. 1: Research for emerging infectious diseases treatment.

It is important to understand the antibody characteristics and titers able to affect the course of disease as well as the role of the recipients' immune response when considering therapeutic options such as convalescent plasma and vaccine candidates for new emerging viruses. Convalescent plasma has demonstrated safety and shown promise without knowledge of viral serotypes or antibody titers.

Mechanism of action

The antibodies present in immune (i.e. "convalescent") plasma mediate their therapeutic effect through a variety of mechanisms. Antibody can bind to a given pathogen (e.g. virus), thereby neutralizing its infectivity directly, while other antibody- mediated pathways such as complement activation, antibody-dependent cellular cytotoxicity and/or phagocytosis may also contribute to its therapeutic effect. Non-neutralizing antibodies that bind to the pathogen but do not interfere with its ability to replicate in in vitro systems -may also contribute to prophylaxis and/or enhance recovery.[14, 15] Importantly, passive antibody administration offers the only short-term strategy to confer immediate immunity to susceptible individuals. This is particularly the case in the setting of a novel, emerging infectious disease such as SARSCoV- 2/COVID-19. While fractionated plasma products (e.g. hyperimmune globulin, monoclonal antibodies) and/or vaccination may offer durable therapeutic options, human anti-SARS-CoV-2 plasma is the only therapeutic strategy that is immediately available for use to prevent and treat COVID-19.

The use of convalescent plasma against coronaviruses

Convalescent plasma has been used in two other coronavirus epidemics in the 21st century: SARS1 in 2003 and MERS in 2012 to the present. Experience from those outbreaks shows that convalescent plasma contains neutralizing antibodies.[16] The largest study involved the treatment of 80 patients in Hong Kong with SARS1.[17] Compared to those given plasma later, patients who were treated before day 14 had improved outcomes as defined by discharge from hospital before day 22, supporting early administration for optimal effect. Limited data also suggested benefit in seriously ill individuals: three patients with SARS-CoV-1 infection in Taiwan were treated with convalescent plasma, resulting in a reduction

in viral load; all three recipients survived.[18] Treatment with convalescent plasma was also reported in three patients in South Korea with MERS.[19] Treatment using convalescent plasma in patients with MERS was limited by a small pool of donors with sufficient antibody levels.[20] Reported dosages and characterization of convalescent plasma (i. e. with respect to antibody titers) is highly variable (Table 1). In this current pandemic, there are reports that convalescent plasma has been used in China to treat patients with COVID- 19.[21,22] In a pilot study of 10 patients with severe COVID-19, the investigators collected convalescent plasma with neutralizing antibody titers at or exceeding a 1:640 dilution.[23] Transfusion of convalescent plasma resulted in no serious adverse effect in the recipients. All 10 patients had improvement in symptoms (e.g. fever, cough, shortness of breath and chest pain) within 1-3 days of transfusion; they also demonstrated radiological improvement in pulmonary lesions. In 7 RNA-emic patients, transfusion of convalescent plasma was temporally associated with undetectable viral loads. Further, screening of 39 of 40 (97.5%) of recovered COVID-19 patients displayed neutralizing antibody titers ≥160. A case series of 5 critically ill patients in China also reported improvement in clinical status following transfusion with convalescent plasma (SARS-CoV-2 IgG titers >1000) as evidenced by weaning off mechanical ventilation, reduction in viral loads, improved oxygenation and clinical stabilization.[21] Although constrained by small sample sizes and limitations of study design and concomitant treatment modalities (e. g. remdesivir, ribavirin, corticosteroids, etc.), these findings suggest that administration of convalescent plasma is safe, reduces viral load and may improve clinical outcomes. Such has led to calls for the wider adoption of convalescent plasma for COVID-19.[24] Nonetheless, while the data support safety and potential efficacy of convalescent plasma, randomized trials are needed. Similarly, high-dose intravenous immunoglobulin (IVIg) has been suggested as a potential therapy for COVID-19;[25] however, supporting data are few and marred by potential confounders.

Table 1 Dosing of convalescent plasma in coronavirus epidemics.

Disease	Location	Dose of CP	Titre	Summary finding	Reference
SARS1	Hong Kong, China	Mean volume 279.3±127.1ml (range, 160–640 ml)	Not performed	• Retrospective chart review of 80 patients who received CP • ~14 (range, 7–30 days) following the onset of symptoms • Good clinical outcome in 33 (41.3%) patients as defined by hospital discharge by day 22 • Improved outcome associated with early administration • No adverse events	[17]
SARS1	Taipei, Taiwan	500 ml	Serum antibody (IgG) titer was >640	• Uncontrolled case series of 3 severely ill patients • Improvement in clinical status of all 3 patients	[18]
SARS1	Hong Kong, China	200 ml	Not stated	• Case report of one patient • Improved clinical status • Other therapies also used • No adverse effect	[26]
SARS1	Shenzhen, China	2 units of 250mL each (total 500mL); transfused 12h apart	Not stated	• Letter to editor/case report of one patient • Improvement in clinical status	[27]
MERS	Seoul, South Korea	4 transfusions of CP to 3 patients; volumes not stated	PRNT negative (n=2), 1:40 (n=1) and 1:80 (n=1	• Uncertain benefit although all 3 patients survived • ELISA IgG Optical density of 1.9 predictive of PRNT titer ≥1:80 with 100% specificity	[19]
MERS	Riyadh, Saudi Arabia	2 units (250–350 mL/unit) proposed for	Of 196 individuals with suspected or confirmed MERSCoV:	• Feasibility study to assess proportion of convalescent donors that had antibodies	[20]

		Phase 2	• 8 (2.7%) reactive by ELISA; 6 of 8 reactive by MN. Of 230 exposed healthcare workers: • 4 (1.7%) reactive by ELISA; 3 of 4 reactive by MN	against MERS-CoV] • No transfusions of CP undertaken	
MERS	Seoul, South Korea	250 ml	Not stated	• Case report (letter to editor) of 1 patient • Possible TRALI reported	[28]
COVID-19	Wuhan, China	200 ml	Neutralizing Anti-SARS-CoV-2–antibody titer >1:640	• Uncontrolled case series of 10 severely ill patients • Other therapies included steroids, antimicrobials, antivirals • Median onset of symptoms to CP 16.5 days (IQR11.0–19.3 days) • Improvement in clinical status of all patients • No significant adverse effect	[23]
COVID-19	Shenzhen, China	2 consecutive transfusions of 200-250 mL (400mL total)	• ELISA Anti- SARS-CoV-2–antibody titer >1:1000 •Neutralizing antibody titer >40	• Uncontrolled case series of 5 critically ill patients • Administration of CP 10-22d post-admission • All had had steroids and antivirals • Improvement in clinical status of all patients	[22]

Abbreviations (Table 1)
CP-Convalescent plasma; TRALI- Transfusion related acute lung injury ELISA- Enzyme Linked Immunosorbent Antibody assay; PRNT-plaque reduction neutralization assay; IFA- Indirect fluorescent antibody testing; MN- Microneutralization assay

Effective convalescent plasma should contain high-titer specific antibodies which bind to SARS-CoV-2 and neutralize the viral particles, block access to uninfected cells, and activate potent effector mechanisms.[29] There are scientific, operational and logistical considerations for availability to obtain plasma in recovered patients and convert this to a therapy.[29] The following elements will be essential parts of a convalescent plasma program:

1. Available donors who have recovered from the disease and meet eligibility criteria to donate convalescent serum; special attention will be necessary to assure that plasma donation will be safe for the recovering patient/donor.
2. Develop approach to screening recovered COVID patients to identify potential donors a Recovery will need to be demonstrated with appropriate standardized viral nucleic acid and antibody screening which is important because severe cases have tested positive for SARS-CoV-2 at or beyond day 10 post-onset.[30]
3. Recently approved serological assays are necessary to detect SARSCoV- 2 in serum and virologic assays to measure viral neutralization[31] a) Infrastructure and personnel to perform antibody titers in eligible donors; b) Understanding of type of antibody being measured.
4. Selection of desired antibody level in donors, preferably with high neutralizing antibody titers a FDA has recommended a titer of>1:320 for eIND.
5. Identify blood banking facilities to process the plasma donations.
6. Select specific product to be prepared (e. g. FFP, fresh plasma, or lyophilized plasma) and determine and standardize amount of plasma to be collected and product volume.
7. Establish a dosage schedule based on knowledge of SARS-CoV-2 antibodies.
8. Establishment of a registry for possible future donations should be considered.

Convalescent plasma collections workflow
Convalescent plasma can be mobilized rapidly using the established blood collection and transfusion infrastructure. Specifically, convalescent plasma is obtained and administered using standard collection and transfusion practices that are available around the world. As the number of individuals who resolve their infections increases, so does the number of potential

eligible donors of convalescent plasma. Nonetheless, there are multiple logistical hurdles if to procure a satisfactory inventory of convalescent plasma. As explained in below section, a workflow has been developed to illustrate the individual steps that need to be undertaken spanning assessment of donor eligibility, donor recruitment, collections and transfusion itself. Each brings its own challenges.

Donor eligibility

First is the question of what constitutes a convalescent donor. Relying only on absence of symptoms invites test-seeking behavior that could overwhelm - or at least burden unnecessarily - collection services with inappropriate donors. Currently proposed criteria for potential donors include a history of COVID-19, as confirmed by approved molecular testing (e.g. nasopharyngeal [NP] swab), at least 14 days passing after the resolution of symptoms (e.g. fever, cough, shortness of breath), and a negative follow-up molecular test for SARS-Cov-2 (e.g. NP swab). Individuals need to be virus-free at the time of blood collection given the potential risk posed to blood collections staff and other donors.

Donor recruitment

Those who have recovered from COVID-19 will be recruited to serve as potential blood donors. Given the magnitude of the pandemic, finding donors is not anticipated to be a problem. Approaches include community outreach in areas with robust epidemics, advertising and communication through media, and/or directly through providers (e.g. at time of discharge) and their professional organizations (e.g. databases, websites - https://ccpp19.org). There is also consideration about messaging those who receive positive results either prospectively or after the fact. The latter poses some ethical concerns, which weigh public health need against patient privacy and confidentiality. A limited waiver of HIPAA in the US may allow for greater freedom in this regard.[32] Blood centers have well-developed infrastructure for donor recruitment; while they may be best equipped to oversee recruitment in collaboration with partner hospitals, their primary responsibility is to ensure an adequate blood supply to meet clinical demand. Confronted with recent, severe blood shortages given cancelled blood drives, blood centers are forced to prioritize their efforts accordingly, while still planning for convalescent plasma collection. The latter presents additional burden on the blood centers, particularly while contending with the logistical constraints posed by COVID-19 (e.g. limited staffing, a contracted donor pool, travel restrictions etc.). Of note, while convalescent plasma could compete with routine plasma collections, this may be offset by lowered demand for standard plasma given COVID-19 mitigation measures such as cancelled elective surgeries.

Pre-donation screening to qualify convalescent donors

There is still uncertainty surrounding the optimal workflow for pre-donation screening. Heterogeneity in approaches based on local capacity and needs is expected. We have proposed a two-step process that divorces the blood center from the predonation screening; the pre-donation screening is left to the clinical provider who performs an assessment of the donor, collects an NP swab for nucleic acid testing to confirm that the individual is virus free (i.e. in the event that a negative test has not yet been obtained, and collects a blood sample for antibody testing before referring the donor to a collection facility. Anti-SARS-CoV-2 provides evidence of resolved infection. Nonetheless, current FDA guidance mandates evidence of a negative molecular test to ensure a reasonable measure of caution. This recommendation reflects the overriding mandate to protect safety given the current state of knowledge, which associates the presence of SARS-CoV-2 RNA in NP specimens with potential infectivity.

Antibody testing

Antibody testing comes with its own challenges as is reflected in the FDA guidance. In general, one cannot qualify donors or manufacture a therapeutic agent using tests that have not been vetted appropriately. However, there is uncertainty as to which antibodies are optimally effective in the context of COVID-19. Neutralizing antibodies are likely to correlate better with function. However, neutralizing antibody assays are not amenable to high throughput screening in clinical laboratories and are not widely available. By contrast, quantitative assays (e.g. ELISA) are available but commercially available assays have not been rigorously validated. Further, the relationship between total anti-SARS-CoV-2 antibodies and neutralizing anti-SARS-CoV-2 antibodies remains unclear. There is also uncertainty as to whether total antibodies or subclasses (e.g. IgM, IgG or IgA) are the optimal measure and which antigen is most informative; in this regard, various forms of the spike or S protein have been tested and used.[33,34] Limited data are currently available on the ELISAs. One group reported findings, demonstrating both "strong reactivity against IgG3, IgM and IgA" using assays targeting spike antigens as well as low cross-reactivity when testing other human coronaviruses.[33] Another group reported on performance of a point of care antibody test for combined detection of IgM and IgG, demonstrating a sensitivity and specificity of 88.7% and 90.6% respectively.[35] The antibody titer will be impacted by the timing of collection relative to onset of infection. While data are limited, seroconversion has been observed to occur between 8 and 21 days after the onset of symptoms.[36] Coupled with reports from China of high titers of anti-SARS-CoV-2 antibodies in the overwhelming majority of convalescent patients, the findings suggest that units of plasma that are collected ≥14 days after resolution of symptoms should contain high titers of antibodies. In the setting of a temporizing

therapy, one needs to balance acuity of need with a desire for a highly validated assay and a refined treatment modality. Indeed, the FDA guidance manages this uncertainty by suggesting, rather than requiring testing i.e. *"Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)".* This will certainly change as antibody testing becomes more widely available. One could even foresee routine serosurveillance of blood donors, which would bypass the need for pre-donation screening, particularly if the convalescent plasma is produced from whole blood collections.

Collection and testing

Donors who have successfully completed pre-donation screening are directed to the blood center. We have developed a specialized form to alert the blood center of a convalescent plasma donor; the form confirms that all prescreening criteria have been met, and that the plasma will be administered under IND. This ensures that donors have largely been vetted prior to collection. Upon presentation to the blood center, donors still need to qualify as community volunteer blood donors, through completion of a donor history questionnaire and standard physical examination as specified by FDA and professional standards of practice. It is recommended that common deferrals be ruled out during pre-donation screening (e.g. through administration of the questionnaire) to minimize on-site deferral at the blood center for reasons that would otherwise disqualify the individuals from community donation (e.g. risk factors for transfusion-transmissible infections). Apheresis (rather than whole blood donation) is recommended to optimize the yield of convalescent plasma. Apheresis refers to an automated technology in which whole blood is continuously centrifuged into its components (i.e. red blood cells, plasma, platelets); this allows for selective collection of the desired blood fraction with return of the other components to the donor. This is highly efficient: approximately 400-800mL of plasma from a single apheresis donation, which then provides 2-4 units of convalescent plasma for transfusion. The units are frozen within 24 hours of collection and quarantined - as is routine - pending results from standard blood donor testing. The latter fulfills regulatory requirements and mostly comprises testing for transfusion-transmissible infections (e.g. HIV, hepatitis B and C viruses etc.). There is also required testing of female donors with a history of pregnancy for HLA antibodies to mitigate the risk of transfusion related acute lung injury (TRALI).

Pathogen reduction of convalescent plasma

Available PRTs are effective in reducing infectious pathogen load in blood products.[37] Generally, PRT is intended to reduce or eliminate detectable infectious organisms, including bacteria, viruses, and parasites, from blood components intended for transfusion. Two widely used examples of PRT include the INTERCEPT Blood System (Cerus) and the Mirasol PRT System (Terumo BCT) and are briefly reviewed here.[38] In the United States, the INTERCEPT Blood System for Platelets is approved to reduce the risk of transfusion-transmitted infections from platelet transfusions. The Mirasol PRT System is currently undergoing a clinical study under an IDE with the US FDA for the treatment of platelets. Both of these PRTs are used for treatment of plasma in some countries outside of the United States. Mirasol treatment efficiently reduces EBOV titers to below limits of detection in both serum and whole blood and immunoglobulin concentrations and antibody titers remain within reference ranges.[37] Mirasol treatment also effectively inactivates MERS (> 4 log reduction, internal data on file).

The INTERCEPT Blood System has been used to treat convalescent plasma from EBOV survivors.[37] Solvent/detergent for use on single-donor plasma or mini-pools of plasma has also been used as a PRT method but this process uses large pools of plasma and takes several months to complete so would not likely be of value in this current urgent situation. The use of PRT may add a layer of safety for the use of convalescent plasma, particularly with emerging viruses for which the pathogenesis and immune response is not fully understood. Further, the use of PRT of convalescent plasma may also support use of pools, or less strict donor selection criteria in this devastating and rapidly evolving pandemic.

Convalescent plasma treatment for the West African EBOV outbreak is an example in which the WHO has proposed a PRT-based approach to increase the donor pool and add a layer of safety when there is a lack of information on pathogenesis.[12]

Distribution of convalescent plasma

In the traditional model of blood collections in the US and other high-income countries, the blood center recruits its own voluntary non-remunerated blood donors, after which there is equitable distribution based on need. The distribution model in COVID-19 employs convalescent individuals as "directed donors". The term "directed donor" typically refers to a friend or family member who donates specifically for a given patient. Directed donation is not actively encouraged given that social pressure may disincentivize the donor's admission of high-risk behavior. By contrast, the COVID-19 model employs the process differently, directing units to institutions (i.e. hospitals) - rather than to individual patients- for transfusion to patients under emergency IND. Nonetheless, if institutions are left to recruit their own donors to support internal needs (i.e. for emergent use for individual patients), it raises the question as to whether the blood centers have the ability to allocate units equitably. Many hospitals lack the experience and capacity to recruit donors, limiting their access to the supply of convalescent plasma. This model could also prove inefficient should donors pass pre-donation screening at the clinical provider yet later fail qualification upon presentation to the blood center. Once

adequate donors are recruited and high throughput testing is available, the model will likely change. Proposed under the FDA's expanded access program-would be to regionalize or centralize the recruitment, collections and inventory management. Nonetheless, major obstacles remain with extant acuity of need and little time to construct an inventory as proposed.

Optimal dosing and transfusion

Historically, the dosing of convalescent plasma has been highly variable, which may be ascribed to differences by indication (i.e. prevention versus treatment). Pertinent to the current pandemic, a study in China employed a single (200 mL) unit of plasma.[23] In the planned clinical trials, one unit has been proposed for use for post-exposure prophylaxis and one to two units have been proposed for treatment. The antibodies' duration of efficacy is unknown but is postulated to last weeks to a few months.[39] The selected dosing was based on experience with previous use of convalescent plasma therapy in SARS, where 5 mL/kg of plasma at a titer of ³ 1:160 was utilized.[17] Historically, prophylactic doses (in some cases only a quarter of that of the proposed treatment dose) have been used successfully. This was considered when designing the clinical trials. Considering first-order linear proportionality, 3.125mL/kg of plasma with a titer of >1:64 would provide an equivalent immunoglobulin level to one-quarter of 5ml/kg plasma with a titer of ³ 1:160. For a typical patient (~80 Kg), this would result in 250 mL of plasma (3.125 ml/kg x 80 kg = 250 mL > 1:64), approximating the volume of a standard unit of plasma in the US. This scheme imparts logistical ease to product preparation for adult transfusions. In pediatric transfusions (trials are being planned), there will be the need to aliquot large volume units and dose by body weight. Given the current level of uncertainty, more precise models to estimate bioavailability in tissues where virus and host interact are not yet possible.

Safety and efficacy of COVID-19 convalescent plasma

Adequately assessing safety and efficacy of such an approach is essential. As mentioned earlier, all prior studies involving convalescent plasma for the treatment of viral diseases with lung tropism are poorly controlled.[40] A randomized trial, assessing safety and efficacy upfront, would be the most scientifically-sound approach, and is therefore the preferred option. Setting up such trials in transient acute infectious epidemics settings is quite a challenge. A case-control study would be less satisfactory, but may still be a reasonable option if the controls are closely comparable to the cases for all known and unknown factors impacting the study endpoint. In that respect, adequate control patients may be eligible patients but for whom ABO compatible plasma is unavailable. However, adjustments may be necessary to take into account potential center, date, recipient/donor ABO groups,[41] and consenting/non–consenting related effects.

Whatever the format of the study, we suggest that convalescent plasma be administered early in the course of the disease in patients at high risk of subsequent deterioration (i.e. age above 70 or dependence on oxygen with a baseline oxygen saturation of less than 94%). As discussed earlier, administration before SARS-CoV-2 seroconversion may be critical. Early treatment should be favored. Based on the most recent data available,[42] initiating treatment no later than day 5 may be the most appropriate. The main study outcome in such patient population should be survival whereas secondary outcomes could be the absence of clinical deterioration (i.e. no need to transfer to an intensive care unit) and shortening of hospitalization. We suggest the transfusion at day 5 of two plasma units of 200 to 250 ml each in patients weighing between 50 and 80 kg, volume to be adjusted for patients weighing outside this range. Infusion should be at a slow rate and under close monitoring, notably to identify and treat circulatory overload occurrence or other transfusion-related immediate side effects. Close monitoring should obviously be maintained after transfusion to detect any further unintended side effects, in particular evidence of increased inflammatory in the lungs or systemically. A repeat infusion of 2 units 24 to 48 hours later may be considered after verifying adequate tolerance in a first group of treated patients.

Potential Risks

Human plasma transfusion is a routine, daily event in modern hospitals. Human Anti-SARS-CoV-2 plasma differs from standard plasma only by virtue of the presence of antibodies against SARS-CoV-2. Donors will satisfy all criteria for blood donation based upon federal and state regulations for volunteer donor eligibility and will be collected in FDA licensed blood centers. Therefore, the risks to transfusion recipients are likely to be no different from those of standard plasma. Risk of transfusion-transmissible infection is very low in the US and other high-income countries. Typically cited estimates are less than one infection per two million donations for HIV, hepatitis B and hepatitis C viruses.[43] There are also noninfectious hazards of transfusion such as allergic transfusion reactions, transfusion associated circulatory overload (TACO), and transfusion related acute injury (TRALI).[44] While the risk of TRALI is generally less than one for every 5,000 transfused units, TRALI is of particular concern in severe COVID-19 given potential priming of the pulmonary endothelium. However, routine donor screening includes HLA antibody screening of female donors with a history of pregnancy to mitigate risk of TRALI.[45] Of note, risk factors for TACO (e.g. cardio respiratory disease, advanced age, renal impairment etc.) are shared by those at risk of COVID-19, underscoring the need for careful attention to fluid volume management.

Specific risks pertaining to Human Anti-SARS-CoV-2 plasma include transfusion-transmitted SARS-CoV-2. This is largely theoretical since the recipient is already

infected and there has never been a report of transmission of a respiratory virus by blood transfusion. There is no donor screening in effect for common respiratory viruses such as influenza, respiratory syncytial virus and parainfluenza. SARS-CoV-2 is not considered to be a relevant transfusion-transmitted infection and only 1% of symptomatic patients have been reported to have detectable SARS-CoV-2 RNA in their blood.[46,47] In Wuhan, 2430 blood donations were screened in real-time (January 25 to March 4, 2020): a single (0.04%) – asymptomatic-donor was found to be positive for SARS-CoV-2 RNA.[48] A second (0.02%), asymptomatic, SARSCoV- 2 RNA positive donor was identified on retrospective screening of 4995 donations (December 21 to January 22, 2020), an additional two donors were identified as being RNA-emic through follow-up of donors who had developed fever subsequent to their donations. Nevertheless, donors will still need to wait 14 days following resolution of their symptoms to be eligible to donate; they will also need to be negative for SARS-CoV-2 as determined by molecular testing (e.g. of an NP swab).

There is also the theoretical possibility of antibody-dependent enhancement (ADE) following transfusion of human anti- SARS-CoV-2 plasma. ADE refers to a process whereby antibodies that developed during a prior infection exacerbate clinical severity as a consequence of infection with a different viral serotype. This phenomenon is well-known for some viruses, notably Dengue virus.[49] The largely theoretical risk of ADE in COVID-19 would be attributable to antibodies potentiating infection upon exposure to other strains of coronavirus; this mechanism has been offered as a possible reason for the geographic variation in disease severity.[50] Concerns about coronavirus-ADE stem primarily from *in vitro* studies using monoclonal antibodies (mAbs), whose relevance is uncertain to the polyclonal antibody composition found in convalescent plasma.[51] In this regard, mAbs have been shown to have very different properties when acting as single molecules rather than in combination with other mAbs.[52] Nonetheless, although ADE is unlikely to be relevant to the proposed use of convalescent plasma in prevention and treatment of a disease with the same virus, caution is warranted. Somewhat reassuring is the apparent absence of ADE reports with the use of convalescent plasma for SARS, MERS or COVID-19.

CONCLUSION

Convalescent plasma has the potential to provide an immediate promising treatment option while evaluating existing drugs and developing new specific vaccines and therapies. Time is of the essence to identify donor criteria and eligible donors, adjust blood processing facilities and testing capabilities, develop sufficient serologic assays for screening, and identify dosing protocols for convalescent plasma from apheresis collection to respond to the current pandemic. Given the lack of information around the natural history of this COVID virus, PRT should be considered to add a layer of safety to protect recipients of convalescent plasma.

The risks of COVID-19 infection are profound. Human plasma from recovered COVID-19 patients is projected to be a safe and potentially effective therapy for treatment and post-exposure prophylaxis alike. Substantial evidence of benefit with prior use for viral infections offers strong precedent for such an approach. However, it is critically important to perform well controlled clinical trials to confirm efficacy, thereby informing rational evidence-based decision- making.

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As the global pandemic of COVID-19 began, scientists and researcher are trying to understand and mitigate the threat, sharing their view with others in order to find possibilities of treatment and prevention. In this regard, we academician have took the step to collect the recent information and have submitted a manuscript for publication.

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