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A Review Article On: Deployment of Convalescent Plasma Therapy for the Prevention and Treatment of Covid- 19.

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ABSTRACT: Currently, there are no approved specific antiviral agents for novel coronavirus disease2019 (COVID -19) and Coronavirus disease 2019 (COVID -19) has reassessed the usefulness of historic convalescent plasma transfusion (CPT). The Convalescent plasma therapy has been introduced since early 1900s to treat the infectious disease based on evidence that polyclonal neutralizing antibodies can reduce duration of viremia, so for today's situation convalescent plasma therapy as life-saving treatment. The main findings from available data are (a). Convalescent plasma therapy reduce mortality in critically ill patients. (b). Beneficial effect on clinical symptoms after administration of convalescent plasma. (c).Increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was detected in almost all the patients after CPT therapy. Herein, we discuss the possible History, introduction, what is plasma therapy, mechanism of action of CP, Production and composition, clinical uses of convalescent plasma therapy against COVID-19 Convalescent plasma and outflow, Optimal dosing and transfusion, Potential Risk, Risk benefits analysis.

Key-words: Covid-19, Convalescent plasma therapy, Risk benefit analysis.

I. INTRODUCTION:

Historically, convalescent plasma (CP), a passive immunotherapy, has been used as a possible therapeutic option when no proven specific vaccine or drug is available for emerging infections.[1] In a rapidly evolving pandemic, therapeutic options must be available quickly. Use of convalescent plasma transfusions could be of excessiveworth in the present 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 COVID19 [2].Viruses of the Coronaviridae family have a positive-sense, single strand, RNA structure with 26 to 32 kilobases length [3].Coronaviruses have been recognized in numerous avian hosts and in several mammals, such bats, camels, mice, cats, dogs and more recently in scaly anteaters [4,5]. Most of Coronaviruses are pathogenic to humans butalso, they produce mild symptoms or asymptomatic infections. However, in the last two decades two lethal viruses have emerged within this family: the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) [6] and the Middle East respiratory syndrome (MERS) coronavirus (MERSCoV) [7]. In December 2019, a new member of the Coronaviridae family associated with severe pneumonia was detected in Wuhan, China [8]. Patients showed similar clinical findings to SARS-CoV and MERS-CoV given by high fever, dyspnea, and chest radiographs revealing invasive multilobed lesions [9,10]

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Interestingly, phylogenetic analysis revealed that SARS-CoV and MERS-CoV were close to COVID-19 in about 79% and 50%, respectively. Recently, it has been discussed that the similar sequence of the virus with human proteins could be deleterious and associated with autoimmune phenomena [11,12]. Although the current situation argues for prompt vaccination strategies, it has been suggested that it would be safer to test cross-reactivity of different viral antigens with those in humans to reduce the probability of autoimmune reactions (i.e., molecular mimicry), especially in individuals with genetic background for autoimmunity [11,13]. A recent randomized controlled trial with Hydroxychloroquine, showed reduction in body temperature and cough remission in the intervention group compared with controls [14]. Given the lack of evidence for treatment of COVID-19 and vaccines, classical and historical interventions have remerged as options for the control of disease. That is the case of convalescent plasma (CP), astrategy
of passive immunization that has been used in prevention and management of infectious diseases since early 20th century [15]

The CP is obtained using apheresis in survivors with prior infections caused by pathogens of interest in whom antibodies against the causal agent of disease are developed. The major target is to neutralize the pathogen for its eradication [16]. Given its rapid obtaining, CP has been considered as an emergency intervention in several pandemics, including the Spanish flu, SARS-CoV, West Nile virus, and more recently, Ebola virus. [17,18]. CP early administered after symptoms onset showed a reduction in mortality compared with placebo or no therapy in severe acute respiratory infections of viral etiology like influenza and SARSCoV, however, a similar response in Ebola virus disease was not observed [17,19]. During apheresis, in addition to neutralizing antibodies (NAbs), other proteins such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins and other undefined proteins are obtained from donors [20]. In this sense, transfusion of CP to infected patients may provide further benefits such as immunomodulation via amelioration of severe inflammatory response [21]. The latter could be the case of COVID-19 in which an over-activation of the immune system may come with systemic hyper-inflammation or "cytokine storm" driven by IL-1β, IL-2, IL-6, IL-17, IL-8, TNFα and CCL2. This inflammatory reaction may perpetuate pulmonary damage entailing fibrosis and reduction of pulmonary capacity [22,23]

History:

The English Physicist Sir William Crookes identified plasmas in 1879 ,although it was an American physicist .Dr. Irving Langmuir who first applied the word Plasma to ionized gas in 1929 .In the late 1850S , the Siemers company used plasma discharge to generate ozone , which acted as an agent to remove contaminant and toxin from water .Nevertheless for the next 100 years little research was conducted exploring the relationship between plasma and biological cells .From the 1960s tp1980s plasmas were mainly utilized as a secondary agent to indicate biological sterilization yet diminutive cause and effect knowledge was advanced . It was not until the mid-1990s that Scientist made considerable progress in cold plasma technology. As the news of plasma science spread visionary researchers, took notice and began to explore various way to utilize plasmas unique properties. plasma, science was is its infancy in the 1990s but by 1947 multidisciplinary teams set out, to understand the effect that plasmas had on pathogenic and nonpathogenic micro-organism and advance proof of concept lessons to demonstrate that plasma could be used as a decontaminant or sterilizing agent. Since the late 1990s plasma research has involved at a rapid pace as technology expanded into areas such as biochemical, environmental aerospace and the military[86, 87]

What is convalescent plasma therapy:

Convalescent plasma (CP) therapy is an intervention in which plasma collected from convalescent or recovered patients is used to treat various infectious diseases, and it has been proposed for emerging viral infections.[24]It is theorized that CP, which contains disease-specific antibodies that could neutralize the viral particles in COVID-19 patients, can be used to treat the disease. [25]. CP therapy involves transfusion of a blood product and is therefore associated with a risk of adverse events including anaphylaxis, transfusion related lung injury, transfusion associated circulatory overload, and transmission of infections[26].

The Public Health Agency of Canada reported an overall risk of adverse events related transfusion of blood components as 1 in 2,405 transfusions over the period of 2011 to 2015. Transfusion associated circulatory overload was the most common adverse transfusion reaction (18.1

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per 100,000 units transfused).[27]. To mitigate the risk of transfusion related acute lung injury due to donor-derived human leukocyte antigen (predominantly found in females who have been pregnant), male plasma donors may be preferred.[28,29]. A risk of TECHNOLOGY REVIEW Convalescent Plasma Therapy for the Treatment of COVID-19 4 antibody dependent enhancement of infection, in which antibodies to one type of coronavirus could amplify infection to another viral strain, has been theorized. [30]. A possible molecular mechanism for antibody dependent enhancement has been described in other coronaviruses like the Middle East respiratory syndrome coronavirus. [31]

Mechanism of action:

The antibodies present in immune 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 [32,33]. 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.

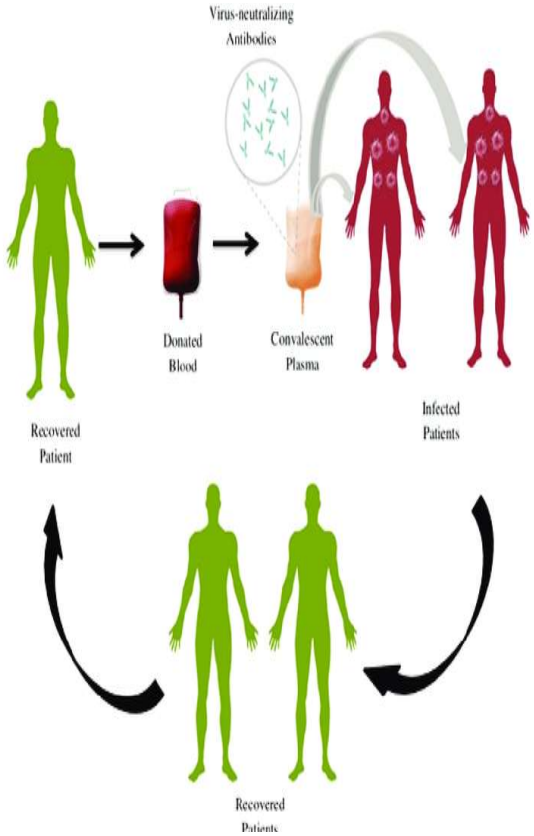

Fig. no. 1. General mechanism of action, convalescent of plasma therapy.

Production and composition:

Historical perspective:

The principle of CP infusion was established in 1880 when it was shown that immunity against diphtheria relied on existing antibodies in blood from animals intentionally immunized with non-lethal doses of toxins, that could be transferred to animals suffering from active infections[34,35]**.** Then, it was recognized that immune plasma not only neutralizes the pathogen, but also provides passive immunomodulatory properties that allow the recipient to control the excessive inflammatory cascade induced by several infectious agents or sepsis [20,35].In the early 1950s, purification and concentration of immunoglobulins from healthy donors or recovered patients provided an option to treat serious infectious diseases as well as immune conditions including primary immunodeficiencies, allergies, and autoimmune diseases [34,36,37]. Several convalescent blood products such as intravenous immunoglobulins (IVIg) and polyclonal or monoclonal antibodies have been developed to treat infectious conditions [15].

However, in situations of emergency, they are difficult and expensive to produce, and may not yield an appropriate infectious control. Thus, the use of CP has been widely used in different outbreaks as the first therapeutic option given the lack of effective medications or vaccines, and often as last chance or experimental treatment [20]**.** From the Spanish influenza to the current pandemic caused by SARS-Cov-2, it has been observed that the use of CP significantly reduces the case fatality rates. That is the case of Influenza A (H1N1) pdm09, Spanish Influenza A (H1N1), and SARS-CoV infections in which the use of CP was associated to reduction in fatality rates, mortality [6,38-50]**.** The safety of the use of CP is another issue that has been historically relevant in epidemics. Currently, evidence exists of the safety of CP in situations of emergency. In epidemics of Influenza A (H1N1), SARS-CoV and MERS-CoV, studies did not find any adverse event associated to CP administration. In the case of Ebola, CP administration was associated with mild adverse reactions such as nausea, skin erythema, and fever [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 [51].The largest study involved the treatment of 80 patients in Hong Kong with SARS1 [52]**.** 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 [53]**.** Treatment with convalescent plasma was also reported in three patients in South Korea with MERS [54].Treatment using convalescent plasma in patients with MERS was limited by a small pool of donors with sufficient antibody levels [55]**.** Reported dosages and characterization of convalescent plasma (i.e. with respect to antibody titers) is highly variable. In this current pandemic, there are reports that convalescent plasma has been used in China to treat patients with COVID19 [56, 57]

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 patents 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 [57]. Although constrained by small sample sizes and 5 limitations of study design and concomitant treatment modalities (e.g.ribavirin, corticosteroids, etc.) these findings advise 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 [58]. Nonetheless, while the data support safety and potential efficiency of convalescent plasma, randomized trials are needed [58]. Similarly, high-dose intravenous immune globulin (IVIg) has been suggested as a potential therapy for COVID-19 [59].

Convalescent plasma collections workflow:

Convalescent plasma can be prepared rapidly using the recognized blood collection and transfusion infrastructure. Specifically, convalescent plasma is obtained and administered using standard collection and transfusion practices that are available around the world.

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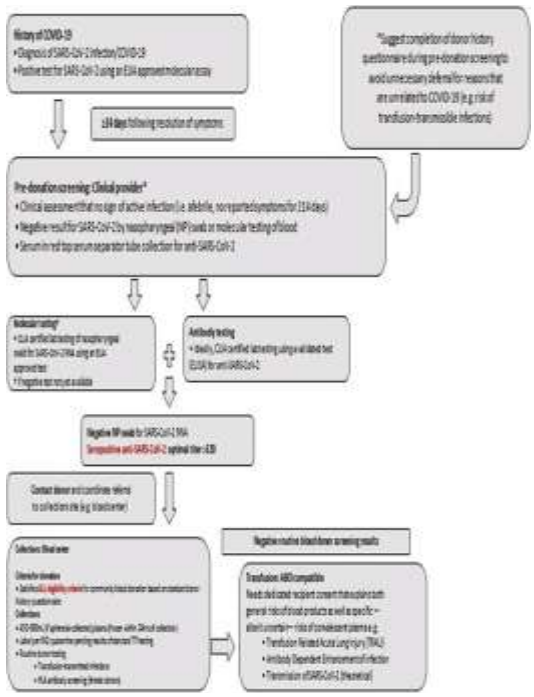

Fig. no. 2. Convalescent plasma collections workflow. EUA, EmergencyUse Authorization; TTI, transfusion-transmitted infection.

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 postures some decent 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. [60].

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 [61,62].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 [19].

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 [63].The antibody titter 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 [62,64].Coupled with reports from China of high titters 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 titters of antibodies [65].

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 8 suggesting, rather than requiring testing i.e. "Defined SARS-CoV-2 neutralizing antibody titters, if testing can be conducted (e.g., optimally greater than 1:320)[66].

Optimal dosing and transfusion:

Historically, the dosing of convalescent plasma has been extremelyinconstant, which may be ascribed to changes by indication (i.e. prevention versus treatment). Pertinent to the current pandemic, a study in China, employed a single (200 mL) unit of plasma [66]. 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

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last weeks to a few months [67,68]. 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 1:160 was utilized [52].

Potential Risks:

Human plasma transfusion is a monotonous, everyday event in modern hospitals. Human Anti-SARS-CoV-2 plasma varies from standard plasma lone by virtue of the existence 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 centres. 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 [69]. There are also non-infectious hazards of transfusion such as allergic transfusion reactions, transfusion associated circulatory overload (TACO), and transfusion related acute injury (TRALI) [70]

Adverse Reaction	Patients no. (%)
Serious adverse reaction	0
Any adverse reaction	8 (8)
Increase in temperature	5 (5)
Itching or skin rash	4 (4)
Nausea	1 (1)
Reaction requiring reduction in infusion rate	2 (2)
Reaction requiring temporary or permanent interruption of infusion	0

* Two patients had two adverse reactions each (fever and nausea in one patient and fever and itching in another).

Table no. 1. Associated adverse effects of convalscent plasma therapy.

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 [71]. Risk factors for TACO (e.g. cardiorespiratory disease, advanced age,etc.) are joint by those at risk of COVID-19, underscoring the necessity for careful attention to fluid-volume supervision. 12 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 [72,73]

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[74]. 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 contributors who had advanced fever consequent 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 antiSARS-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 [75].

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 [76].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 [77]. In this regard, mAbs have been shown to have very different properties when acting as single molecules rather than in combination with other mAbs[78]

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 re-assuring is the seeming absence of

ADE reports with the usage of convalescent plasma for SARS, MERS or COVID-19. For completion, it is unidentified to what amount convalescent plasma might blunt the advancement of a natural immune response, especially when directed for prophylaxis.

Risk-benefit analysis:

We constructed a stochastic age-specific susceptible-exposed-infected-removed (SEIR) model of COVID-19 transmission reflective of the demography of Baltimore City to estimate the daily number of asymptomatic and symptomatic cases per day [79].Age-specific mixing was estimated using the POLYMOD data set for the United Kingdom obtained from the socialmxr R package (https://cran.rproject.org/web/packages/socialmixr/socialmixr.pdf).The symptomatic to asymptomatic ratio was set to 80%/20% [80].Age-specific mortality were calculated using the age-specific case fatality ratio from the CDC [81].Age-specific severity rates were estimated using the National Centre for Health Statistics on hypertension, diabetes, and cancer where we assumed that the percentage of incident cases that become severe was roughly the average percentage of individuals who have any of the above co-morbidities. Transmission parameters were extracted from the literature to reflect both a moderate (R0 = 2.2) and high (R0 = 2.5) transmission setting [82].

Multiple stochastic simulations were run (n=500) with the 95% quantile and average are provided. We considered incident cases for individuals between 20 – 74 to reflect the age range of healthcare workers. Healthcare workers may have a higher than the population average contact rate with infected individuals; however, given uncertainties in this value we adopted a conservative approach and assumed that mixing for healthcare workers was deep of the general residentslacking the deployment of any non-pharmaceutical involvements. Given uncertainties in the effectiveness of the intervention, we assumed 25%, 50%, or 75% effectiveness. We then calculated the break-point where the fatality ratio would need to be higher than this value for the treatment to be worse than the fatality ratio from the disease. The model high point sirresistiblead vantage from prophylaxis otherwise treatment with convalescent plasma even when conservative (e.g. 25%) guesses of effectiveness are demonstrated. For example, the proposed clinical trial was designed with a projected attack rate of 20% (10.5-35%)[83,84]. A high proportion of those who are infected will go on to severe disease including death (~1-4%) [2]. By contrast, a total of 41 transfusion-associated fatalities (1 in 414,634 blood products) were reported to the FDA in 2015 [85].

CONCLUSION:

CP is a safe and potentially effective strategy for the treatment of emerging and re-emerging pathogens, especially in those scenarios without proved antiviral agents or vaccines. IVIg and CP shared similar mechanisms of action. The potential antiviral and immunomodulatory effects of CP are currently evaluated in COVID-19. According to the physiopathology of COVID-19 severe patients should be privileged over critical ones in order to reduce mortality and improve outcomes.

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