

Convalescent Plasma Therapy for Management of COVID-19: Perspectives and Deployment in the Current Global Pandemic

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Abstract: The world is striving against the severe crisis of the COVID-19 pandemic. Healthcare professionals are struggling to treat their patients based on nonspecific therapies. Amidst this uncertainty, convalescent plasma therapy (CPT) has appeared to be an interim adjuvant therapy for severely ill patients of COVID-19 until long-term clinical trial treatment options are available. Considering the transfusion-related hazards, especially lung injuries and microbial transmission, where sensitivity is not ensured, rigorous trials should be conducted to determine this therapy's efficacy. Moreover, the ratio of recovered cases to plasma donors is not satisfying, which questioning this therapy's availability and accessibility. Although some countries are making the treatment free, the attributable cost mandates a justification for its suitability and sustainability. Our article aimed to review the published facts and findings of CPT's effectiveness in lowering the mortality rate of COVID-19. This pandemic showed that healthcare systems worldwide need core reform. A unified global collaboration must align and coordinate to face the current pandemic and enhance world readiness for future outbreaks based on health equity and equality.

Keywords: convalescent plasma therapy, safety, risk, availability, accessibility, COVID-19, global pandemic

Introduction

According to WHO's situation report (October 16, 2020), the total confirmed cases of COVID-19 are 38,789,204, with a total death estimate of 1,095,097 globally.¹ The number of affected persons and deaths are increasing in two hundred sixteen countries.¹ About 5.48 million people have already recovered from this virus globally.¹ Although precautionary measures have been notable for preventing transmission, including maintaining social distancing, personal hygiene, and face-protection with masks, there is currently no approved vaccine for curing this virus. Scientists have been extensively looking into cures for this disease. They have suggested medicines including Hydroxychloroquine, Favipiravir, Remdesivir, dexamethasone, and a few others that have been used by healthcare professionals for the antiviral effect against the COVID-19.^{2,3} Some of these treatments have proved useful in the healing process of COVID-19, but these medications' long-term clinical benefits are not yet well established. Nevertheless, convalescent plasma therapy (CPT) has recently become the focus of attention as it has earlier evidence supporting this CPT as a treatment option among COVID-19 patients.^{4,5}

Taking into account the limited data available for the treatment of COVID-19, long-established and traditional interventions have re-emerged as viable options in the regulation of this disease.⁴ This is typical in the case of CPT, a technique that entails passive immunization, which has been adopted in the management and prevention of diseases since the early 20th century.⁵ The production of CPT consists of apheresis plasma from survivors with previous infections caused by the same infective microbes who have developed antibodies against the causative agent. The focus here is to enhance resistance against the pathogen by neutralization of the offending antigen.⁶ CPT has indications as an emergency intervention in several pandemics: West Nile virus, Spanish flu, SARS-CoV, and, in recent times, the Ebola virus, based on its availability, accessibility, and cost-effectiveness.^{7–11} Instances of severe acute respiratory infections of viral origin, such as influenza, resulted in a decline in mortality rate after early CPT administration compared with placebo or untreated cases.^{7,12}

One study suggested that CPT plays a critical role, especially in low-and-middle-income countries (LMICs), as this therapy minimizes ventilator-need. Additionally, access to ventilators are extremely costly, therefore, either the patient cannot afford them, or availability is limited.¹³ It appears that CPT works effectively at the primary stage of being infected with the virus.¹⁴ Bangladesh being an LMIC, has also adopted the CPT strategy since the country's population affected by the COVID-19 is increasing day by day. A total of confirmed cases, recovered, and deceased were 249,651, 143,824 [57.6% (Recovery Rate)], and 3306 [1.3% (Fatality Rate)], respectively till August 7, 2020.¹⁵ The recovered patients remain instrumental donors in the recovery process for the currently infected patients.^{16,17} Overall, this trend has now necessitated the need to investigate CPT's reliability as a cure for COVID-19 victims.

The Rationale of Convalescent Plasma as a Treatment Option

To manage infection of certain diseases, the patient may be prescribed antibodies against the specific antigen.^{18–21} The immune system and antibodies respond to any infectious ailments either due to infective pathogenic microbes or due to the response towards a specific vaccine against particular infective disorders.²² The production of antibodies requires time, and the time necessary for the immune

system depends on individual patients or the recipient immune system.^{23–26} Therefore, antibodies recovered from similar patients or artificially generated in animals are considered one way to offer instant immunity among susceptible cases for a brief period.^{27–29} This therapeutic concept has a long-standing history. It was practiced as far back as the late nineteenth century (the 1890s) as whole blood or plasma administration among patients vulnerable to microbial infectious diseases.^{5,24,30–34} The German physiologist, the first Nobel laureate in Medicine and the father of serum therapy, Emil Adolf von Behring (1854–1917), won the prestigious Prize in 1901 for his discovery of serum therapy for the treatment of diphtheria.^{35,36} Additionally, Emil Adolph von Behring and a Japanese physician and bacteriologist Shibasaburo Kitasato (1852–1931) revealed tetanus immunity's treatment strategy utilizing rabbit serum.^{37,38}

The fundamental physio-pharmacological concept comprising passive immunization have added efficacy when used prophylactically than for the curative purpose of the infectious disease. Moreover, if the antibodies are administered as curative therapy, these need to be given as early as possible when the symptoms and signs develop of the particular infectious disease to maximize efficacy and to obtain the desired treatment outcome.¹⁸ This timing has not been clearly determined. It may be possible that the amount of antigens are much higher than the antibodies when the disease process turns to a full-blown severe disease reducing the effect.^{39–41} Another study revealed that antibodies work through inhibiting inflammatory processes, and this inhibitory effect is principally achieved when the infectious disease process is at the beginning stage, or the patient still asymptomatic.^{42,43}

Objectives of the Review

The aim and scope of this review is to highlight the role of CPT as a therapeutic option in the management of the current global pandemic COVID-19 pandemic.

Materials and Methods

The literature search for this narrative review was performed by searching two core scientific literature databases (Google Scholar and PubMed). The authors relied on open access journals and access to journals granted by the Universiti Pertahanan Nasional Malaysia [(UPNM), the National Defence University of Malaysia], Kuala Lumpur, Malaysia, since the current work was unfunded. Articles for which full text was not available and those not

written in English were excluded. The only non-English papers utilized refer to the history of CPT. The study was conducted between July-22-2020 to September-10-2020. The search terms used were: “Convalescent Plasma Therapy”, “Convalescent Plasma”, “CPT”, “CP”, “Plasma Therapy”, “Viewpoints”, “Arrangement”, “Management”, “Treatment”, “Therapeutic Options”, “Treatment Choices”, “Existing”, “Present”, “Prevailing”, “Worldwide”, “International”, “COVID-19” followed by snowballing references cited by critical articles. We had included all types of peer-reviewed articles published in English. Subsequently, after the search’s first round, additional references were recognized by a labor-intensive search in the selected references. The present article’s narrative nature, recent papers, and older papers with historical significance were incorporated. No systematic review or meta-analysis was performed.

The Fatality of the COVID-19 Global Pandemic

The COVID-19 pandemic has affected mankind with jet-like speed across the globe. As countries imposed strict lockdown policies on human movement with stay-home office activities, and most outstandingly, social distancing to halt the spread of the virus, thereby, all trade, commerce, financial and economic activities almost ceased.^{44,45} Currently, two-hundred-fifteen countries are affected around the planet.³ The WORLDOMETER reported that 19,259,406 confirmed cases of the COVID-19 existed.⁴⁶ Our World in Data⁴⁷ and WORLDOMETER⁴⁶ revealed that till August 7, 2020, the COVID-19 related mortality was 707,715 (Figure 1) and 717,687 respectively [Scatterplot (Figure 2) illustrating daily vs, confirmed deaths, and new confirmed cases (Figure 3)].

At present, researchers worldwide are working hard to understand and develop COVID-19 viral physiology, epidemiology, and intervention strategies.^{48–51} Yet no specific medicine and vaccine targeting COVID-19 is available to safeguard mankind.⁵² It has been reported that COVID-19 replication potential is substantially speedier than any other infectious disease affecting human beings.^{53,54} Thereby, the COVID-19 has jeopardized almost all health care systems and health equity of our world, even of most affluent and developed countries^{55–58} The COVID-19 gained attention as the “great leveler” because it affects both rich and poor equally.⁵⁹ Despite this, other studies reported that this COVID-19 pandemic has principally

affected the USA’s poorest people and is termed the “inequality virus”.^{58,60} Around 20% of diagnosed COVID-19 cases progress to clinically severe stages, affecting vital organs, and often end with multiple organ dysfunction.⁴⁵ These patients require intensive care units, ventilation, and in some cases, extracorporeal membrane oxygenation (ECMO). ECMO supports bypassing the lung for oxygen and carbon dioxide exchange.^{61,62} In general, it has been observed that the COVID-19 patients aged over 60-years with multiple comorbidities have a poorer prognosis and worse clinical outcomes.^{63,64} On the contrary, a smaller segment of the younger population suffers a high morbidity and mortality rate.⁵³

A Brief History of Convalescent Plasma Therapy

Trauma-related bleeding is the top cause of death after injury and is considered preventable.^{65,66} Early transfusions of whole blood and fresh plasma are known to augment survival, alleviate the acute coagulopathy induced by physical injury, and restore the endothelial glycocalyx.^{67,68} Several plasma formulations are currently available worldwide. Those plasma formulations include fresh frozen plasma, thawed plasma, liquid plasma, plasma frozen within 24 hours, solvent-detergent plasma, and lyophilized plasma.⁶⁹ A freeze-dried formulation of plasma termed as lyophilized plasma was initially introduced in clinical medicine during World War II in the 1930s by the American and British military^{70,71}, and is currently preferably used in parts of South Africa in a modern form. The concept of CPT is much older (since the 1800s) for the treatment of infectious disease.^{5,72} The first-ever utilization of CPT was dated to 1892 for the management of diphtheria. Later the 1920s, CPT was used for scarlet fever and pertussis till 1970.^{5,73} It has been reported that CPT has been utilized during the 1918 Spanish flu pandemic with beneficial effects with some complications.⁷⁴

Furthermore, CPT has also been used in several viral diseases. Those viral ailments comprise measles, mumps, Argentine hemorrhagic fever, influenza, chickenpox, infections by cytomegalovirus, parvovirus B19, and, more of late, Middle East Respiratory Syndrome coronavirus (MERS-CoV), H1N1 and H5N1 avian flu, Ebola, and Severe Acute Respiratory Infections (SARIs) viruses.^{5,72–78} Considering the fatal outcome of some of these viral diseases without therapeutic interventions,

CPT's overall clinical outcome for viral infections was reasonably satisfactory.

Initiation of Convalescent Plasma Therapy in the Management of the COVID-19

Initially, research from two teams from the USA detailed the theoretical context for the employment of CPT in the management of COVID-19.^{79,80} Regarding collated reports until early July 2020, only two case series have been published.^{81,82} These revealed positively that there were changes in better oxygenation, sequential organ failure assessment (SOFA) scores, and ultimately, the need for ventilator use reduced.^{81,82} Although these were not well-designed controlled studies; additionally, these patients had other medication along with CPT.^{81,82} One Chinese study comprising one hundred and three patients compared CPT with standard treatment alone did not find a statistically significant beneficial effect within twenty-eight days.⁸³ They also reported that the study was stopped prematurely. Thereby, the potential impacts of CPT might not be accurately reflected from the reported results.⁸³

Mode of Plasma Therapy Infusion and Its Association with COVID-19

As illustrated (Figure 4), patients who recovered from COVID-19 had been regarded as a valuable donor source of CPT, and especially those recovered COVID-19 individuals with a high neutralizing antibody titer at or over 1:640 dilution. Subsequently there is a need to obtain more clarity to maximize the potential clinical benefits and minimize risks associated with convalescent blood products of the COVID-19.^{16,81,84} The use of CPT for patients with COVID-19 has been attributed to either preventing infection or reducing the disease severity. The convalescent serum is beneficial in a prophylactic mode as it can minimize virulence of ailments and illnesses by neutralization of antigen by specific antibodies that may arise in individuals who are at high risk of acquiring infections, thereby reducing the rate of mortality.^{79,85} Individuals with multiple comorbidities, elderly susceptible patients, and healthcare providers are the classic example of convalescent serum recipients for the COVID-19 current global pandemic with the intention of minimizing virulence and intensity of infection, symptoms, and mortality. Research has justified the above-mentioned use of

convalescent serum, for example, with rabies viruses and hepatitis B treated with rabies immunoglobulin and hepatitis B immunoglobulin, respectively.⁸⁶ Critics claim this approach's efficacy should be questioned, especially when there is no clinical trial evidence to support this concept. However, through historical facts and with clinical shreds of evidence, it is often predicted that the administration of convalescent antibodies is likely to show effectiveness in the prevention of diseases as opposed to the treatment of already established disease.^{79,85,86}

Figure 4 depicts an individual who had COVID-19 but has recovered from this condition. Blood is drawn and then screened for virus-neutralizing antibodies. Those with high titers of neutralizing antibodies are identified. Thereafter an administration of serum containing these virus-neutralizing antibodies is given prophylactically to slow down progress or prevent infection in high-risk cases through neutralization of antigen by specific antibodies.⁸⁷ As a last resort to improve survival with SARS-infection, the use of CPT has been widely accepted in recent times.⁸⁸ Even though the use of passive antibody treatments has been recognized, there is a limited opinion that they should be used as initial therapies as opposed to their use against emerging and pandemic infectious threats.⁷⁴ In terms of additional value added by CPT, research claims that while its antibodies contribute to restrictions of viral replication,⁸⁹ its other plasma components are beneficial in replenishing coagulation factors, especially for those patients with concurrent coagulopathy when they are given to patients with hemorrhagic fevers like Ebola. Notwithstanding these trends, individual CPT shows a donor-dependent variation in antibody specificities and titers.^{79,90,91}

Considering that CPT is already being used in several diseases in general alongside its simplicity without adverse reactions, the evidence supplements the ideology that it can easily be used to treat individuals infected with COVID-19. Due to the increasing incidence, the quest to find a treatment for the SARS-Cov-2 pandemic remains a daunting challenge. Nevertheless, those patients who have recovered from COVID-19 are well suited to be capable of serum donors who can then be used for treating SARS-Cov-2 patients. The sample obtained can be stored and then used later when needed. Although it is often suggested that the potency of convalescent serum antiviral effects may not be completely reliable, they often show an increasingly significant variation.⁹² Overall, in the absence of specific therapy, CPT's use is likely to reduce disease severity positively.

Risk Factors and Safety Precautions Linked with CPT

Several studies have been conducted to determine the safety and associated risks of convalescent plasma therapy for COVID-19 patients.^{80,81,93,94} However, few reported any serious adverse effects of introducing CPT as a therapeutic measure for the COVID-19 pandemic. It is important to note that due to the sensitivity and idiosyncrasy attached to this matter, blood safety and quality must not be compromised for practical therapeutic approaches. Recognizing this fact, the focus on evaluating the risk associated with this therapy, particularly in vulnerable groups such as children, pregnant women, elderly individuals, and people with co-morbidities is essential.

Most of the studies conducted to determine the efficacy of CPT showed a significant reduction in viral load and relative risk of mortality. Generally, researchers hold the view that viremia mostly peaks in the first week of most viral infections. These patients then go on in the second week to develop a primary immune response, followed by either virus clearance or cytokine storm. Consequently, this trajectory could lead to multi-organ failure and, eventually, death. Taken together, CPT proponents have emphasized its usefulness by stating that CPT administration would be more effective in the very early stages of the disease, as confirmed in patients with SARS.^{95,96} The most common adverse reactions of CPT therapy are transfusion-related events such as chills, fever, anaphylactic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), hemolysis, antibody-dependent enhancement (ADE), and transfusion-transmitted virus.^{97,98} However, to date, it appears that the administration of convalescent plasma (CP) in COVID-19 cases is not associated with the onset of severe adverse effects.⁹³ To obtain safe and very effective therapeutic results, donor-recipient screening with antibody titer (at least 1:160, standard 1:640) remains very crucial. However, other forms of selection are appropriate for COVID-19 patients in the CPT process. The CPT screening for COVID-19 patients includes testing for transfusion-transmission infections like human immunodeficiency virus (HIV), hepatitis B virus, and most importantly, the hepatitis C virus (since SARS-CoV-2 is a respiratory virus, it is not transmitted via blood and hence no risk of transmission from the donor). Similarly, human leukocyte antigen (HLA) antibody screening of female donors with a

history of pregnancy tends to mitigate the risk of TRALI along with ABO blood compatibility testing.^{80,99,100}

Biochemistry and blood profiles such as complete blood count and metabolic tests should be encouraged for the recipient's safety. Little or no evidence regarding the safe use of CP for vulnerable groups suffering from COVID-19 has been reported to date. Multiple studies reported that CPT among children with COVID-19 showed more positive recovery from the disease than adults without any adverse effects.^{80,101} In the same vein, the therapy conducted on critically ill patients with comorbid conditions involving a pregnant woman and elderly individuals showed an increased production of anti-SARS-CoV-2 IgG antibodies; hence, projected significant reduction of viral load alongside improved symptoms without showing adverse reactions.¹⁰² This same pattern was identified in a study conducted in Guinea that involved Ebola virus cases that were treated with CPT, which included 99 patients of various age groups (including eight pregnant women) who were recipients of ABO-compatible CP and infected with the Ebola virus. No severe adverse reactions resulted from this transfusion with (including the pregnant women and their fetuses).¹⁰³

Furthermore, a study carried out on two elderly COVID-19 patients with ARDS showed signs of improvement with no adverse reactions.¹⁰⁴ Although adverse effects cannot be completely ruled out, a study of CPT conducted on ten⁷⁹ COVID-19 patients showed improved recovery from the disease without severe adverse reactions. Hence, one of these patients faced minor side effects showing an evanescent facial red spot.⁸¹ Overall, despite the limitations of the current evidence, it may be inferred that CPT could be useful for the recovery of COVID-19 even among vulnerable age groups without having adverse effects on their health. This ideology helps to reiterate the fact that more studies to demonstrate the safety and efficacy of CPT among COVID-19 patients are required,^{105–108} mainly when applied for both early and advanced phases of illness and prevention.¹⁰⁹

Recent Clinical Trials Regarding Convalescent Plasma Therapy in the Management of COVID-19

Casadevall et al reported that therapeutic success against such a novel and complicated disease as COVID-19 involving multiple vital organs with a vast spectrum of signs and symptoms will necessitate more than one particular treatment strategy.¹¹⁰ Casadevall et al,¹¹⁰ commenting on the first randomized clinical trials of CPT

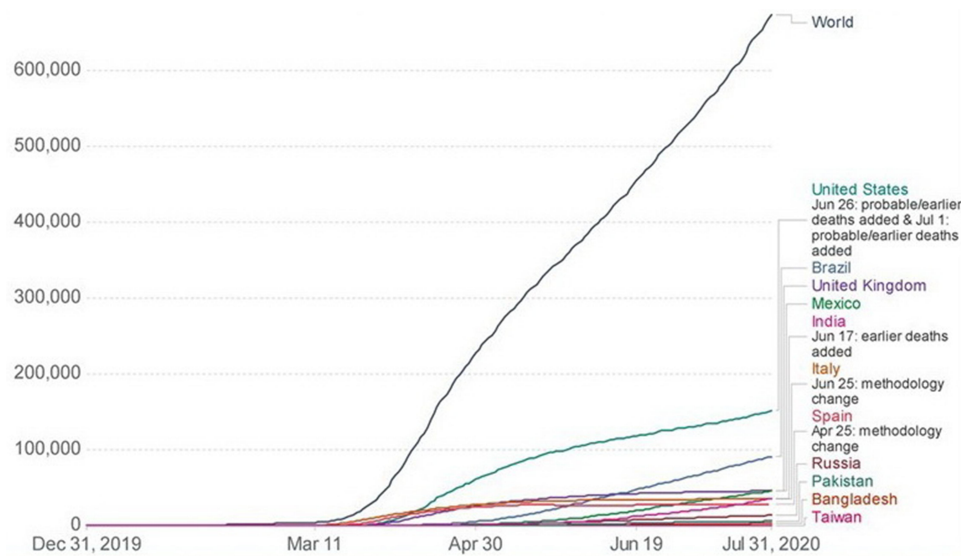


Figure 1 Cumulative confirmed COVID-19 deaths world and selected countries till July-31-2020.

Notes: This figure is reproduced from Our World in Data. Statistics and Research. Coronavirus Pandemic (COVID-19). Available from: <https://ourworldindata.org/coronavirus>.⁴⁷

for COVID-19 patients in China,⁸³ expressed a hope for plasma therapy or antibody administration the treatment options. Moreover, two studies have reported that COVID-19 convalescent plasma (CCP) transfusion improves outcome, including decreasing viral load, radiological findings improving pulmonary function, oxygenation level increase, and decreased mortality.^{81,82} These studies encouraged the US Food and Drug Administration (FDA) and the US blood-banking authorities to transfuse CCP on a record level.⁸⁰ Thereby, in

the USA alone, more than 26,000 COVID-19 patients received CCP, primarily through the US government-run extended program.¹¹¹ Additionally, multiple studies reported that CCP is well tolerated and possess no additional risk or adverse effects.^{112–115} COVID-19 brings a new research opportunity for CPT. Several clinical trials around the globe are ongoing to define the role of CPT. Furthermore, confirming the benefits of CPT will also enhance the progress regarding hyperimmune globulin and vaccine invention. However, the authors

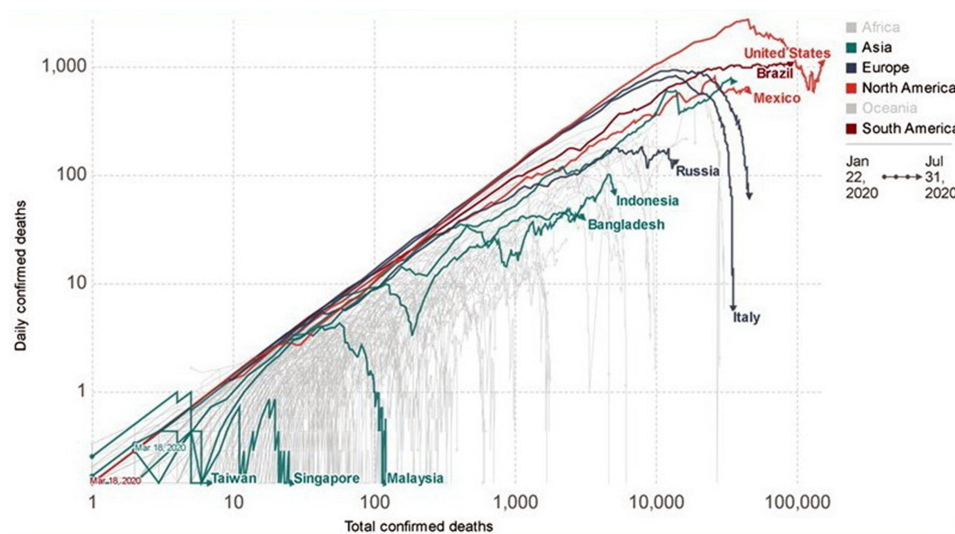


Figure 2 Scatterplot illustrating daily vs confirmed deaths due to COVID-19 cases of selected countries till July-31-2020.

Notes: This figure is reproduced from Our World in Data. Statistics and Research. Coronavirus Pandemic (COVID-19). Available from: <https://ourworldindata.org/coronavirus>.⁴⁷

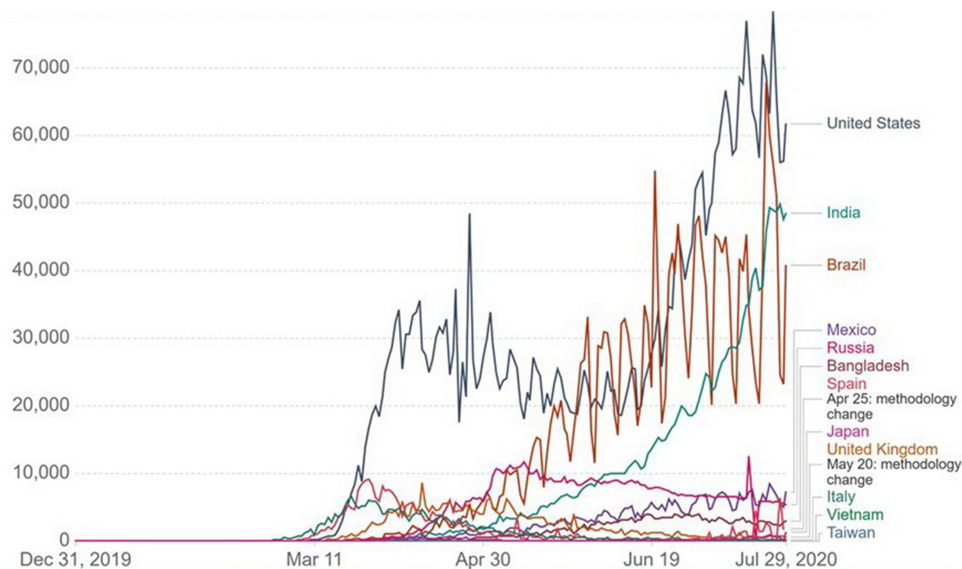


Figure 3 Daily new confirmed cases selected countries till July-31-2020.

Notes: This figure is reproduced from Our World in Data. Statistics and Research. Coronavirus Pandemic (COVID-19). Available from: <https://ourworldindata.org/coronavirus>.⁴⁷

recommended the need for coordination and synchronization of clinical trials to limit research challenges.¹¹¹ There are 2630 clinical trials of COVID-19 that are currently registered by the World Health Organization.¹¹⁶ While COVID-19 appears as a significant public health challenge, many clinical trials were ongoing.^{117–119}

FDA Recommendation for the Use of Convalescent Plasma Therapy in COVID-19

The FDA on September-2-2020 pronounced a directive to offer endorsements to health care providers and investigators on the use of CCP under an emergency use authorization (EUA) or investigational CPT under an Investigational New Drug (IND) approval during the public health emergency.¹²⁰ Full text of the recommendation of FDA regarding CCP is available from the link (<https://www.fda.gov/media/136798/download>).

CPT and the Potential of Microbial Transmission

So far, CPT has been proven to have very minimal chances of transmitting infection to recipients due to the standard guidelines authorized by the Food and Drug Administration (FDA). Notwithstanding this, certain risks still exist.¹²¹ The possible risks associated with this

transfusion include allergic reactions, damage to the lungs, and difficulty in breathing. Other fatal risks have been linked with the transmission of microbial infections such as HIV and Hepatitis B and C.^{123,124} Patient eligibility testing is a series of processes that involve the collection of relevant information from both the donor and recipient, which are then categorized and recorded for use. This data collection ultimately then helps to reduce the risk of the spread of various infections during blood transfusions.^{124–127}

There is always that probability of an error occurring at any step of the transfusion process. The resulting effects in these situations can be fatal, so proper implementation of necessary safety measures should be taken.¹²⁸ To ensure the appropriate donation of samples, the recruitment process tops the list. This aims to collect the blood correctly, to avoid wastage, and in a timely fashion. Pre-donation information is collated. Its goal is to protect both donor and recipient of these risk factors. The pre-donation details include interviews of the donor during collection, medical history, medication habits, any known risk factors, and traveling history.¹²⁹ Information remains vital as the history of any self-administered drugs should also be listed, which should also be followed by the post-donation information, which aims to add to the involved patient's safety. This step will also include an examination of the body and screening for hemoglobin.¹³⁰ The third and most sensitive section is the preparation and testing stage, which are to prepare and test

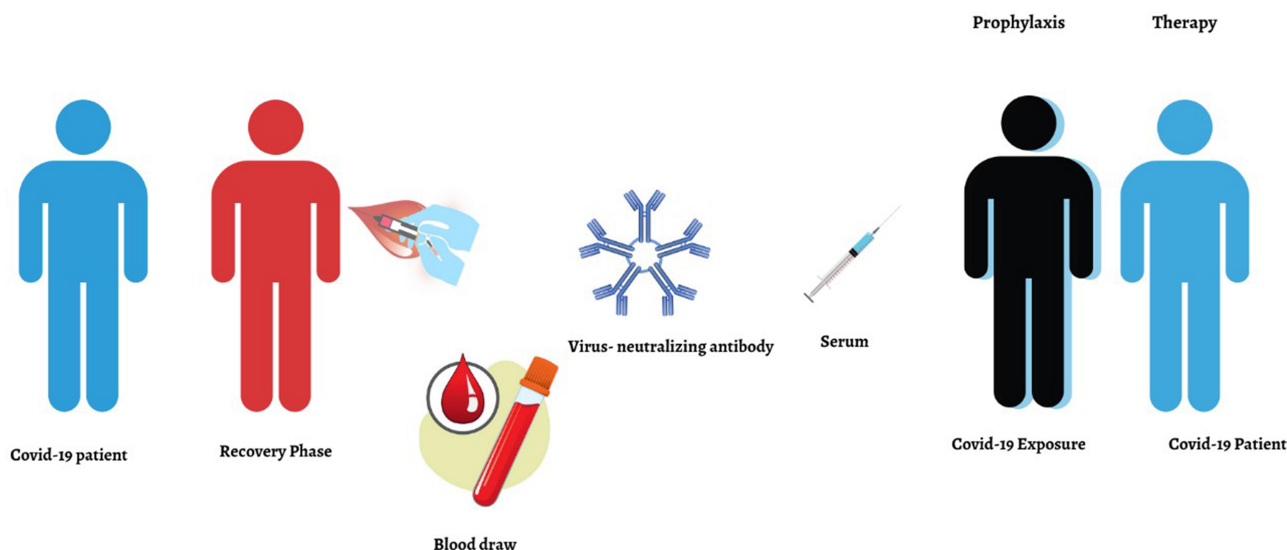


Figure 4 Infographics are showing the mode of convalescent plasma therapy for the treatment of COVID-19.

blood components on a donor's sample. The component testing mostly consists of disintegration, alteration, and quality check of samples, which entails the bacterial examination of the platelets, plasma separation,¹³¹ and pathogen inactivation.¹³² In the donor testing step, along with blood grouping and antibody testing, serological and nucleic acid tests for sexually transmitted diseases and other viral infections are usually performed.¹³¹ Studies suggested pre-donation tests should include blood grouping and even screening for HCV, HIV, HBV, syphilis, and other locally spread diseases to reduce the risk of transferring other infections.^{133,134} Although serological and nucleic acid tests are more common in developed countries, the same procedures can be replicated elsewhere based on the commonality of the disease among many people and the accessibility of resources.^{135–138}

Specific categories should be considered for eligibility and to maximize benefit, such as gender and pregnancy history, to avoid any complication or risks from¹³⁹ procedures to cause minimal risk of transmitting infection.¹⁴⁰ After completing these phases, it is vital to ensure that hospital management and clinical staff provide an aseptic transfusion.¹²⁹ Furthermore, the blood collection process must follow best practice, using sterilized equipment for its collection and storage and employing trained personnel for these procedures.^{135–138} Similarly, other studies showed that there are risks to staff from infectious blood samples.¹⁴¹ Implementation of standardized safety measures¹⁴² and expertise that provides quality training and knowledge of these procedures' risks should be continuously integrated to ensure the safety of the health care workers.¹⁴¹

Accessibility and Availability of CPT

Individuals who have recovered from COVID-19 are eligible to donate their plasma for infected individuals.¹⁴³ A study conducted by Cameo and Lahoz showed that before the pandemic peaks the number of recovered patients at any specific period is usually far lower than the number of infected patients. They also referenced the fact that 1–5% of patients are receiving CPT. The leading cause of concern is typically the scarcity of donors and blood shortage.¹⁴⁴ This has been further explained as surveys have shown that most individuals with COVID-19 are elderly people who sometimes have physical disabilities that prevent them from making donations.¹³⁰ References can be discussed using some countries' profiles in terms of ongoing CPT. Although in Bangladesh, a lower-middle-income country, most affected patients with COVID-19 range from 21–40 years of age, along with inadequate testing, contact tracing, follow-up, and awareness have constrained the processes to identify affected people and collect blood samples from the recovered patients.^{145,146} It would be better to create a central plasma bank to deliver plasma to emergency patients.¹⁴⁷ Dhaka Medical College Hospital (DMCH), Bangladesh is one of the government hospitals situated in Dhaka, Bangladesh's capital that has pioneered collecting plasma from recovered patients and treating COVID-19 patients with CPT. It provides no-cost treatment to all patients.^{145,146}

The plasma collection from donors involves the use of a particular kit worth BDT Taka 12,000/- (US\$142/-), and additional compulsory equipment is for the ALIZA test,

which presents the number of antibodies in a donor's blood, which amounts to a total of BDT 1,50,000 (US \$1770) Each kit is aimed at testing only 90 patient samples.¹⁴⁷ Considering this, it has become increasingly expensive to cater to the many COVID-19 patients through the national health coverage as Government hospitals have limited funds to finance this many people's treatment. On the contrary, a few private hospitals have provided plasma therapy and COVID-19 treatments but at very high costs. These variations of COVID-19 testing pricing projects inequality as private hospitals demand a higher price than public hospitals, which is not affordable for low- and middle-class individuals.¹⁴⁷

To support the need for this treatment, a study conducted on COVID-19 patients within sub-Saharan Africa showed the effectiveness of CPT as it reduces the mortality rate by 50% compared to those who did not get CPT. Furthermore, this study also focused on reducing the treatment costs for patients, which ultimately increased their accessibility within the health care system and then cut the number of deaths.¹⁴⁸ In China, CPT has shown a trend toward reduction of death rates. China can effectively combat this disease using CPT as they continually adapt testing strategies and understand its efficacy in saving these patients.¹⁴⁹ Unfortunately, the public hospitals could not maintain this considerable pressure of testing and treatment so this might deter the quality of treatment obtainable in public hospitals. Due to the high influx of people who visit hospitals to get treatment, there is increased vulnerability to COVID-19 by healthy individuals. Also, in many cases, people cannot access treatment or testing from these clinics and may be left unattended, leading to fatalities.¹⁵⁰⁻¹⁵² With the current global crisis this has affected income due to restrictions and loss of jobs, and the overall socio-economic condition has been detrimental to healthcare accessibility and affordability.¹⁵³ If strategies are taken to make the therapy available, affordable, and accessible for general patients, similar to other previously occurring infectious diseases, COVID-19 mortality can also be addressed.^{93,154}

Efficacy as Well as Lack of Efficacy of CPT Treatment on COVID-19 Patients

The COVID-19 expanded access program has been operating with the support of the U.S government through which plasma has been collected in support of recovered

COVID-19 patients.^{81,155,156} It has been reported that more than 2500 sites for plasma collection, more than 12,000 physicians, and more than 70,000 patients were involved in this program. According to data from this program, more than 45,000 patients have received CPT.^{155,156} Having this considerable number of patients who have received CPT, studies have focused on different CPT aspects. A study indicated that CPT's efficacy in reducing mortality is somehow limited in cases of severely ill patients and those who have comorbidities.¹⁵⁷ Besides, this study also showed less CPT efficiency for the patients treated on median day 21.5 during viral shedding.

Furthermore, the rate of recovery was poor in the case of the late transfusion of CPT. Among 21 patients, six of them got CPT and fifteen patients kept in the non-CPT (control) group to observe CPT's efficacy. After infusing the precise quantity of plasma, there were no significant side effects observed among the patients, but 5 of 6 patients died in the treatment group, and 14 of 15 died in the control group, although the treatment group had an extended survival period compared to the control group. Ultimately only one patient recovered from each group.¹⁵⁷ On the other hand, another study was conducted on 1568 severely ill patients, where 1430 patients were under standard treatment, and 138 patients received ABO-compatible CPT in a hospital in China to measure the efficacy of CPT.¹²¹ The result revealed that only three patients died (2.2%) while another three (2.4%) were admitted to ICU for a period in the CPT group. However, the number of patients admitted to ICU was higher (5.1%) in the standard treatment group than the patients in the CPT group.¹⁵⁸ Joyner et al studied 20,000 hospitalized patients in America, where they observed a seven-day mortality rate of COVID-19 affected patients after transfusing CP.¹¹⁴ A total of 1711 patients with COVID-19 died after receiving CPT. In that case, the mortality rate was 8.56%. Moreover, after receiving CPT, the mortality rate was higher in the case of severely ill patients, with 10.5% of patients admitted to ICU, 12.1% were mechanically ventilated, and 14.0% had either septic shock or multiple organ dysfunctions.¹¹⁴

The Stability of Anti-COVID-19 Antibodies in Convalescent Plasma

The therapeutic intention of CPT is to provide passive immunity to COVID-19 patients via antibodies. One earlier study examined physicochemical antibody stability

under refrigerated conditions assessed using “turbidity, UV spectrometry, DLS, ion chromatography (CEX), gel exclusion chromatography (SEC), and light microscopy” and no signs of physicochemical alteration after seven days of storage at 4 or 25°C was found.¹⁵⁹ However, slow oligomerization was noticed from day fifteen, however this was below 0.5%. However, long-term impact was not evaluated by this study.¹⁵⁹ One more study reported that antibody remains most stable in whole blood and plasma kept at 4 °C, for seventy-two hours and five days, respectively, while being stable for at least a year in plasma kept at -20 °C.¹⁶⁰

Additionally, another recent study revealed the long-standing constancy and steadiness of anti-COVID-19 antibodies among locally sourced donors CP samples collected from a local transfusion center.¹⁶¹ Another recent European study showed that the permanency and reliability of the anti-COVID-19-IgG neutralizing potential remain comprehensive (100%) for CP preserved at -30° C for up to 9 days.¹⁶² That document commented that freshly collected CPT has potential in the management of COVID-19, especially in resource-limited countries. Health professionals should remember CPT only provides passive immunity for a brief period; the infused antibodies in the recipient only last a couple of weeks and will thus not induce immunity the same way a natural endogenous immune response (active immunity).⁵

Effects of Convalescent Plasma on the Coagulopathy of COVID-19

Coagulopathy is defined as any disorder of hemostasis. The consequence is a combination of excessive bleeding or inappropriate clot formation, while most classically, coagulopathy is explained as a compromised clot development process.¹⁶³ Multiple studies reported that severely ill COVID-19 patients with severe respiratory complications recurrently develop hypercoagulability, especially among hospitalized COVID-19 patients. These hypercoagulability patients develop microangiopathy, local and systemic coagulation disorders, pulmonary embolism, and organ failure.^{164–169} Raised D-Dimer levels were frequently reported among severe COVID-19 patients, correlated with poor prognosis and high mortality.^{169–171}

Moreover, it has been observed among COVID-19 that prothrombin time (PT) and activated partial thromboplastin time (aPTT) often increases, fibrin degradation products increase, with severe thrombocytopenia leading to

fatal disseminated intravascular coagulation (DIC), which demands relentless alertness, observance, and quick intervention.^{169,172} It has been reported that CP contains neutralizing antibodies, anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins, and other proteins obtained from recovered donors.^{173–175} Subsequently, the transfusion of CP to infected patients had a high possibility of providing additional clinical benefits through immunomodulation by inhibiting the severe inflammatory process.^{176–179}

The mechanism of action CP in the management of COVID-19 has been categorized into two major groups: 1) immune, and 2) non-immune mechanism.¹⁸⁰ Multiple reports documented that CP's most important immune-related mode of action is by minimizing viral load through antibodies developed in recovered COVID-19 patients.^{113,181–184} A similar observation has been revealed among earlier viral epidemics.^{12,185–187} Additionally, another possible mechanism in neutralizing and suppressing viremia includes antibody-dependent cellular cytotoxicity, complement activation, and phagocytosis.^{188–190} Moreover, CP modifies the inflammatory responses of the COVID-19 disease process. The earlier transfusion of CP maximizes this beneficial effect, even for asymptomatic patients.^{82,115,191} Furthermore, CP has been reported to restore coagulation factors (the non-immune related mechanism), thereby combating the coagulopathy induced by COVID-19.^{69,123}

Discussion

Plasma from recovered patients from infectious microbial disease, predominantly after severe infection, possibly contains high levels of polyclonal, pathogen precise antibodies.⁵ These antibodies provide deliberate passive immunity to recipients with similar infection disorders.¹⁹² Convalescent plasma in viral pathogenic diseases are thought to act principally by neutralizing viral constituents.¹⁶ CPT, or purified antibodies from the plasma (hyperimmune globulin) of infected but recovered or well individuals, has been utilized in medical practice before the dawn of vaccines, including the influenza pandemic 1918.^{7,193,194} Hyperimmune globulin is defined as comparable to intravenous immunoglobulin (IVIG) apart from that it is organized from the plasma of recovered infected individuals with high titers of antibody counter to an exact microorganism or antigen.^{195,196} Hyperimmune globulin is currently used for post-exposure prophylaxis in the treatment of several viral

infections, including hepatitis B (HBV), rabies, tetanus toxin, varicella-zoster, rubella, measles, etc.^{30,197–199} The COVID-19 pandemic attracted much new research to develop therapeutic drug options,^{200–203} including CPT^{80,88,93,102,113,204} to treat patients as no specific medication is available. Initially, the US FDA approved and served EUA,^{80,205} regarding CPT but later amended the earlier policy (September-2-2020).¹²⁰ Multiple studies reported positively regarding the utilization of CCP transfusion among severe cases of COVID-19, particularly concerning CP safety and benefits. Nevertheless, almost all studies concluded the need for randomized, controlled clinical trials to assess CP efficacy and safety.^{104,206–211}

It has been reported that COVID-19 has been a neglected issue in LMICs.^{212,213} Internationally, eight of the ten nations with the highest numbers of new cases of COVID-19 are upper middle income (Peru, Russia, South Africa, Argentina, Colombia, Mexico, Brazil) or lower-middle-income states (India).²¹² It has been reported that in compassion to high-income countries (HICs), CCP transfusions have received scant attention in LMICs.²¹³ Multiple reasons have been identified as the systemic challenges of resource-poor settings. Several LMICs do not possess a safe and reliable blood transfusion facility; this situation existed before COVID-19 due to poor donor enlistment and deployment, collections process, distribution, lack of infectious testing capability, and transfusion itself.^{214–217} Against this background, CPT has been reported to reduce the need for ventilation among COVID-19 cases from LMICs.^{13,81,82} Another issue with CCP transfusion, especially in LMICs, is care to maintain proper ethical control of CCP transfusion and avert black market sales of CCP.^{214,218,219}

Conclusion

In the past two decades, CPT has been successfully used to treat SARS, MERS, and H1N1 pandemic in 2009 with an acceptable level of safety and efficacy. The understanding that virological and clinical characteristics have been recognized to have similarities among SARS, MERS, and COVID-19, means that CPT may be a potential treatment option for the COVID-19 pandemic. Taking a critical look at strategies for available treatment, the patients who have recovered from SARS-CoV-2 infection could donate their plasma, which can then be transfused to the current COVID-19 positive severely ill patients, with the expectation that antibodies would reduce the severity of viral insult to the recipient vital organs. Studies from different countries

have reported that CPT could significantly reduce the mortality rate of COVID-19 patients.^{107–109,121,122} Consequently, several countries around the globe are utilizing CPT for the management of COVID-19 patients and have achieved positive results.^{2,4,108,109,121–123} Therefore, to ensure maximum recovery from the severity of this pandemic, appropriate safety regarding transfusion and effective management of CPT's adverse effects should be considered.

Recommendations

COVID-19 is currently an enormous global public health crisis and is causing much misery in human life.^{220–222} Moreover, no specific anti-COVID-19 therapy is presently available for its management.^{115,162,203,223,224} Therefore, COVID-19 remains a significant threat to mankind. Given the gravity of the situation, CPT appears as an evolving defensive treatment option for near-fatal cases of COVID-19.^{81,82,225} Earlier studies reported that CPT had improved the survival rate among patients with several viral diseases, including SARS, MERS, influenza, Ebola virus disease, etc.^{226,227} The adverse reactions regarding CPT are reported as transfusion-related reactions.^{206,228} Although many limitations exist regarding CPT, nevertheless, considering the absence of specific treatments, CPT remains a viable option for treating COVID-19.^{79,188,207,227,229,230}

Professionals Annotation

The rapidly increasing incidence and death rates of COVID-19 cases remain continuously reported around the world.¹ Currently, more than ten coronavirus vaccines are in the development phase, and the world is awaiting a breakthrough in research that will offer a medical solution for this devastating and detrimental pandemic. The foundation evidence-based preventive measures proved that their effectiveness in halting this virus's spread includes social distancing, personal hygiene, and face-protection with shields. These practices have helped about 29,925 172 (October 18, 2020) people across the world who were infected with the virus recover.²³¹ The virus has changed the planet and affected the world at different levels, including demographic to economical, and triggered social and ethical dilemmas. The world is struggling with the unknown (ie, virus) and the uncertainty (ie, cure). The quest to find a treatment for the SARS-Cov-2 pandemic remains a daunting challenge. While some medicines, including hydroxychloroquine, Favipiravir, Remdesivir, and dexamethasone, have shown promise, they have not supported by randomized

controlled studies.^{2,3} In view of these challenges, the adoption of traditional interventions has re-emerged as viable options in regulating this disease.⁴ A classic option has been the use of CPT. This method involves using apheresis in survivors with previous infections caused by pathogens of interest who have now developed antibodies against this causative agent. It is noteworthy to understand its history as surveys have linked its existence to the early 20th century in managing and preventing diseases alongside emergency interventions for various pandemics like the West Nile virus, Spanish flu, SARS-CoV, and, in recent times, the Ebola virus.^{5,7-11} In recent times, reports undoubtedly claim that the use of CPT as a measure in curbing COVID-19 has been very vital, particularly in low-and middle-income countries, as people struggle to afford ventilators or abide by restriction policies over the long-term.¹³ Surprisingly, this virus has been deemed capable of replication at a substantially higher speed than other infectious diseases affecting humans.^{53,54} The virus is no respecter of persons as it affects both rich and poor individuals equally, which prompted its name as the “great leveller”.⁵⁹ Nevertheless, the pandemic has been detrimental to most health care systems and has negatively influenced health equity worldwide with an extension to people of affluence, even in western countries.⁵⁵⁻⁵⁸ On the other hand, reports in the US have proposed that this global crisis has principally affected the community’s poorest people. Thus, it has been termed as the “inequality virus” in these regions.^{58,60} Admittedly, studies that support the use of CPT as a measure for the COVID-19 virus remain minimal. A good example from a theoretical perspective was reported from the US, which detailed the use of CPT in the management of COVID-19 around early July 2020. During this period, only two case series were identified.⁷⁹⁻⁸² Meanwhile, the findings showed a positive difference that resulted in better oxygenation, sequential organ failure assessment (SOFA) scores, and ultimately reduced need for ventilator use.^{81,82} Two major drawbacks of this study were that it was not a well-designed controlled study, and the CPT uptake was combined with the use of other medications.^{81,82} In furtherance to its advantageous nature, research claims that while its antibodies contribute to restrictions of viral replication,⁸⁹ its other plasma components are beneficial in replenishing coagulation factors when they are given to patients with hemorrhagic fevers like Ebola. To obtain samples, patients free from COVID-19 are regarded as a valuable donor source for CPT, especially those having a high neutralizing antibody titer. It is important to note that due to the sensitivity and peculiarity attached to this matter, blood safety and quality must not be compromised for practical therapeutic approaches. Several studies have been conducted

to determine the safety and associated risks of CPT for COVID-19 patients.^{80,81,93,94} However, only a few reported cases have mentioned any serious adverse effects of introducing CPT as a therapeutic measure for the COVID-19 pandemic. Recognizing this fact, the focus should be on the risk evaluation associated with this therapy, particularly in vulnerable groups such as children, pregnant women, elderly individuals, and people with co-morbidities. The most common adverse events from CPT are transfusion-related events such as chills, fever, anaphylactic reactions, TRALI, TACO, hemolysis, ADE, and transfusion-transmitted virus.^{97,98} The possible risks associated with this transfusion include allergic reactions, damage to the lungs, and difficulty in breathing. Other fatal risks have been linked with the transmission of microbial infections such as HIV and Hepatitis B and C.^{122,123} To reduce the risk of transferring other infections, studies suggested pre-donation tests should include blood grouping and even screening for HCV, HIV, HBV, syphilis, and other locally spread diseases.^{133,134} To obtain safe and very effective therapeutic results, donor-recipient screening remains very crucial. For instance, a study carried out on two elderly COVID-19 patients with ARDS showed signs of improvement and no adverse reactions.¹⁰⁴ However, side effects cannot be completely ruled out, as another study of CPT conducted on ten⁷⁹ COVID-19 patients showed improved recovery from the disease without severe adverse reactions. Hence, one of these patients faced minor side effects showing an evanescent facial red spot.⁸¹ Overall, despite the limitations surrounding CPT, it may be inferred that CPT is beneficial for recovering COVID-19 persons even among vulnerable age groups. This ideology helps to reiterate the fact that more studies that demonstrate the safety and efficacy of CPT among COVID-19 patients are required¹⁰⁴⁻¹⁰⁷ at the various phases of the illness and prevention.¹⁰⁵⁻¹⁰⁹

Five to Ten Year Expectation Regarding Global Pandemic

Pandemic is not a word to use lightly or carelessly. It is a word that, if misused, can cause unreasonable fear, or unjustified acceptance that the fight is over, leading to unnecessary suffering and death.²³²

The experience from earlier epidemics and pandemics has highlighted the critical role of robust primary health care supported by advanced tertiary care to combat the COVID-19 global pandemic.²³³⁻²³⁷ There is no vaccine, or specific antiviral agent, thus the control of the current pandemic is based on several prophylactic. Those

preventive actions include detecting individuals affected with COVID-19 viral infection, ensuring medical care, following up on contacts, preparing healthcare facilities to deal with an influx of many patients, and training health professionals.²³⁸ Multiple studies echo the WHO statement²³⁸ that health systems defensive capabilities are quite highly performing in Japan, Singapore, Hong Kong, Taiwan. Thereby, these countries' robust primary health care can manage much better than others.^{239–241} Singapore, Japan, Taiwan, and Hong Kong heavily invested in primary health care after the last epidemic of SARS. Thereby, the development of resilient and durable public health systems based on primary health care requires extensive support from all sectors of every country and must be capable of a range of interventions.^{242–244} Health-systems throughout the globe need to overhaul with lessons learned from the COVID-19 pandemic to minimize human misery.

“Researchers are searching for effective and suitable vaccine candidates and therapeutics for controlling the deadly COVID-19”.²⁴⁵

It has been reported that the research risk of COVID-19 remains high because of the potentially dangerous consequences among research volunteers. Additionally, critics state that if adverse consequences among research volunteers lead to life-threatening severe complications or death there is a high possibility of negative impacts on all challenging human-related research studies. As there is a potential harm when conducting these studies, national and international authorities should maintain excellent communication with their population by regularly updating the status of research, thereby minimizing potential repercussions.²⁴⁶ The scientific community is indeed putting a lot of effort into finding a way, and there is some progress regarding prevention, control, and treatment strategies of COVID-19. Nevertheless, the well-designed long-term clinical statistics on different therapeutic interventions for COVID-19 are rare. Additional studies have been recommended in suitable animal models for analyzing replication, transmission, and pathogenesis.²⁴⁵

Singapore confirmed its first COVID-19 case on January-23-2020, seven weeks (March 11–2020); later, WHO Director-General Dr. Tedros Adhanom Ghebreyesus announced the outbreak a Global Pandemic.^{247,248} Singapore has very high numbers of travelers because it is one of the top business hubs globally. Additionally, the country has an exceptional level of tourists, which include medical tourism.^{249–252} Thereby,

Singapore is particularly at risk of massive spreading and affecting its' population with the COVID-19. Nevertheless, on time, Singapore installed vigorous and assertive public health measures to avert the spread of the COVID-19.²⁵³ The country used their earlier experiences with the Severe Acute Respiratory Distress Syndrome (SARS) and the Influenza H1N1 pandemic epidemic in 2003 and 2009, respectively.^{253–256} It has been reported that Singapore's healthcare system had promptly recognized the COVID-19 public health threat and immediately responded to the disaster, based on a robust primary health care viewpoint.^{257–259} As the early symptoms and signs of the COVID-19 viral infection are broad-based, with many patients visiting primary health care clinics with mild upper respiratory tract symptoms.^{260,261}

The healthcare system of Singapore is profoundly based on primary health care concepts and methods.²⁶² The general practitioners (GPs) surgeries in Singapore are the first contact point for most diverse cases, and around 80% of total healthcare-seekers visited GP surgeries for primary health care daily.²⁶³ These GPs clinics also provide treatment for non-COVID-19 patients. Additionally, it protected them from the transmission of the COVID-19 during their visit to the surgeries.²⁴⁹ Furthermore, Singapore successfully also ensures healthcare professional safety and mitigates irrational fear, as they are the frontline fighters to maintain people's health.²⁶⁴ Thereby, GPs' health center remains the basis of initial spotting and segregation of suspected COVID-19 victims within the large number of patients.²⁴⁹

Similarly, Taiwan controlled the pandemic of COVID-19 more effectively than many other countries around the planet.^{240,265} The Taiwanese people entrusted the provision of a public healthcare system to supportive family doctors and community health care groups. Furthermore, a patient-centered integrated health care delivery system was established long-ago as an efficient solution to hazard in the medical care system.^{266–268} All these improvements in the Taiwanese healthcare system are based on primary health care. We are aware there are many issues in the development of vaccines or specific medicine for COVID-19. We expect these research-related issues will be resolved by the next five to ten years' time. After that, the scientific community will be able to provide a better solution for current or future such pandemics. This research finally projects in the next five to ten years there will be a massive change towards the improvement of public health care on the underlying primary health care

concept, to effectively combat future epidemics and improve access and equity healthcare.

Special Note

Nevertheless, the Indian Council of Medical Research put out an open-label phase-2 multicenter randomized controlled trial (placid trial) on October 22, 2020. Their research concluded CPT was unable to minimize COVID-19, both morbidity and mortality.²⁶⁹

Article Highlights

- CPT possesses the potential to reduce morbidity and mortality COVID-19.
- CPT induced side effects in treated patients, and risk-benefit assessment should identify potential recipients.
- If sensitivity is not maintained, possible health risks due to transfusion-associated contaminations overwhelm the benefits.
- The low ratio of cured cases to plasma donors leads to unavailability and inaccessibility.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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