Plasma therapy: a passive resistance against the deadliest

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ABSTRACT
Convalescent plasma therapy provides a useful therapeutic tool to treat infectious diseases, especially where no specific therapeutic strategies have been identified. The ongoing pandemic puts back the spotlight on this age-old method as a viable treatment option. In this review, we discuss the usage of this therapy in different diseases including COVID-19, and the possible mechanisms of action. The current review also discusses the progress of therapeutic applications of blood-derivatives, from the simple transfer of immunized animal sera, to the more target-specific intravenous administration of human immunoglobulins from a pool of convalescent individuals, in both infectious and non-infectious diseases of various etiologies.

Introduction
The ongoing pandemic of Severe Acute Respiratory Syndrome (SARS) coronavirus-2 (CoV2), with no specific therapeutics available so far, has led to a re-evaluation of the effectiveness of the century-old plasma therapy technique. Plasma therapy has been used throughout history, both in association with other drugs and often as the only option to combat various infectious diseases. Convalescent plasma (CP) is the antibody-rich blood plasma procured from an animal or human who has “convalesced” or recovered from a particular infection. CP is the most basic of all immunotherapeutic strategies, but it can be very effective during a time of emergency. Active immunization by the conventional vaccines containing live-attenuated or inactivated microorganisms, proteins, or toxins derived from pathogens, generates highly specific antibodies that can neutralize the target pathogen in subsequent encounters. In contrast, CP offers passive immunity with the help of donor-derived antibodies to fight invading pathogens immediately. CP potentially contains neutralizing antibodies (NAbs) and immunoglobulin (Ig) G or M that decrease the microbial load and eventually control the symptoms. Transfusion of CP introduces donor-derived antibodies without transferring antibody–producing plasma cells. This strategy does not lead to the generation of long-lived plasma cells or memory B cells in the recipient, unlike in an active immune response post-vaccination. Therefore, in CP therapy, although the protection is not long-lasting, the borrowed antibodies can greatly reduce disease burden and duration, especially when a quick response is necessary, thereby being a potential game-changer in grave situations. Such artificial passive immunity can be secured from convalescent blood products like convalescent whole blood or plasma, pooled intravenous high titer human immunoglobulin, and polyclonal or monoclonal antibodies (mAbs). Out of these, the CP is the easiest to obtain and thereby the best alternative in an emergency where well-established therapeutic strategies are lacking and/or quick neutralization of the pathogen itself or pathogen-derived toxins is required.

To effectively neutralize disease-causing pathogens and provide clinical benefit in recipients, blood plasma used in CP therapy must contain disease-specific neutralizing antibodies in sufficient quantities. Also, most data suggest that the CP administration needs to be done at early stages of the disease for positive outcomes. A recent exploratory meta-analysis on severe acute respiratory infections reported a statistically significant decrease in mortality following CP therapy, in comparison to placebo-treated or untreated cohorts. Additionally, there are several other respiratory diseases where CP has been used both as prophylactic measures and therapeutic interventions. Apart from respiratory infections, CP has also served as an efficient ameliorative agent in hemorrhagic diseases like Argentine Hemorrhagic Fever. Importantly, in the ongoing pandemic caused by SARS CoV-2, the effectiveness of CP therapy is once again under consideration, proving the relevance of this age-old technique even in the modern era of molecular medicine. Given its importance, in the current review article, we aim to provide an overview of the therapeutic applications of CP and its derivatives in both communicable and non-communicable diseases and discuss its evolution over the years into more targeted therapeutic approaches like patient-derived mAbs. We also deliberate on the challenges faced in utilizing CP therapy as a treatment modality.

CP therapy: the beginning
CP therapy emerged in the 1890s as an antitoxin-based remedy against diphtheria and tetanus. Emil Adolf von Behring and Kitasato Shibasaburō transferred serum from tetanus toxin-inmunized rabbits to mice, leading to the successful
prevention of disease development in recipient mice. Subsequently, they administered sheep antiserum in a critical diphtheria patient, who recovered within hours and survived. This work not only earned Kitasato and Von-Behring a Nobel Prize in medicine, in 1901, it also opened the floodgates for CP therapy in various infectious diseases.

The usage of convalescent serum to treat maladies soon evolved into a standard therapeutic strategy in several diseases, which previously had very high mortality rates in specific cohorts like children (diphtheria, tetanus, etc.) or the armed forces (tetanus, gas-gangrene, etc.). Notably, in some cases, serum therapy or an evolved version of that, continued till the modern era, only to give way to the administration of more specific passive immunity.

Diphtheria antitoxin (DAT), a solution of globulin proteins and antibodies obtained from horses immunized with diphtheria toxin, is used in actual or suspected cases of diphtheria or for prophylactic measures under exceptional conditions under an Investigational New Drug (IND) protocol sponsored by CDC (https://www.cdc.gov/diphtheria/dat.html). Diphtheria antitoxin neutralizes the circulating diphtheria toxin molecules, thus negating its toxic effects, and preventing disease development. Similarly, the administration of equine antiserum in tetanus, a disease with an almost 90% mortality rate, helped achieve a drastic reduction of fatalities to almost nil, among wounded soldiers as well as in new mothers and neonates. Another disease that was caused by war-time wounds and led to considerable fatalities was Gas Gangrene, a myonecrotic disease caused by the spore-forming anaerobic bacillus *Clostridium perfringens*. It is still treated prophylactically with an antitoxin that consists of equine serum immunoglobulins against three species of gas gangrene toxin-producing bacilli (*C. perfringens* type A, *C. septicum*, and *C. oedematiens*), along with antibiotics immediately after exposure to neutralize the toxin and reduce disease virulence. Eventually, serum therapy was implemented to treat Streptococcal pneumonia and Meningococcal meningitis and was successful in bringing down the high mortality rates in both diseases.

It is worth mentioning here that serum therapy, in addition to treating several infectious diseases, also paved the way for anti-venom therapy to neutralize animal venoms. Antivenoms are typically developed by hyper-immunizing donor animals like horses or sheep with non-lethal doses of one or more venoms to produce a NAb response; these antibodies are then purified from the blood to produce monovalent or polyvalent antivenom.

**Mechanisms of action of CP therapy: the key to success lies in its contents**

The composition of CP is variable and contains large amounts of albumin, immunoglobulins, complement proteins, cytokines, coagulation, and antithrombotic factors, in addition to different inorganic salts and organic compounds. Apart from complement-mediated destruction of pathogens, the NAbS present in CP may be able to neutralize the infecting pathogens by various methods (Figure 1) including blocking the interaction between the pathogen’s membrane proteins and host cell surface proteins that are utilized as ports of entry by the pathogens. For example, viral pathogens like SARS-CoV, SARS-CoV2, and MERS (Middle Eastern Respiratory Syndrome) virus, bind to human ACE2 (hACE2) receptors with the receptor-binding domain (RBD) of the S1 subunit of their spike protein. The NAbS in convalescent sera that can bind to the S1-RBD and N-terminal domain of the S1 subunit, inhibit their entry into new host cells. Similarly, antibodies that bind to the S2 subunit of the spike protein, which mediates membrane fusion during viral entry, can limit viral amplification. Also, natural IgM present in the serum provides defense against a variety of pathogens by virtue of their flexible antigen-binding sites that enable them to bind to various unrelated antigens, while high-affinity IgG probably neutralizes viral pathogens by agglutination as seen with the poliovirus.

**Application of plasma therapy in different diseases**

With time, in medical emergencies or pandemics when vaccines, antivirals, and other specific treatments were unavailable, CP from human patients emerged as a robust therapeutic alternative. While convalescent whole blood was used in early clinical settings, it soon got replaced by CP due to better outcomes with the latter, along with the fact that CP transfusion did not require typing and cross-matching thus further expediting the therapeutic process. Additionally, CP can be administered both via the intravenous as well as intramuscular routes and also can be easily procured without requiring sophisticated techniques for isolation. In the following sections, we discuss the pivotal role of CP therapy in the overall management and treatment of various diseases, and also chart the progress of convalescent blood products as a therapeutic modality.

**Plasma therapy in viral respiratory diseases**

Respiratory infections are among the leading causes of severe illness and death in many countries and are typically known to involve the different parts of the respiratory system. While the common symptoms of respiratory infections include congestion, nasal discharge, cough, fever, and sometimes shortness of breath and fatigue, it may have systemic effects as well. Infections of the respiratory tract can be of viral, bacterial, protozoan, or fungal origin, which may cause acute as well as chronic respiratory disorders.

Among respiratory pathogens, viruses cause the largest number of respiratory infections, which can affect both the upper and lower respiratory tracts. The common viruses that establish infection in the respiratory tract are rhinoviruses, respiratory syncytial virus (RSV), influenza and parainfluenza viruses, human metapneumovirus, measles, mumps, adenovirus, and coronaviruses. (CDC Reports: https://wwwnc.cdc.gov/travel/yellowbook/2020/posttravel-evaluation/respiratory-infections). Although most viral respiratory infections are transitory and self-limiting, there also exist examples of viruses causing severe pandemics. Vaccines and antiviral agents are
available for only some of these viruses. CP has been used successfully both as prophylactic as well as therapeutic in various cases of infectious respiratory diseases.

**CP therapy during influenza outbreaks**

From time to time, the world has faced several flu outbreaks apart from the standard seasonal ones; the most prominent and arguably the first recorded one being the H1N1 influenza pandemic of 1918. The H1N1 virus infected about one-third of the world population at that time and lasted for 36 months. During this critical period, plasma administration was reported to cause a reduction in the fatality rate, making it the first recorded usage of CP therapy as well. A meta-analysis of eight reports contributed by physicians at that time, demonstrates that patients who received early CP transfusion (after less than 4 days of pneumonia complications) had a statistically significant reduction in mortality and also showed general improvement of symptoms.\(^\text{18}\) While some adverse effects like chills and aggravation of symptoms were noted in a few seriously ill patients, it could be due to the lack of proper quality control of the transfused CP. Since 1918, three additional pandemics in 1957, 1968, and 2009 were caused by H2N2, H3N2, and H1N1 influenza virus strains, respectively. During the 2009 outbreak, in a study involving 93 seriously ill patients, 20 patients who were administered CP, showed reduced respiratory tract viral load and serum cytokine response, and also a lower mortality rate compared to the control group without any adverse effects.\(^\text{19}\) Such studies resulted in a better understanding of the role of CP therapy and equipped the global public health community with an executable plan to handle future influenza outbreaks.

Severe respiratory illness in humans due to the avian influenza virus, especially the H5N1 subtype, first appeared in Hong Kong in 1997,\(^\text{20}\) and has continued to occur over the years. Convalescent H5N1 plasma has been considered as a therapeutic approach to lower the mortality rate\(^\text{18}\) in a few studies with small sample size. A global approach and large-scale population-based investigations are required to successfully utilize the potential of CP therapy in tackling H5N1 influenza outbreaks.

**CP therapy in Severe Acute Respiratory Syndrome (SARS) outbreaks**

Coronaviruses are single-stranded RNA viruses of the family *Coronaviridae* that can infect a range of hosts among mammals and birds.\(^\text{21}\) There are seven identified coronavirus strains including SARS-CoV, MERS-CoV, and

![Figure 1. Schematic representation of the mechanism of action of Convalescent plasma (CP). Convalescent plasma can act in several ways to neutralize pathogens. 1. Apart from the broadly reactive natural IgM antibodies (Abs), specific neutralizing Abs present in CP can bind to viral landing proteins (S protein in case of SARS-CoV2) and prevent its interaction with the cell surface receptors (ACE-2). 2. Abs can also bind to bacterial membrane protein and opsonize the pathogen. 3. Opsonized pathogens are recognized and engulfed by macrophages. 4. Other components of CP like anti-inflammatory cytokines (IL-4, IL-10) can help in suppressing effector T cell function/inflammatory response and the complement proteins help in opsonization of pathogens that eventually leads to destruction of the pathogen.](Image)
SARS-CoV2 that infect humans (https://www.cdc.gov/coronavirus/types.html). The SARS-CoV outbreak in 2002–2003 in China led to the deployment of CP therapy initiatives to tackle the disease. CP infusion in SARS patients in combination with ribavirin and corticosteroids treatment had successful clinical outcome with no observed side effects, and overall reduction in mortality rates.22

Almost 10 years after the SARS pandemic, another highly pathogenic and transmissible strain of coronavirus, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was detected in 2012 in the Middle East. Importantly, the World Health Organization (WHO) has established a protocol for CP therapy in MERS-CoV infection. A recent study at a tertiary care center during the 2015 Korean MERS outbreak suggests that donor plasma with a plaque reduction neutralization test titer equal to or greater than 1:80 is required to obtain a significant serological response after infusion.23 However, larger efficacy trials are required to establish CP as a therapeutic option for MERS. CP therapy in the ongoing pandemic caused by SARS-CoV2 is discussed in detail in later sections.

**Plasma therapy in other viral diseases**

One of the deadliest diseases of modern times is the Ebola virus infection, which is a highly contagious disease with a 40–90% fatality rate. In 2014, a particularly severe outbreak of this disease spread in several east African countries as well as in a few countries in Europe and the USA. Reports of the effectiveness of the passive transfer of antibodies in immunodeficient mice infected with the Ebola virus,24 led to the investigation of the efficacy of CP in humans. While transfusion of CP with unknown antibody concentrations did not show any improvement in survival,25 administration of plasma from recovered individuals with high-titer anti-Ebola virus antibodies did achieve a decline in viral load in patients.26

Notably, CP therapy has shown great promise in treating some geographically localized viral diseases like Argentine hemorrhagic fever,4 and Lassa fever.27 Argentine hemorrhagic fever (AHF) is a zoonotic infection caused by the Junin virus of family Arenaviridae, which is endemic to Argentina. While Candid#1, an indigenously developed live-attenuated vaccine against AHF has been able to reduce disease incidence,28,29 disease-specific therapy still involves CP transfusion. Several studies have demonstrated that administration of CP containing specific amounts of disease-specific neutralizing antibodies30 during early stages of the infection,4 or within 8 days of appearance of symptoms,31 drastically reduces the mortality rate to 1%, which can be as high as 15–30%, if left untreated.4,32 The advantages of CP therapy have also been observed in other severe diseases like Hantavirus disease.33 Furthermore, in animal models of Zika viral disease and Hepatitis E, CP therapy has shown promising results.34,35 The results obtained by the infusion of CP in various viral diseases are summarized in Table 1.

**From serum therapy to monoclonal antibodies: the passive approach to immediate immunity**

Plasma therapy is the instigating foothold that unlocked the era of antibody-based therapeutic approaches against several diseases. With the advent of new technology to separate different blood components, the field evolved toward a more target-specific approach involving intravenous immunoglobulin (IVIG) products as therapeutic agents. IVIG, isolated and pooled from a large number of donors, is composed of polyclonal antibodies and can be used for the management of primary immunodeficiencies, as well as against infectious diseases. Later with the arrival of mAbs, the scope of target-specific immunotherapy was unraveled to a far greater extent than previously possible.

IVIG is a pool of immunoglobulins obtained from several healthy donors who have produced antibodies against different microorganisms and their products. IVIG can also be collected from convalescent donors recently exposed to infectious diseases, vaccines, or ubiquitous microorganisms, in which case, it is known as Hyperimmune polyclonal immune globulin or Hyperimmune IVIG. IVIG is composed mainly of IgG of different subclasses; IgA, traces of other Ig, cytokines, and soluble receptors. IVIG can be further enriched for IgG through cold ethanol precipitation process and some components are added to stabilize the proteins and prevent IgG aggregation.47

IVIG was first used as a therapeutic strategy in a young child with gamma globulin deficiency who suffered from recurrent pneumococcal sepsis, with extraordinary success.48 It is used as a major remedy in several neurological disorders, like

### Table 1. Outcomes of CP therapy in various viral diseases.

| Sl. No. | Diseases                              | Outcomes on CP therapy                                                                 | References |
|--------|--------------------------------------|---------------------------------------------------------------------------------------|------------|
| 01.    | Spanish Flu                          | Reduction in fatality rate, improvement in clinical symptoms on early transfusion      | 18         |
| 02.    | Avian Influenza                      | Lower mortality rate                                                                  | 18         |
| 03.    | Swine Flu                            | Reduction in the viral load and relative mortality risk                                | 19         |
| 04.    | Severe Acute Respiratory Syndrome (SARS) | Overall reduction in mortality rate                                               | 22         |
| 05.    | Middle East Respiratory Syndrome (MERS) | Seroconversion on therapy in case of donor plasma PRNT titer ≥1:80                    | 23         |
| 06.    | Coronavirus Disease (COVID 19)       | Conflicting reports about success of CP therapy has been documented                   | 36–46      |
| 07.    | Lassa fever                          | Decrease in mortality on early administration                                        | 27         |
| 08.    | Argentine hemorrhagic fever          | Lower case fatality rate on early administration                                      | 4,28–32    |
| 09.    | Ebola                                | Lower viral load, improvement of clinical symptoms                                    | 26         |
| 10.    | Hantavirus Pulmonary Syndrome        | Decrease in case fatality rate in treated cases                                       | 33         |

References:
1. [https://www.cdc.gov/coronavirus/types.html](https://www.cdc.gov/coronavirus/types.html)
2. 2006026-4
3. e2006026-4
4. A. HANSDA ET AL.
Guillain–Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, stiff-person syndrome, etc. In GBS, administration of IVIG leads to enrichment of preexisting regulatory T cell population, with a concomitant decrease in the levels of proinflammatory T cell subsets and cytokines in the cerebrospinal fluid. Furthermore, IVIG has a considerable impact on the treatment of hematological diseases like immune cytopenias, hypogammaglobulinemia, and post-bone marrow transplantation. IVIG treatment also ameliorates a whole gamut of diseases like Kawasaki syndrome, vasculitis, uveitis, skin-related inflammatory diseases, as well as autoimmune disorders like mucous membrane pemphigoid and systemic lupus erythematosus. Some of the IVIG products that have been approved by USFDA for therapeutic usage in primary immunodeficiencies as well as neurological, hematological, autoimmune, or other inflammatory diseases are listed in Table 2.

IVIG treatment was also found to be quite useful in tackling fatal bacterial infections like toxic shock syndrome caused by group A streptococcus, where antibodies against staphylococcal and streptococcal superantigens are administered as a treatment strategy. In addition to toxin neutralization, IVIG treatment in these infections dampens the associated strong proinflammatory responses. Likewise, IVIG is found to be significantly better at reducing mortality in Pertussis or whooping cough, an infanthood disease with a high mortality rate during the 1920s, and also in Botulism, an otherwise fatal neuro-paralytic syndrome caused by the Clostridium botulinum neurotoxin.

The only therapeutic modality against HIV/AIDS to date is the administration of antiretroviral drugs, to which the virus has been found to develop resistance in the sub-Saharan African population. IVIG treatment in AIDS patients showed a rapid decrease in the HIV structural protein ICD p24 antigen in the recipient’s serum, due to neutralizing anti-p24 antibodies present in the donor-sera. However, no alteration in the plasma HIV RNA copy number was reported after the infusions, even at the high-

| Product name | Manufacturer name | Diseases | Source |
|--------------|-------------------|----------|--------|
| Flebogamma DIF 5% & 10% | Instituto Grifols, SA | Primary immunodeficiency, X-linked gammaglobulinemia, Severe combined immunodeficiency, Wiskott-Aldrich syndrome | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/flebogamma-dif-5-10](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/flebogamma-dif-5-10) |
| Gammagard Liquid | Baxter HealthCare Corp | Primary immunodeficiency, Multifocal Motor Neuropathy | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/gammagard-liquid](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/gammagard-liquid) |
| Octagam | OCTAPHARMA Pharmazeutika Produktionsges.m.b.H. | Chronic immune thrombocytopenic purpura, Dermatomyositis | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/octagam](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/octagam) |
| Vigam-S | Bio Products Laboratory Limited | Primary immune thrombocytopenia, Guillain Barré Syndrome, Kawasaki disease, Chronic inflammatory demyelinating polyradiculoneuropathy, Multifocal motor neuropathy | [https://www.medicines.org.uk/emc/product/5556/smpctgref](https://www.medicines.org.uk/emc/product/5556/smpctgref) |
| Gamunex-C | Grifols Therapeutics Inc | Primary immunodeficiency, Idiopathic thrombocytopenic purpura, Chronic inflammatory demyelinating polyneuropathy | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/gamunex-c](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/gamunex-c) |
| Carrimmune NF | CSL Behring AG | Primary immunodeficiency, Immune thrombocytopenic Purpura | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/carrimmune-nf-nanofiltered](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/carrimmune-nf-nanofiltered) |
| Privigen | CSL Behring AG | Primary immunodeficiency, Immune thrombocytopenic Purpura, Chronic inflammatory demyelinating polyneuropathy | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/privigen](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/privigen) |
| Asceniv | ADMA Biologics, Inc. | Primary immunodeficiency, Chronic inflammatory demyelinating polyneuropathy | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/asceniv](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/asceniv) |
| Bivigam | Biotest Pharmaceuticals Corporation | Primary immunodeficiency, Chronic inflammatory demyelinating polyneuropathy | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/bivigam](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/bivigam) |
| PANZYGA | Octapharma Pharmazeutika Produktionsges.m.b.H. Hindlization | Chronic inflammatory demyelinating polyneuropathy, Primary immunodeficiency, Chronic immune thrombocytopenia | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/panzyla](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/panzyla) |
| Gammaked | Kedrion Biopharma | Chronic inflammatory demyelinating polyneuropathy, Primary immunodeficiency, Idiopathic thrombocytopenic purpura | [http://www.gammaked.com](http://www.gammaked.com/) |
| Gammaplex 5% & 10% | Bio Products Laboratory | Primary immunodeficiency, Chronic immune thrombocytopenic purpura | [https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/gammaplex-5-10](https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/gammaplex-5-10) |
strategies for disease control, which includes post-exposure administration of rabies immunoglobulins (RIG) of human or equine origin, in addition to vaccination. While the vaccine helps the generation of circulating serum antibodies in the exposed individual after 10-14 days, the immediate administration of the RIG in the wound-bed itself helps protect high-risk rabies-exposed patients in this window period by neutralizing the virus deposited at the bite-wound site.59

After extensive and rigorous clinical testing, some IVIG products have been licensed to be used in clinical settings by USFDA, to combat various infectious diseases. Many of these IVIG-based drugs are used for post-exposure prophylactic interventions to combat pathogens like Rabies (KEDRAB) or Varicella zoster (VariZIG). Similar IVIG products like HepaGamB, are used both as a preventive and a prophylactic drug in Hepatitis B. Moreover, the main line of treatment in cases of inhalation anthrax and infant botulism involves IVIG products like Anthrasil, BabyBiG, etc. The details of the licensed IVIG drugs currently in use are summarized in Table 3.

| Product Name/ Manufacturer | Disease | Disease | Condition/s of disease therapy | Reference |
|----------------------------|---------|---------|-------------------------------|-----------|
| AnthraSil (Cangene Corporation) | Anthrax | Sterile solution of purified human IgG, stabilized with 10% maltose and 0.03% polysorbate 80 | Adult and pediatric patient of inhalational anthrax in combination with appropriate antimicrobial agent | https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/anthrasil |
| BabyBIG (California Department of Public Health) | Botulism | Sterile, lyophilized powder of IgG, stabilized with 5% sucrose and 1% human albumin | Infant botulism infected with type A and type B toxin | https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/babybig |
| CytoGam (Saol Therapeutics Inc) | Cytomegalovirus (CMV) | Liquid solution of IgG against CMV, stabilized by 5% sucrose and 1% Human Albumin | As a prophylactic measure to organs (kidney, lung, liver, pancreas and heart) transplant associated CMV infected patients. | https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/cytogam |
| HepaGam B (Cangene Corp) and Nabi-HB (Nabi Biopharmaceuticals) | Hepatitis B | Prepared from plasma donors with high-titers of anti-HBs and formulated as 5% protein solution with 10% maltose and 0.03% polysorbate 80 | As a prophylactic to Hepatitis B recurrence post liver transplantation in HBsAg-positive patients. Also, as post-exposure treatment to acute HBV infected, HepB contaminated blood exposed, infants born to HepB positive mothers | https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/hepagam-b |
| KEDRAB (Kamada Ltd.) | Rabies | Liquid solution of anti-rabies purified IgG immunoglobulin, stabilized with 0.3 M glycine | Post-exposure prophylaxis of rabies infected patient, given promptly after contact with rabid animal and in combination with rabies vaccine. | https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/kedrab |
| VarizIG (Cangene Corporation) | Varicella-zoster virus | Lyophilized preparation of purified IgG, formulated as 0.04 M sodium 197 chloride, 0.1 M glycine and 0.01% polysorbate 80 | As a post-exposure prophylaxis in high risk individuals such as immunocompromised children and adults, newborns of mothers with varicella, infants below one-year age and pregnant women | https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/varizig |
| GamaSTAN S/D (Grifols Therapeutics Inc) | Hepatitis A Measels Rubella | Sterile solution of immunoglobulin, formulated as 15–18% protein and contains 0.21–0.32 M glycine as buffer | Used as a prophylactic measure in Hepatitis A, Measels and Rubella virus exposed person | https://www.fda.gov/media/86789/download |
| RespiGam (MedImmune Inc) | Respiratory Syncytial Virus (RSV) | Pooled hyperimmune polyclonal immunoglobulins from donors with high titer anti-RSV antibodies | Discontinued since 2003 due to long intravenous infusion, high dosage volume and high risk to blood borne pathogens | https://www.sec.gov/Archives/edgar/data/873591/0000873591-96-000038.txt | https://www.intechopen.com/chapters/65931 |

IVIG showed promising trends as cancer therapeutics as well, especially in preclinical mouse models. Administration of IVIG in mice with melanoma or sarcoma induces increased production of IL-12 from mononuclear cells that exert anti-angiogenic function, and also activate Natural Killer cells. IVIG treatment restricts the invasiveness of cancer cells by downregulating matrix metalloproteases, modulates anti-tumor immune response by inducing M2 to M1 polarization in macrophages, and can also neutralize VEGF to prevent vascularization of tumors.60

Convalescent immunoglobulin therapy has also been used as a therapeutic and preventive approach for IgE-mediated allergic hypersensitivity reactions. Allergen-specific IgG antibodies can block IgE-mediated inflammation by inhibiting the activation of basophils and mast cells, thus eliminating the immediate allergic responses.61

Perhaps, the final step to the ultimate refinement of CP therapy is the development of patient-derived mAb as a therapeutic approach. In the ongoing COVID-19 pandemic, patient-derived investigational mAbs have been considered for emergency use to treat mild to moderately ill patients. Combination therapy with two such mAbs derived from recovered COVID-19 patients, bamlanivimab, and...
esevimab, with the approval of the FDA-Emergency Use Authorization (EUA) committee, resulted in a significant decrease in viral load and hospitalization in comparison to placebo. The EUA of the bamlanivimab plus etesevimab combination therapy has been further expanded for post-exposure prophylactic use for certain high-risk cohorts (https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-mono
cal-antibodies/). Another mAb, sotrovimab, originally isolated from a SARS survivor in 2003, was found to be able to bind to a conserved epitope in the receptor-binding domain of the spike protein of both SARS-COV and SARS-COV2. Thus, this mAb has also been approved by the FDA-EUA committee as an investigational treatment for COVID-19 and is currently being monitored for clinical efficacy (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-addi
tional-mono-clonal-antibody-treatment-covid-19). Patient-derived mAbs have been used in Ebola viral disease (EVD) as well. MAb114 is a memory B cell-derived mAb isolated from an EVD survivor, obtained 11 years after clinical infection, which can block the viral entry into host cells. Treatment with MAb114 in EVD patients at early disease onset resulted in lower fatality in specific cohorts. Presently, MAb114 is being tested in an ongoing clinical trial (https://clinicaltrials.gov/ct2/show/NCT03478891?term=MAb114&cond=Ebola&draw=2&rank=4).

**CP therapy in tackling the COVID-19 pandemic: to do or not to do**

In times of extreme need, when there is no documented therapeutic modality available, CP therapy often gives a fighting opportunity against the disease. The ongoing COVID-19 pandemic, where no specific treatment has been found to be unequivocally effective against the virus, and standard treatment involves the administration of common antiviral agents with limited efficacy, represents such a dire situation. Therefore, modern medical approaches went back to the basics, and trials with the century-old technique of CP therapy are being widely undertaken. In general, CP infusion has been found to be effective in decreasing the requirement of mechanical ventilation and promoting general improvement of patient condition. While some studies demonstrated dramatic improvement of critically ill patients on mechanical ventilation when transfused with CP, other studies have shown the benefit of CP therapy largely confined to less critical patients. Resolution of ground-glass opacities (GGOs) in the lung high-resolution computed-tomography (HRCT) images in patients accompanied by an immediate increase in anti-SARS-CoV-2 antibody titers could be achieved by CP administration, even when done in later stages of the disease. In contrast, some records documented positive outcomes of CP therapy only when administered in the early stages of disease development. Typically, transfusion of plasma retrieved from recently recovered patients with high NAb titers showed significant improvement of clinical symptoms in recipients within 3 days of treatment or slowed disease advancement at the very least.

Notably, few studies have also reported completely different outcomes of CP therapy in COVID-19. In a recent multicentre trial involving 12 clinics in Argentina, CP therapy in severely ill patients did not affect mortality or show any significant improvement in patient condition, when compared to placebo-treated subjects. Similarly, multicenter trials in China also hinted at minimal and insignificant effect of CP therapy on disease outcome, in comparison to standard treatment. In another randomized clinical trial involving a single academic medical center in Chile, no significant benefit of immediate CP administration versus that upon worsening of symptoms was recorded. While these findings point to the perceived inefficacy of CP therapy in COVID-19 management, several points need to be taken into consideration. Most of these studies used CP therapy in conjunction with standard treatment, which itself has oscillated between hydroxychloroquine, dexamethasone, ivermectin, etc. over the last few months. The effect of these drugs, which may be synergistic or antagonistic to CP therapy, needs to be considered while interpreting the results of these clinical trials. Additionally, most studies have been done in a single city or country, which may have affected the outcome, depending on the genetic homogeneity of the population. Therefore, multi-center and multi-country clinical trials need to be undertaken to further prove the efficacy or inefficacy of CP therapy. Furthermore, some of the described studies did not account for the NAb titer of the donor CP, which may affect the outcome either way. Another important point to note while interpreting the clinical trial data is the possibility of antibody-dependent enhancement of the infection, which is currently under investigation in SARS-COV2.

In general, even in studies that showed positive outcomes of CP therapy in COVID-19, the benefits are most experienced when administered at earlier disease stages, and to younger patients without any comorbidities. Thus, timely recognition of critical cases and early transfusion is crucial. Standard guidelines for the use of CP therapy in children, pregnant women, and nursing mothers also need to be established before administration of CP in these cohorts of patients.

In addition to CP therapy, IVIG has also been used in many clinical trials to assess its efficacy in ameliorating SARS-COV2 infection. In a randomized case study, patients who were administered with IVIG displayed reduced in-hospital mortality rate, compared to placebo controls. Furthermore, the use of IVIG in conjunction with standard treatment resulted in reduced hospital stay, lessened the requirement of mechanical ventilation, and ensured early recovery. Similarly, IVIG used at high doses within 14 days of disease onset increased patient survival and stabilized the ensuing cytokine storm.

**CP therapy: addressing the variables**

From the above discussion, it is evident that CP therapy and its more modern derivatives have proven efficacy in treating many life-threatening diseases, over the years. During
infectious disease outbreaks like the presently ongoing pandemic, when no known or specific treatment is readily available, CP therapy is the simplest therapeutic modality that can be employed to treat critical cases. Although the advancements in modern medical research have led to the development of highly specific mAbs that can disrupt the infective process of pathogens, it takes time, personnel, and resources to develop them. In a time of global medical emergency, several of these factors may be in shortfall. The economic commitments of treating the global population with such antibodies will be prohibitive as well. Similarly, in managing diseases that are endemic to specific geographical locations, high-end GMP (Good Manufacturing Practice) facilities required for mAb production may not be available. Isolation and transfusion of CP, on the other hand, requires minimal infrastructural support and therefore presents the most economically feasible and practical strategy of disease management in such scenarios. Thus, the success of CP therapy in times of global or local emergencies, even in the modern era of molecular medicine is manifold and well established.

However, several points need to be noted and addressed while dealing with CP as a therapeutic strategy. For example, stringent quality control steps must be followed to minimize the risk of transfusion-associated infections. Also, optimizing the dose of NAb titer in the CP is required prior to transfusion to improve its efficacy. The dosage and timing of administration of CP and tolerability of recipients are also important points for consideration. Donor selection should be done following rigorous validation of recovery from concerned disease. Apart from established criteria pertaining to the general health and age of the donor, the sex of the donor is an important consideration for plasma donations. Donations are mostly accepted from males, and females with no pregnancy history; as multiparous females are more likely to bear anti-HLA antibodies in their plasma that can cause severe complications in the recipient. In addition, it is also preferred if the donors and recipients come from the same geographical area to account for any location-specific mutations in the viral pathogen. Several other challenges such as lack of NAbs in patient plasma, waning of plasma antibodies, detrimental possibilities like antibody-dependent enhancement of infection, etc., need to be considered, to clearly understand the effects of CP therapy. Addressing these issues will further help establish CP therapy as a therapeutic modality and increase its success rate against emerging contagions.

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