Ortho Clinical Diagnostics

Convalescent Plasma Learning Cards

July 2020 - v01

The information on this document is intended for healthcare professionals.
Patients should consult a healthcare professional regarding specific medical conditions and treatments.

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Table of Contents

Overview

Key terms and definitions

CONVALESCENT PLASMA

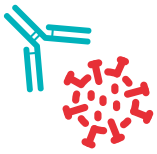
Plasma obtained from a patient who has survived a previous infection and developed humoral immunity against the pathogen responsible for the disease. The plasma contains specific antibodies against the pathogen and can neutralize the pathogen and eventually lead to its eradication. Convalescent plasma has been used as a passive immunization for prevention or treatment of human infectious diseases for decades.

IMMUNITY

The body's acquired ability to fight infection and to prevent/protect the host from reinfection by the same pathogen. Immunity to a given pathogen relies on the immune response, but not all immune responses can achieve immunity or protection. Immunity is often achieved by both humoral and cellular immune responses.

NEUTRALIZATION

In Immunology, neutralization refers to the ability of antibodies to block the site(s) on bacteria or viruses that they use to enter their target cells.



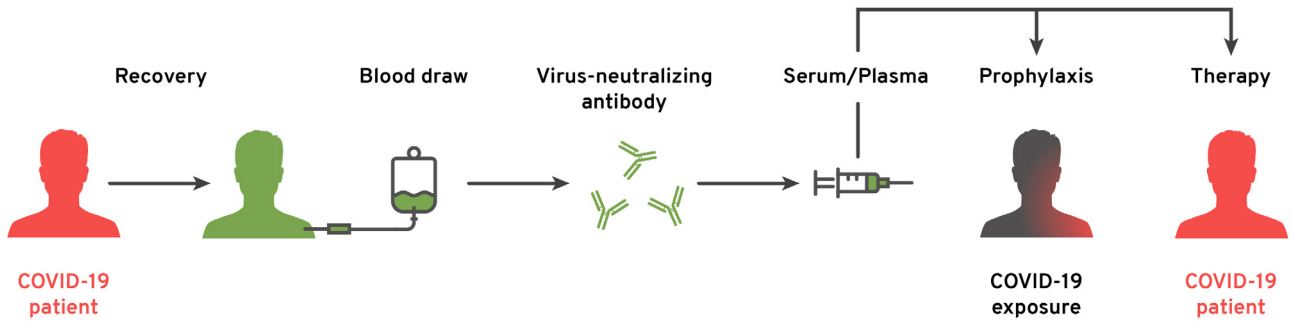
NEUTRALIZING ANTIBODY

A neutralizing antibody (NAb) is an antibody that defends a cell from an infectious pathogen by blocking its interaction with the host cells and renders the pathogen no longer infectious or pathogenic. Neutralizing antibodies are part of the humoral immune response of the adaptive immune system against viruses, bacteria, and toxins. Virus neutralizing antibodies typically recognize proteins on the virion surface.

What is Convalescent Plasma

When a person contracts a virus like Sars-COV-2, the virus causing COVID-19, their immune system creates antibodies to fight the virus. These antibodies are found in plasma, which is the liquid part of blood. Plasma with these infection-fighting antibodies is called “Convalescent Plasma (CCP).”

Through a blood donation process, this antibody-rich plasma can be collected from a recovered person, then transfused to a sick patient who is still fighting the virus. This provides a boost to the immune system of the sick patient and may help up speed the recovery process.



Immune (i.e. “convalescent”) plasma refers to plasma that is collected from individuals, following resolution of infection and development of antibodies. Passive antibody therapy, through transfusion of convalescent plasma, may prevent clinical infection or blunt clinical severity in individuals with recent pathogen exposure. Antibody therapy can also be used to treat patients who are already manifesting symptoms of varying severity. A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms.

Human convalescent plasma may be an option for prevention and treatment of COVID-19 disease that could be rapidly available when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing plasma. However the clinical efficacies with CCP therapies in different disease settings were rather anecdotal. There is a lack of large-scale, randomized and placeable controlled clinical trials to provide definitive evidence.

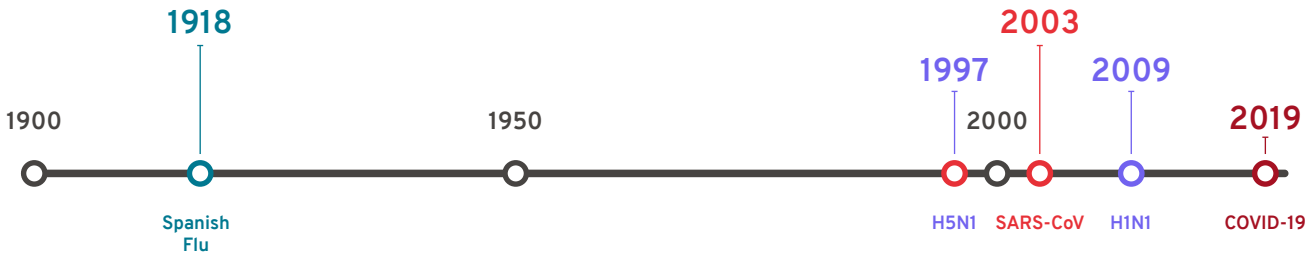
AABB Covidplasma.org resources page

The Journal of Clinical Investigation. Convalescent sera option for containing COVID-19 - Arturo Casadevall and Liise-anne Pirofski. Department of Molecular Microbiology and Immunology, Johns Hopkins

Schematic: School of Public Health, Baltimore, Maryland, USA. Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA. April 2020

The Journal of Clinical Investigation. Deployment of convalescent plasma for the prevention and treatment of COVID-19. Johns Hopkins University School of Medicine, Division of Transfusion Medicine, Department of Pathology, Baltimore, MD et al

History of Convalescent Plasma



- The use of Convalescent Plasma, has been used as strategy of passive immunization in prevention and management of infectious diseases since early 20th century.

- In the early 1950s, purification and concentration of immunoglobulins from healthy donors or recovered patients provided an option to treat serious infectious diseases as well as immune conditions including primary immunodeficiencies, allergies, and autoimmune diseases.

- In the case of **Influenza A (H1N1) pdm09**, **Spanish Influenza A (H1N1)**, and **SARS-CoV** infections, the use of CCP was associated to reduction in fatality rates, mortality and mild adverse events. In relation to the use of mechanical ventilation, in **Influenza A (H1N1) pdm09**, and **avian influenza A (H5N1)**, administration of CCP reduced the duration of invasive ventilation.

- Given the ability to be rapidly obtained, Convalescent Plasma has been considered as an emergency intervention in several pandemics, including the **Spanish flu**, **SARS-CoV**, West Nile virus, and more recently, Ebola virus.

- The use of CCP in other coronaviruses such as **SARS-CoV**, reduced days of hospital stay in critically ill patients. It has been described that the use of CCP in **SARS-CoV** and **avian influenza A (H5N1)** decreased the viral load in the respiratory tract.

STUDY

The largest study involved the treatment of 80 patients in Hong Kong with SARS1. Compared to those given plasma later, patients who were treated before day 14 had improved outcomes as defined by discharge from hospital before day 22, supporting early administration for optimal effect.

Convalescent plasma in Covid-19: Possible mechanisms of action. Center for Autoimmune. April 11/2020. Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia

The Journal of Clinical Investigation. Deployment of convalescent plasma for the prevention and treatment of COVID-19. Johns Hopkins University School of Medicine, Division of Transfusion Medicine, Department of Pathology, Baltimore, MD et al

Mechanism of Action, Collecting & Testing

Potential Mechanism of Action

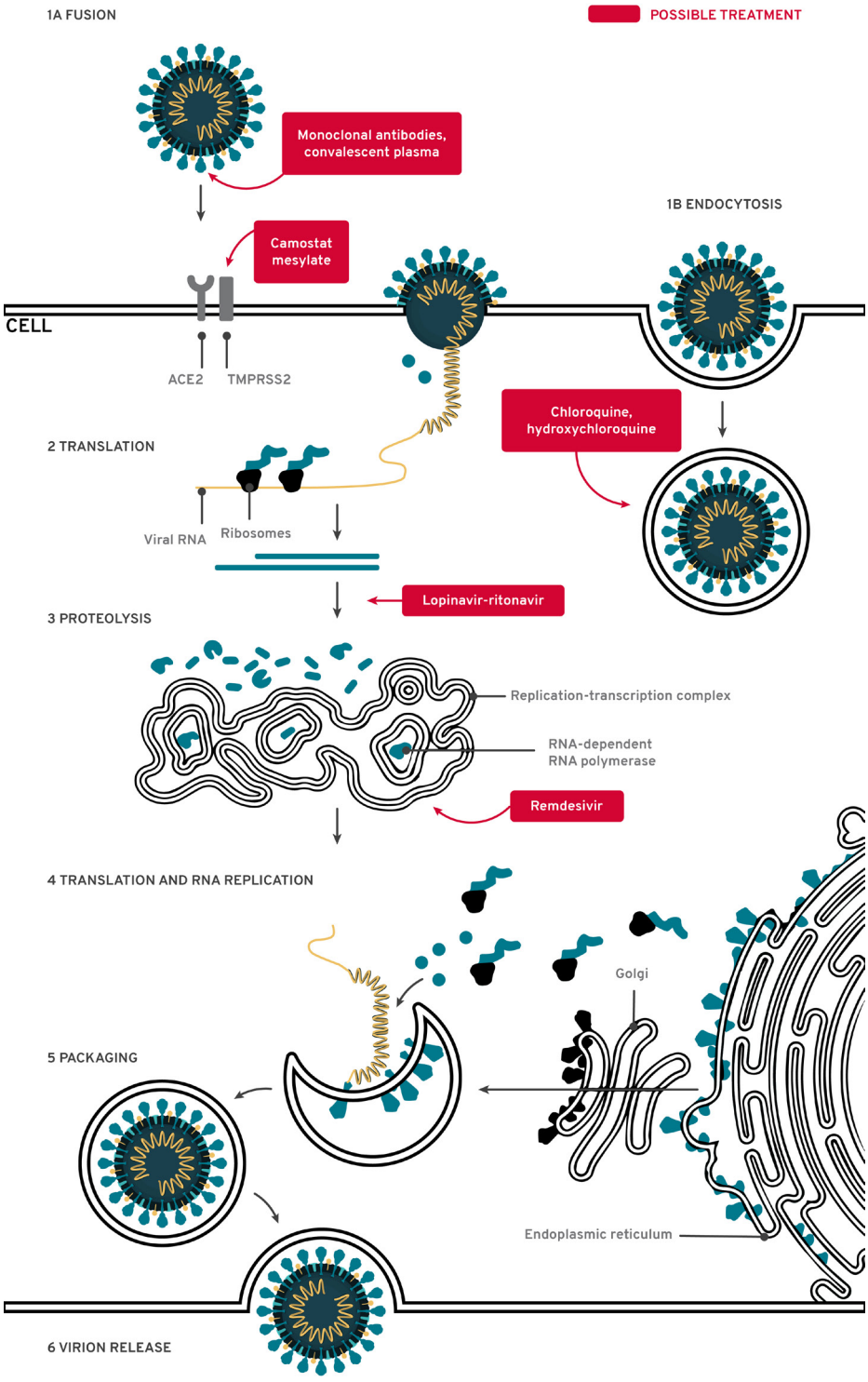
In the case of SARS-CoV-2, the anticipated mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. The antibody can bind to a given pathogen (e.g. virus), thereby neutralizing its infectivity directly.

Other antibody- mediated pathways such as complement activation, antibody-dependent cellular cytotoxicity and/or phagocytosis may also contribute to its therapeutic effect.

Non-neutralizing antibodies that bind to the pathogen — but do not interfere with its ability to replicate in in-vitro systems — may also contribute to prophylaxis and/or enhance recovery.

LINES OF ATTACK

Experimental treatment strategies attempt to interfere with different steps (numbered) in the coronavirus replications cycle.



The Journal of Clinical Investigation. Convalescent sera option for containing COVID-19 - Arturo Casadevall and Liise-anne Pirofski. Department of Molecular Microbiology and Immunology.

Johns Hopkins School of Public Health, Baltimore, Maryland, USA. Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA. April 2020

Active Vaccination vs Passive Antibody Therapy definition

ACTIVE VACCINATION

Requires the induction of an immune response that takes time to develop and varies depending on the vaccine recipient

PASSIVE ANTIBODY THERAPY

Involves the administration of antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent.

Passive antibody administration through transfusion of convalescent plasma may offer the only short-term strategy to confer immediate immunity to susceptible individuals. Limited data suggests COVID-19 convalescent plasma as a passive antibody therapy with clinical benefits, including radiological resolution, reduction in viral loads and improved survival.

However the clinical efficacies with CCP therapies in different disease settings were rather anecdotal. There is a lack of large-scale, randomized and placeable controlled clinical trials to provide definitive evidence

The Journal of Clinical Investigation. Convalescent sera option for containing COVID-19 - Arturo Casadevall and Liise-anne Pirofski. Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, Baltimore, Maryland, USA. Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA. April 2020

Collection & testing of Convalescent Plasma

COLLECTION

Apheresis (rather than whole blood donation) is recommended to optimize the yield of convalescent plasma. Apheresis refers to an automated technology in which whole blood is continuously centrifuged into its components (i.e. red blood cells, plasma, platelets); this allows for selective collection of the desired blood fraction with return of the other components to the donor.

This is highly efficient: approximately 400-800mL of plasma from a single apheresis donation, which then provides 2-4 units of convalescent plasma for transfusion.

- ☑ Where feasible, pathogen inactivation of plasma using a licensed technology in place in the blood establishment, is desirable to control residual risks of transfusion transmitted infectious diseases and to allay concern about possible superinfections with SARS-CoV-2.
- ☑ Whole blood should be stored between 2°C and 6°C for a duration depending upon the anticoagulant and preservative used.
- ☑ Liquid plasma may be stored between 1°C and 6°C for up to 40 days.
- ☑ Plasma frozen at -18°C or colder within 24 hours after blood collection can be stored for up to 12 months.
- ☑ Convalescent plasma collected from donors who do not fulfill post-COVID-19 suitability criteria for routine blood donation should be stored separately from other blood products in inventory.
- ☑ Convalescent plasma should bear special labeling as an investigational product for treatment of COVID-19.
- ☑ Donor blood/serum/plasma samples obtained at the time of donation should be saved frozen at -20°C or colder for retrospective testing of the total and neutralizing titers of anti-SARS-CoV-2 antibodies and further scientific investigations.

Collection & testing of Convalescent Plasma

TESTING

The units are frozen within 24 hours of collection and quarantined —as is routine— pending results from standard blood donor testing. The latter fulfills regulatory requirements and mostly comprises testing for transfusion-transmissible infections (e.g. HIV, hepatitis B and C viruses etc.). There is also required testing of female donors with a history of pregnancy for HLA antibodies to mitigate the risk of transfusion related acute lung injury (TRALI).

For INDs (Investigation New Drug Application) for use of COVID-19 convalescent plasma, the IND would therefore need to contain, among other things, adequate information to demonstrate that the plasma will contain SARS-CoV-2 neutralizing antibody titers, if available.

The Journal of Clinical Investigation. Convalescent sera option for containing COVID-19 - Arturo Casadevall and Liise-anne Pirofski. Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, Baltimore, Maryland, USA. Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA. April 2020

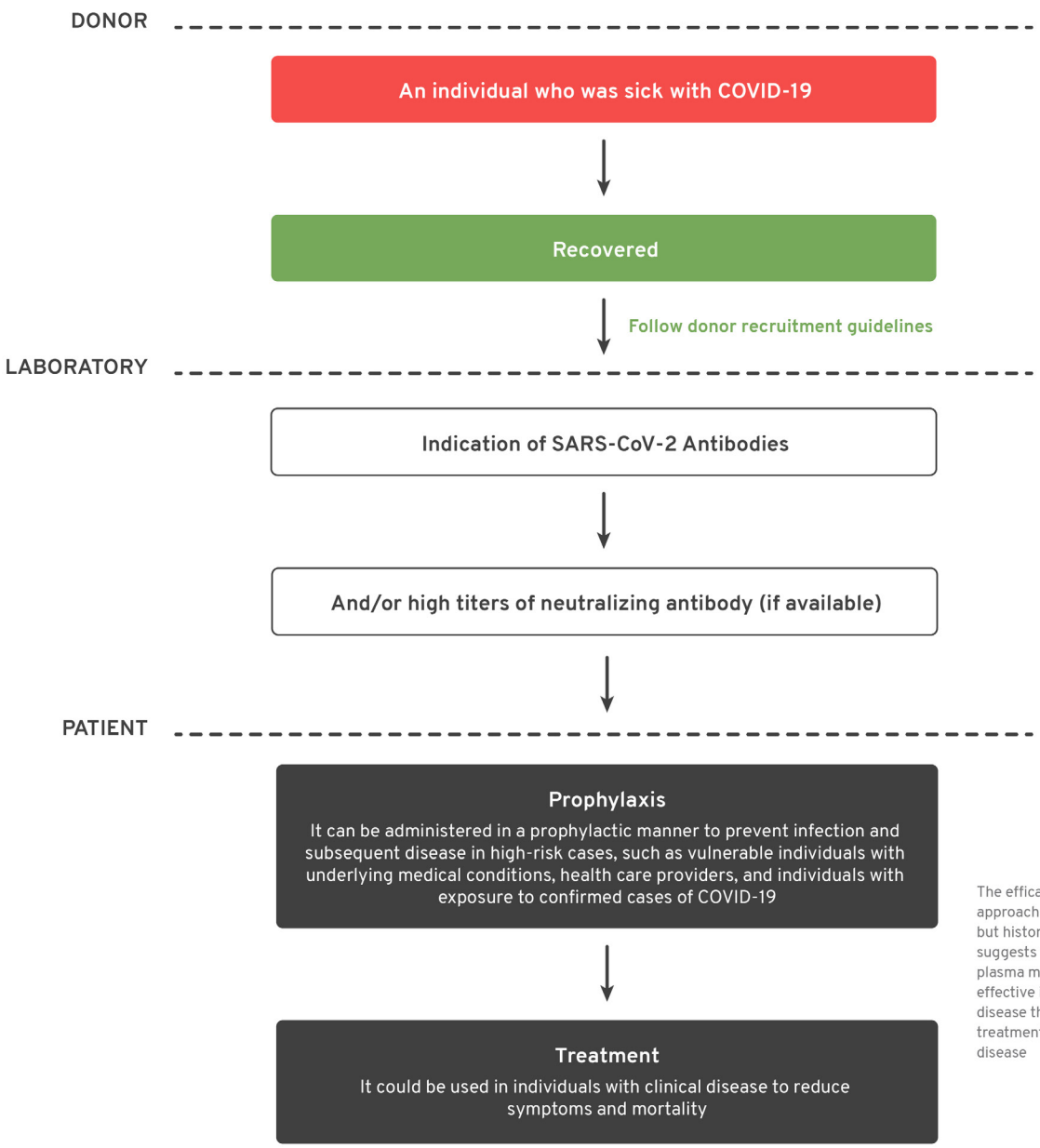
FDA site https://www.fda.gov/

Points to consider in the preparation and transfusion of COVID-19 convalescent plasma in low- and middle- income countries. Organizing Committee of the ISBT Working Party on Global Blood Safety* April 2020

WHO - Convalescent Plasma "Position paper" on the preparation of immune plasma to be used in the treatment of patients with COVID-19.

Uses & Clinical Outcomes

Convalescent Plasma uses



The efficacy of these approaches is not known, but historical experience suggests that convalescent plasma may be more effective in preventing disease than in the treatment of established disease

NOTE

There is a huge unmet medical need for specific treatment and effective vaccine for COVID-19 (despite the encouraging clinical trial data about Remdesivir). Main treatment approach for COVID patients is supportive care and treat complications. Convalescent plasma (CCP) therapy has been used as an investigational treatment for severe or critical COVID-19 patients.

The Journal of Clinical Investigation. Convalescent sera option for containing COVID-19 - Arturo Casadevall and Liise-anne Pirofski. Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, Baltimore, Maryland, USA. Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA. April 2020

Anecdotal clinical outcomes & data findings

Summary of 3 cases series examining the use of Convalescent Plasma in the setting of SARS-CoV-2.

STUDY - SHEN et Al (2020)	STUDY - DUAN et Al (2020)	STUDY - ZHANG et Al (2020)
NUMBER OF PATIENTS (AGE RANGE IN YEARS)		
5 (36-73)	10 (34-78)	4 (31-73)
PATIENT CHARACTERISTICS		
• qRT-PCR confirmed COVID-19 infection • Severe PNA • Pao_2/Fio_2 <300 mmHG • Mechanically ventilated	• qRT-PCR confirmed COVID-19 infection • 2/4 of the following: 1) ≥ 18 years 2) Respiratory distress 3) O2 saturation <93% at rest 4) Pao2/Fio2 <300 mmHG	• Confirmed COVID-19 infection (3/4 RT-PCR positive) • Respiratory failure requiring mechanical ventilation (2 required ECMO)
VOLUME OF CCP TRANSFUSED (AVERAGE DAY FROM ADMISSION)		
400 mL (18.2)	200 mL (16.5)	200-2400 mL (15.25)
CCP ANTIBODY PROFILE		
SARS-CoV-2-specific antibody titer > 1:1000 neutralizing antibody titer > 1:40	Neutralizing antibody titer > 1:640	Not measured
SUMMARY OF OUTCOMES OBSERVED POST-TRANSFUSION (RATIO OF PATIENTS DEMONSTRATING OUTCOME)		
• Increased in Pao2/Fio2 within 12 days • Decrease in viral loads within 12 days • Increase in SARS-CoV-2-specific and neutralizing antibody titers • Resolution of ARDS withing 12 days (4/5) • Mechanical ventilation weaned withing 14 days (3/5) • Discharged between days 51-55 (3/5) • Remained mechanically ventilated (2/5)	• Clinical symptoms were significantly reduced within 3 days • Trend in increased lymphocyte counts • Trend in decreased C-reactive protein • Imaging showed varying degrees of absorption of lung lesions within 7 days • Undetectable viral load (7/10)	• Negative qRT-PCR • Imaging showed absorption, or partial absorption, of lung lesions • Discharged between days 18-43 (3/4) • Remained hospitalized with multiorgan failure (1/4)

Anecdotal clinical outcomes & data findings

NOTE

- Even though the cases in the report by **SHEN et Al** are compelling and well-studied, this investigation has important limitations that are characteristic of other “anecdotal” case series.
- The intervention, administration of convalescent plasma, was not evaluated in a randomized clinical trial, and the outcomes in the treatment group were not compared with outcomes in a control group of patients who did not receive the intervention.
- Therefore, it is not possible to determine the true clinical effect of this intervention or whether patients might have recovered without this therapy. In addition, patients received numerous other therapies (including antiviral agents and steroids), making it impossible to disentangle the specific contribution of convalescent plasma to the clinical course or outcomes. Moreover, convalescent plasma was administered up to 3 weeks after hospital admission, and it is unclear whether this timing is optimal or if earlier administration might have been associated with different clinical outcomes.
- Despite these limitations, the study does provide some evidence to support the possibility of evaluating this well-known therapy in more rigorous investigations involving patients with COVID-19 and severe illness.
- In the first report by **SHEN et Al**, 5 critically ill COVID-19 patients showed improvement in their clinical status after receiving convalescent plasma (CCP). However no definitive conclusion regarding to the efficacy of CCP can be drawn from this case study. **ANOTHER STUDY** with 10 severe COVID-19 patients received a 200 mL transfusion of CCP with high titers of neutralizing antibodies (>1:640) showed clinical improvements and suppression of viremia.
- In a **RETROSPECTIVE REPORT** of 4 critically ill patients with 200-2400 mL of CCP treatment showed all patients were recovered from the SARS-CoV-2 infection.
- A study of 6 critically end-stage COVID-19 patients received CCP treatment did not show improved survival in these patients with advanced disease, suggesting CCP should be used in an early phase of the disease to obtain the best effect.
- A study with 25 severe or life-threatening COVID-19 patients was conducted to evaluate the safety and patient’s clinical status at day 14 post-transfusion. The data indicated that administration of CCP is a safe treatment option for those with severe COVID-19 disease.

Convalescent Plasma: Therapeutic Hope or Hopeless Strategy in the SARS-CoV-2 Pandemic. H. Cliff Sullivan , John D. Roback. Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma, C Shen, et al, JAMA. 2020;323(16):1582-1589. doi:10.1001/jama.2020.4783

The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study, Duan et al, Mar 2020, medRxiv preprint doi: https://doi.org/10.1101/2020.03.16.20036145

Treatment of COVID-19 Patients with Convalescent Plasma, E Salazar, et al, AJPA, 2020, DOI: https://doi.org/10.1016/j.ajpath.2020.05.014Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection, Zhang, et al, Chest 2020.

Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. Zeng, et al, J Infect Dis 2020

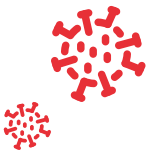
Risk of use of Convalescent Plasma

TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD (TACO)

Noninfectious hazards of transfusion. Of note, risk factors for TACO (e.g. cardiorespiratory disease, advanced age, renal impairment etc.) are shared by those at risk of COVID-19. TACO is now recognized as the most common serious adverse effect of transfusion. The incidence of TACO would be expected to be higher than 12% in elderly COVID-19 patients with acute lung injury who are being supported with mechanical ventilation. This may be especially relevant in the setting of the pulmonary inflammation and increased vascular permeability that characterize SARS-CoV-2 infection.

TRANSFUSION RELATED ACUTE INJURY (TRALI)

Noninfectious hazards of transfusion. While the risk of TRALI is generally less than one for every 5,000 transfused units, TRALI is of particular concern in severe COVID-19 given potential priming of the pulmonary endothelium. However, routine donor screening includes HLA antibody screening of female donors with a history of pregnancy to mitigate risk of TRALI.



ANTIBODY-DEPENDENT ENHANCEMENT OF INFECTION (ADE)

It is a theoretical risk. ADE can occur in several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described, and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain. This phenomenon is observed, when non-neutralizing virus-specific IgG facilitate entry of virus particles into Fc-receptor (FcR) expressing cells, particularly macrophages and monocytes, leading to inflammatory activation of these cells (Taylor et al., 2015).

The Journal of Clinical Investigation - Convalescent sera option for containing COVID-19 - Arturo Casadevall and Liise-anne Pirofski. Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, Baltimore, Maryland, USA. Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA.

MedRxiv. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. March 23/2020.

COVID-19 Convalescent Plasma: Now Is the Time for Better Science. H Cliff Sullivan and John Roback of Emory University in Atlanta.

SARS-CoV-2 & transfusion-transmitted Infection (TTI)

Human Anti-SARS-CoV-2 plasma differs from standard plasma only by the presence of antibodies against SARS-CoV-2. Therefore, the risks to transfusion recipients are likely to be no different from those of standard plasma. Risk of transfusion-transmissible infection is very low. Typically cited estimates are less than one infection per two million donations for HIV, hepatitis B and hepatitis C viruses.

The potential for transmission of SARS-CoV-2 by blood and blood components is unknown at this time. However, respiratory viruses, in general, are not known to be transmitted by blood transfusion, and there have been no reported cases of transfusion-transmitted coronavirus.

In Wuhan, 2430 blood donations were screened in real-time (January 25 to March 4, 2020): a single (0.04%) — asymptomatic—donor was found to be positive for SARS-CoV-2 RNA. A second (0.02%), asymptomatic, SARSCoV-2 RNA positive donor was identified on retrospective screening of 4995 donations (December 21 to January 22, 2020), an additional two donors were identified as being RNA-emic through follow-up of donors who had developed fever subsequent to their donations. In Wuhan, China, four of 7425 qualified blood donors were PCR positive, no virus isolation was attempted, and donors were not followed up with serology. In a lookback to recipients of 17 transfused components from seven South Korean donors who developed COVID-19 6 to 15 days after donation, there was no associated clinical morbidity in the recipients.

Four things are needed for a pathogen to be considered Transfusion Transmitted:

1. The agent must be present in the blood of a donor who can be qualified to donate
2. It must survive in the collected component(s)
3. It must find susceptible cells to infect and in which to proliferate
4. To be a TTI it must make the recipient ill

NOTE

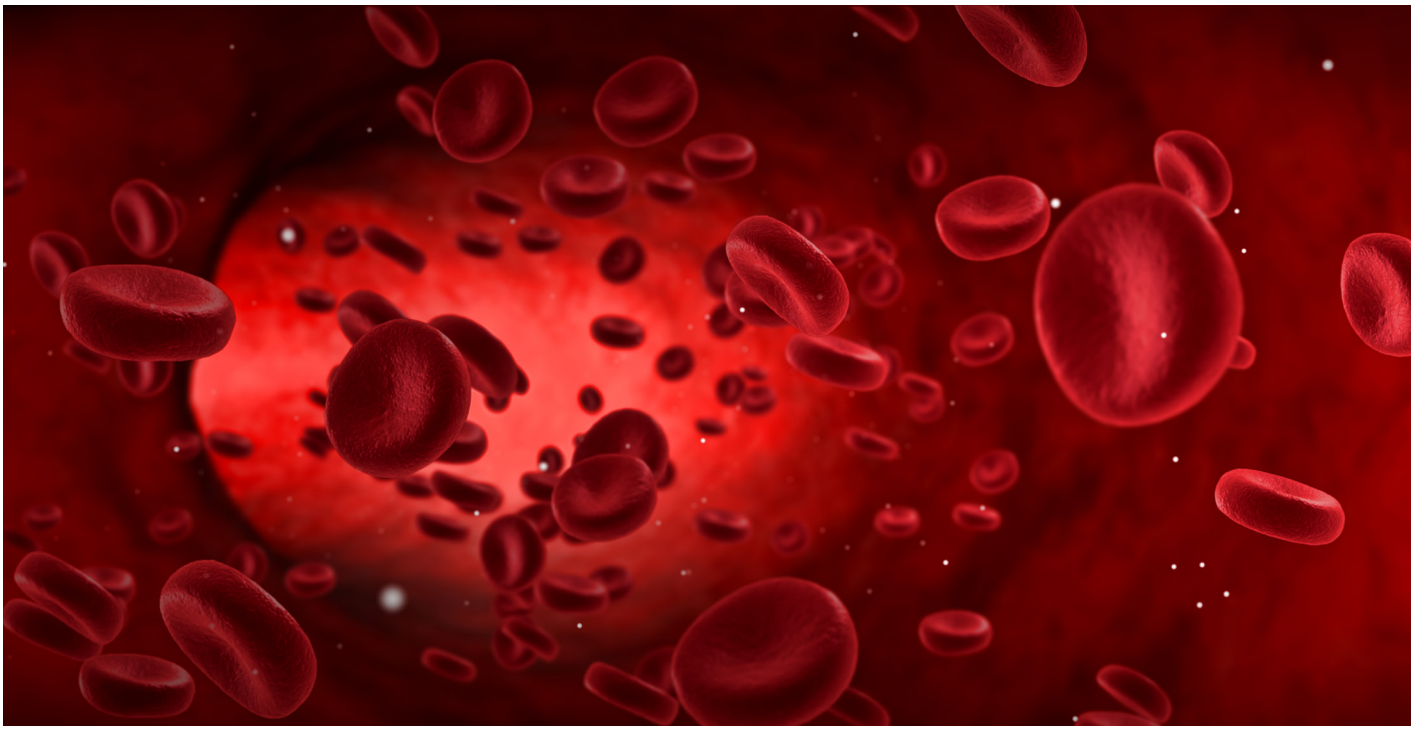
AABB updated their Web site to state that, considering the concern regarding SARS-CoV-2 and blood safety, they would continue to closely monitor the outbreak of respiratory illness.

SARS-CoV-2 & transfusion-transmitted Infection (TTI)

The AABB, FDA, and Centers for Disease Control and Prevention do not currently require any action on blood collection and testing because there are no data suggesting a risk of transfusion transmission of SARS-CoV-2.

Routine blood donor screening measures that are already in place should prevent individuals with clinical respiratory infections from donating blood. For example, blood donors must be in good health and have a normal temperature on the day of donation

The U.S. Food and Drug Administration has said “The potential for transmission of SARS-CoV-2 by blood and blood components is unknown at this time. Respiratory viruses, in general, are not known to be transmitted by blood transfusion, and there have been no reported cases of transfusion Transmitted coronavirus.”



Transfusion News. Sars-Cov-2 SARS-CoV-2 Found in Blood—Is it Transfusion Transmissible?

Coronavirus Disease 2019: Coronaviruses and Blood Safety. National Center for Clinical Laboratories, Beijing Hospital,

FDA Updated Information for Blood Establishments Regarding the Novel Coronavirus Outbreak. March 11

Transfus Med Rev. 2020 Feb 21 Coronavirus Disease 2019: Coronaviruses and Blood Safety Le Chang,a,b Ying Yan,a,b and Lunan Wanga https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7135848/

Is Sars-Cov-2 Transfusion Transmitted. Louis M. Katz, MD. Volume 60, June 2020 TRANSFUSION

Programs for Access & Donor Eligibility

Pathways for access to Convalescent Plasma

The following pathways are available for administering or studying the use of COVID-19 Convalescent Plasma:

CLINICAL TRIALS

A traditional pathway to apply for an IND to support research.

EXPANDED ACCESS PROGRAM

Is an alternative for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials. FDA has worked with multiple federal partners and academia to open an expanded access (master protocol) to facilitate access to COVID-19 convalescent plasma across the nation. Mayo Clinic is the lead institution.

SINGLE PATIENT EMERGENCY IND

This allows a provider to apply for compassionate use in an individual patient with severe or immediately life-threatening COVID-19. Of note, this guidance does not allow for prophylaxis.

NOTE

Because COVID-19 Convalescent Plasma has not yet been approved for use by FDA, it is regulated as an investigational product. As such, administration of COVID-19 Convalescent Plasma by a health care provider must be under an investigation new drug application (IND).

FDA site https://www.fda.gov

Convalescent Plasma Expanded Access Program

Responding to the unprecedented challenge of fighting coronavirus disease 2019 (COVID-19), the U.S. Government is supporting a national Expanded Access Program to collect and provide convalescent plasma to patients in need across the country. Plasma from recovered COVID-19 patients contains antibodies that may help fight the disease.

Working collaboratively with industry, academic, and government partners, Mayo Clinic will serve as the lead institution for the program

FOR PHYSICIANS

Contains all the information to participate and/or enroll patient(s) in the COVID-19 treatment study.

FOR PATIENTS & FAMILY

If you want to know if you, a family member, or someone for whom you are a guardian or health care proxy are eligible for this treatment, discuss this protocol with the treating physician.

Program Participation latest update - June 15 2020

2,491	8,422	31,541	22,655
Sites	Physicians	Patients	Infused

DONATE

Through the American Red Cross:
https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients.html

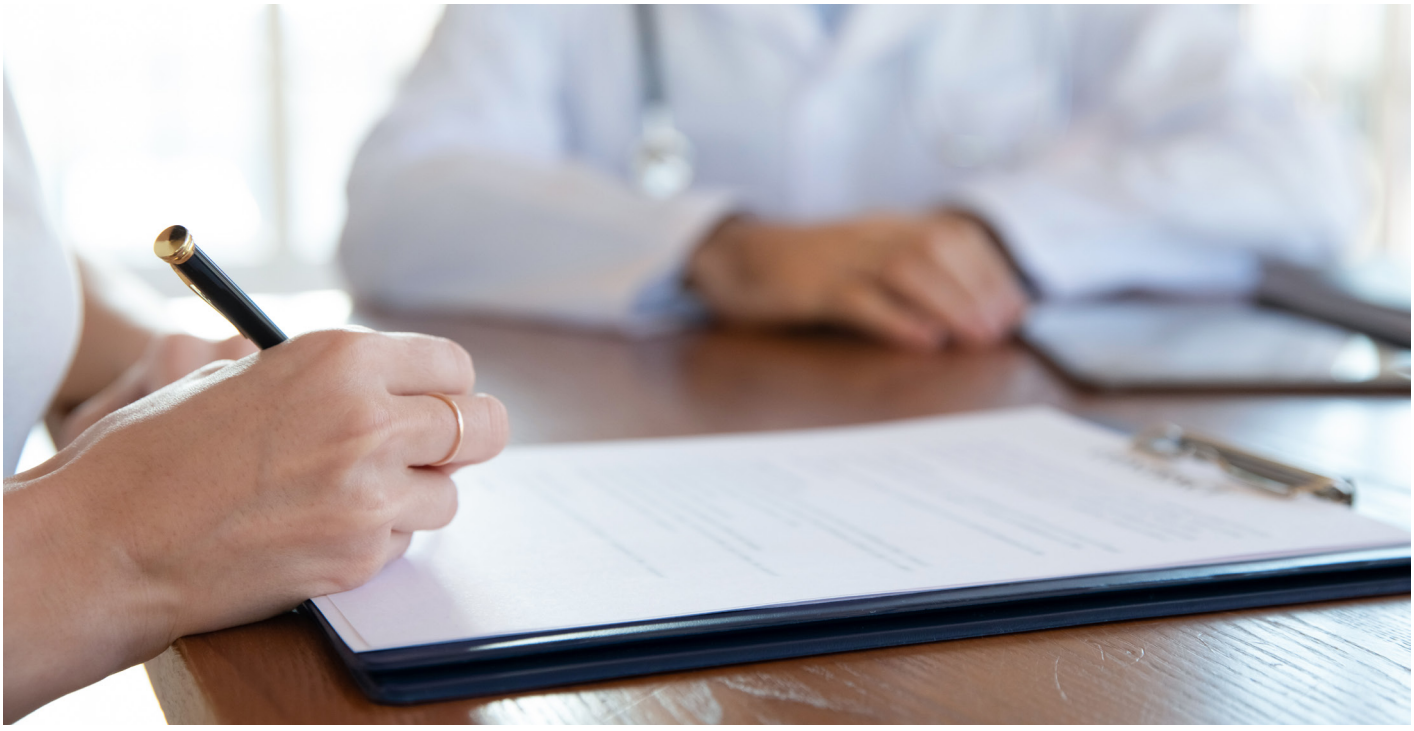
Donor recruitment eligibility

RECRUITMENT

Those who have recovered from COVID-19 will be recruited to serve as potential blood donors. Approaches include community outreach in areas with robust epidemics, advertising and communication through media, and/or directly through providers (e.g. at time of discharge) and their professional organizations.

Blood centers have well-developed infrastructure for donor recruitment; while they may be best equipped to oversee recruitment in collaboration with partner hospitals, their primary responsibility is to ensure an adequate blood supply to meet clinical demand. Confronted with recent, severe blood shortages given cancelled blood drives, blood centers are forced to prioritize their efforts accordingly, while still planning for convalescent plasma collection.

The latter presents additional burden on the blood centers, particularly while contending with the logistical constraints posed by COVID-19 (e.g. limited staffing, a contracted donor pool, travel restrictions etc.). Of note, while convalescent plasma could compete with routine plasma collections, this may be offset by lowered demand for standard plasma given COVID-19 mitigation measures such as cancelled elective surgeries.



Donor recruitment eligibility

ELIGIBILITY

COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements. Donation testing for relevant transfusion-transmitted infections must be performed.

Donor qualifications:

- ☑ Evidence of COVID-19 documented by a laboratory test either by:
  A diagnostic test (e.g., nasopharyngeal swab) at the time of illness, or a positive serological test for SARS-CoV-2 antibodies after recovery.
- ☑ Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.
- ☑ Male donors, or female donors who have not been pregnant, or female donors test negative for HLA antibodies.
- ☑ SARS-CoV-2 neutralizing antibody titers, if available.
- ☑ Neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable. When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.

NOTE

According to the document COVID-19 convalescent plasma in low- and middle- income countries. Organizing Committee of the ISBT Working Party on Global Blood Safety* April 2020 - An interval of at least 28 days after full recovery except: When blood or plasma needs to be collected prior to 28 days after full recovery from illness, the collection should not take place prior to 14 days after full recovery and additional confirmation of the resolution of the infection should be obtained through demonstration of a non-reactive Nucleic Acid Test (NAT) for SARS-CoV-2 performed on a nasopharyngeal swab sample.

The Journal of Clinical Investigation. Deployment of convalescent plasma for the prevention and treatment of COVID-19

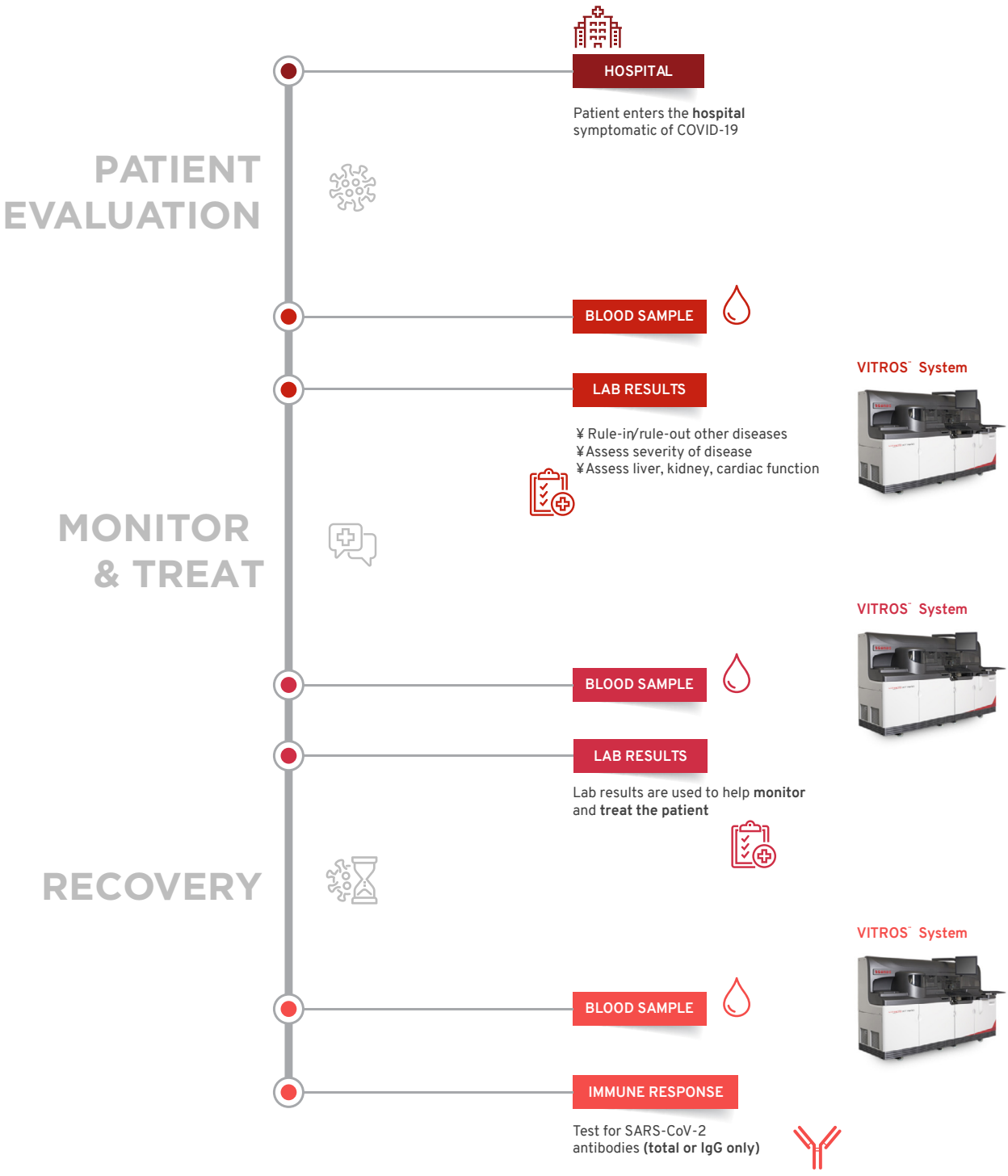
https://www.fda.gov/media/136798/download

COVID-19 convalescent plasma in low- and middle- income countries. Organizing Committee of the ISBT Working Party on Global Blood Safety* April 2020

Serology Testing

Role of Serology testing

Serology tests detect the presence of antibodies in the blood when the body is responding to a specific infection, like COVID-19. In other words, the tests detect the body's immune response to the infection caused by the virus rather than detecting the virus itself



Role of Serology testing

1. High-quality antibody tests (a type of serological test) can help understand a person's and population's exposure to COVID-19. A person who has been exposed to, and recovered from, COVID-19 will likely have antibodies to the SARS-CoV-2 virus in their blood. These tests may be important for guiding next steps in the fight against the pandemic, such as by providing information on disease prevalence and the frequency of asymptomatic infection, and also by identifying potential donors of convalescent plasma.

2. Serology tests could play a role in the fight against COVID-19 by helping healthcare professionals identify individuals have developed an immune response to SARS-CoV-2. Indication of the seroprevalence of SARS-CoV-2 infection. Seroconversion is determined by detection of antibodies that recognize SARS-CoV-2 antigens. And potentially, indication of immunity afforded to the seropositive individual.

3. Such serological assays are of critical importance to determine seroprevalence in a given population, define previous exposure and identify highly reactive human donors for the generation of convalescent serum as therapeutic. Sensitive and specific identification of coronavirus SARS-Cov-2 antibody titers may, in the future, also support screening of health care workers to identify those who are already immune and can be deployed to care for infected patients minimizing the risk of viral spread to colleagues and other patients.

4. Correlation of clinical antibody tests with neutralization activity could serve as a valuable 'roadmap' to guide the choice and interpretation of serological tests for SARS-CoV-2.

5. Surrogate serology tests to neutralizing activity could help to rapidly inform as to the likely effectiveness, as well as immunogenicity, of vaccines against SARS-CoV-2. Accurate quantification using serological assays that predict neutralization activity may improve clinical outcomes through refinement of CCP unit selection for patients of varying symptomatology

6. For vaccines: Clinical trials will undoubtedly include a battery of serological and neutralization assays in test subjects to assess candidate vaccine efficacy

NOTE

A recent study demonstrated that HTSA (High Throughput Serology Assays) and S1 (Spike Protein 1) ELISA assays show the strongest correlation with neutralization activity and may serve to predict the degree of antiviral antibody activity present in recovered patients or vaccine recipients. Importantly, these high dynamic range serological assays had a significant linear correlation with neutralization activity and may aid in predicting immunity at the individual and population levels.

Serological Analysis of New York City COVID19 Convalescent Plasma Donors. Larry L. Luchsinger PhD. New York Blood Center

Guidelines & Protocols

Guidelines & Regulations

Investigational COVID-19 Convalescent Plasma Guidance for Industry

Date: April 23. Update May 1

- Provides recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency.
- Also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

Pan American Health Organization

Date: April 22

- Offer recommendations and references for the collection and experimental use of plasma from “convalescent” COVID-19 donors.
- Facilitate the production of quality scientific evidence for the use of this product in epidemic situations.

Blueprint for testing plans and rapid response programs

Date: April 16

- This Blueprint is designed to facilitate State development and implementation of the robust testing plans and rapid response programs.
- Scope United States.

Guidelines & Regulations

An EU programme of COVID-19 convalescent plasma collection and transfusion Guidance on collection, testing, processing, storage, distribution and monitored use

Date: April 04

- Proposes to bring together the resources of the European Centre for Disease Prevention and Control, EU blood establishments and the European Commission to face the challenge of responding to the COVID-19 crisis by supporting the development of blood-based treatment options.

- It aims to launch a coordinated and effective approach to the collection of convalescent plasma across the EU, supporting the possibilities for the treatment of acutely ill patients (or patients at risk of becoming acutely ill) with the plasma within observational studies or randomized and case-controlled clinical trials, and in the longer term, for the development of immune globulin concentrates by industry.

Points to consider in the preparation and transfusion of COVID-19 convalescent plasma in low- and middle-income countries

Date: April

- The Working Party on Global Blood Safety of the International Society of Blood Transfusion has published “Points to Consider in the preparation and transfusion of COVID-19 convalescent plasma” that are recommended as best current practices to be followed whenever feasible including in low-and-middle income countries.

COMITE CIENTIFICO PARA LA SEGURIDAD TRANSFUSIONAL (MIN DE SANIDAD) (Spanish language)

Recomendaciones para la obtención de plasma de donantes convalecientes de COVID-19

Date: April 15

- El Comité Científico para la Seguridad Transfusional (CCST), órgano asesor del Ministerio de Sanidad en materia transfusional, en reunión mantenida el 15 de abril, acuerda adoptar las directrices contempladas en el documento “Guidance on collection, testing, processing, storage, distribution and monitored use“, publicado por la Comisión Europea el 8 de abril, y en consecuencia, actualizar mediante el presente texto las Recomendaciones del Comité emitidas el pasado 26 de marzo.

Neutralizing Antibodies Guidelines

- SARS-CoV-2 neutralizing antibody titers, if available. When measurement of neutralizing antibody titers is available, we (FDA) recommend neutralizing antibody titers of at least 1:160
- A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.
- When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.

- It is strongly recommended that defined SARS-CoV-2 neutralizing antibody titers be measured in the donated plasma.
- It is suggested that neutralizing antibody titers should optimally be greater than 1:320, but lower thresholds might also be effective.
- Where such testing is not yet available, plasma can be collected and frozen until release for use once the test has been performed on an archived sample and the result is available.
- When the measured neutralizing activity in the collected plasma is considered to be too low, the plasma should be made available for other use (ideally fractionation). In the absence of neutralizing antibody testing, a test for the presence of anti-SARS-CoV-2 antibody should ideally be performed prior to release.
- In emergency cases, where plasma is released for transfusion without any antibody testing, archived samples should be tested at a later date once testing is available. If an adequate correlation between neutralizing activity and Elisa antibody testing were to be demonstrated, this could replace the test for neutralizing antibodies.

FDA site https://www.fda.gov/

An EU programme of COVID-19 convalescent plasma collection and transfusion Guidance on collection, testing, processing, storage, distribution and monitored use

Expanded Access Program (EAP) Protocol

TITLE: Expanded access to CCP for the treatment of patients with COVID-19

STUDY DESCRIPTION: The program will provide access to investigational CCP for patients in acute care facilities infected with Sars-Cov-2 who have severe or life-threatening Covid-19 or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease

OBJECTIVES: Provide access to COVID-19 Convalescent Plasma

DURATIONS: 12 Months

SITES ENROLLING PATIENTS: Acute care facilities treating patients with Covid-19

STUDY POPULATION: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

FLOW:

- A site must be registered first, and then each physician/PI must be registered.
- Following that, they can consent and subsequently register patients for EAP enrollment.
- After receiving confirmation of patient enrollment, the treating physician will be authorized to contact their hospital blood bank to request convalescent plasma from their regular blood supplier.
- For hospitals that do not have a regular blood supplier, Blood Centers of America (BCA), which operates a national resource sharing network, has implemented a toll-free number to help hospitals order convalescent plasma.

NOTE

Is the plasma expanded access program providing antibody testing?
The Expanded Access Program is not directly involved in obtaining serologic testing for COVID-19. If you are interested in obtaining serologic testing, the test would need to be ordered by your local medical provider. This test is being processed at a small number of laboratories across the country.

https://www.uscovidplasma.org/pdf/COVID-19%20Plasma%20EAP.pdf

Clinical Trials for Convalescent Plasma

Clinical trials to evaluate both convalescent plasma and SARS-CoV-2 IVIG for the treatment of COVID-19 are in development.

As of June 17th over 1,300 trials have been registered on clinicaltrials.gov and more than a dozen about Convalescent Plasma.

STUDY - A RANDOMIZED CONVALESCENT PLASMA TRIAL FOR COVID-19 GENERATED HOPEFUL SIGNALS

This was the first reported randomized trial. The study recruited 103 severe/critical COVID-19 patients, 52 patients received convalescent plasma (CP) plus standard treatment and 51 patients received only standard treatment (control).

Clinical outcomes:

The primary endpoint was time to clinical improvement within 28 days
For all patients, a 2.15 days shorter was observed in the CCP group compared with the control group.
Among severe patients, a 4.94 days shorter observed in the CCP group compared with the control group

Clinical improvement at 28 days:
For all patients, 27 patients (51.9%) in the CCP group vs 22 patients (43.1%) in the control group (P = 0.26)
For severe patients, 21 patients (91.3%) in the CCP group vs 15 patients (68.2%) in the control group (P = 0.03).

No difference for either outcomes in patients with critical/life-threatening COVID-19

For other outcomes, CCP group showed favorable trend vs control, but did not reach statistical significance: 28-day mortality (15.7% vs 24.0%, respectively; P = 0.30), rate of discharge at 28 days (51% vs 36%; P = 0.13).

Viral load reduction at 72 hours was in 87.2% of the CCP group vs 37.5% of the control group (P < 0.001).

Convalescent plasma in this study was associated with clinical improvement in severely ill patients, but not in critically ill patients, suggesting CCP treatment was more effective when given early during the diseases.

A Randomized Trial of Convalescent Plasma for COVID-19—Potentially Hopeful Signals, A Casadeval, et al, JAMA., 2020. doi:10.1001/jama.2020.10218

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial, Li, et al, JAMA, 2020 Jun 3. doi: 10.1001/jama.2020.10044.

Other Treatments for COVID-19

Pathogen Inactivation Reduction Treatment

USE OF PATHOGEN-INACTIVATED BLOOD PRODUCTS

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses. Usually, coronaviruses are vulnerable to acid-pH, basic-pH, and heat, but seem to be more stable at 4°C. The infectious titer of virus did not show any significant reduction after 25 cycles of thawing and freezing.

After the outbreak of SARS and MERS, a few studies investigated pathogen inactivation/reduction technologies (PRTs) based on in-house or commercial methods with the aim to decrease or completely eradicate the potential risk of transmission of coronaviruses via blood products or blood derivatives. As CCP production requires high quality standards, it must be free of any infection, so tests for human immunodeficiency virus (HIV), hepatitis B, hepatitis C, syphilis, human T-cell lymphotropic virus 1 and 2, and Trypanosoma cruzi (if living in an endemic area) should be carried out. In this sense, the nucleic acid test for HIV and hepatitis viruses is mandatory to guarantee the safety of recipients.

Other protocols suggest the inactivation of pathogens with riboflavin or psoralen plus exposure to ultraviolet light to improve safety of CCP. Although this treatment is an alternative to ensure blood safety pathogen reduction there are indications that is not ready for prime time given the clinical, operational, and regulatory difficulties of implementation at scale, especially in the midst of the pandemic response.

Transfus Med Rev. 2020 Feb 21 Conavirus Disease 2019: Coronaviruses and Blood Safety Le Chang,a,b Ying Yan,a,b and Lunan Wanga https://www.ncbi.nlm

Convalescent plasma in Covid-19: Possible mechanisms of action. Center for Autoimmune. April 11/2020. Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia

Is Sars-Cov-2 Transfusion Transmitted. Louis M. Katz, MD. Volume 60, June 2020 TRANSFUSION

Vaccine Development

VACCINE

A vaccine to prevent coronavirus disease 2019 (COVID-19) is perhaps the best hope for ending the pandemic. Currently, there is no vaccine to prevent infection with the COVID-19 virus, but researchers are racing to create one. A number of vaccine candidates are already being tested in clinical trials and more are continuing to progress towards clinical testing.

Since SARS-CoV-1 first emerged, the S protein has been favored as the most promising target for vaccine development to protect against coronavirus infection. This particular viral protein has important roles in viral entry and in stimulating the immune response during natural infection and in vaccination studies.

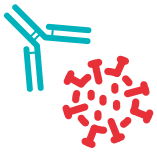
There are more than 100 projects around the world centered on the development of a vaccine for the coronavirus. As of May 11, eight candidate vaccines were being tested in clinical trials in people.

Although some of these vaccine candidates are based on platforms that have been used or tested for other purposes, there remain questions regarding their safety and immunogenicity, including the longevity of any induced responses, that will require continual evaluation.

The newly announced Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) is designed to bring together numerous governmental and industry entities to help address this need. The National Institute of Health and the Foundation for the NIH (FNIH) are bringing together more than a dozen leading biopharmaceutical companies, the Health and Human Services Office of the Assistant Secretary for Preparedness and Response, the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration and the European Medicines Agency to develop an international strategy for a coordinated research response to the COVID-19 pandemic. The planned Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership will develop a collaborative framework for prioritizing vaccine and drug candidates, streamlining clinical trials, coordinating regulatory processes and/or leveraging assets among all partners to rapidly respond to the COVID-19 and future pandemics.

FDA site https://www.fda.gov/ WHO page https://www.who.int https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-vaccine/art-20484859

Other therapies for COVID-19



NEUTRALIZING ANTIBODIES (nAbs)

nAbs are also believed to protect against infection by blocking receptor binding and viral entry. SARS-CoV-1 nAbs also neutralize SARS-CoV-2. SARS-CoV-1 and SARS-CoV-2 consensus sequences share about 80% identity (Tai et al., 2020). Thus, a wide range of SARS-CoV-1 nAbs have been tested for cross reactivity with SARS-CoV-2, as they could help speed up the development of potential COVID-19 treatments. Although recombinant nAbs could provide an effective treatment, they will require a significant time investment to develop, test, and bring production to scale before becoming widely available to patients.

INTRAVENOUS IMMUNE GLOBULIN (IVIG)

SARS-CoV-2 intravenous immune globulin (IVIG) is a concentrated antibody - a concentrated formulation - with enriched levels of pathogen-specific antibodies derived from the plasma of people who have recovered from COVID-19. High-dose intravenous immunoglobulin (IVIg), has been trialed in COVID-19 patients (Cao et al., 2020b; Shao et al., 2020), but further studies are needed to determine the extent to which IVIg is safe or beneficial in SARSCoV-2 infection.

MEDICATION

As of May 8, three medications had received emergency use authorization (EUA) from the Food and Drug Administration (FDA) — the anti-malaria drugs chloroquine and hydroxychloroquine, the anti-viral remdesivir, and a drug used to sedate people on a ventilator. An EUA allows doctors to use these drugs to treat people with COVID-19 even before the medications have gone through the formal FDA approval process.

NOTE

FDA has created a special emergency program for possible therapies, the Coronavirus Treatment Acceleration Program (CTAP). It uses every available method to move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful.

WHO page: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance

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