Guidelines of Convalescent Plasma Therapy for COVID-19 Patient

(Third Edition)

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We dedicate this book to the nation and state of Indonesia which is struggling to face the COVID-19 pandemic to provide a glimmer of hope.

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Alifurrahman
Osmar Tanjung

I pray that God makes me right,
more than smart.
I pray that my patient knows that
I too am human, with my limits.
I pray to admit powerlessness.
As kindness is a sign of strength,
surrender is a sign of confidence.
I pray to have the strength to love
my noble profession, and use its powers,
never abuse them.
I pray to the Great Physician
who holds life and death in His hands.

—Afshine Ash Emrani—
A cardiologist at Los Angeles Heart Specialists

FOREWORD

"Yesterday has passed, tomorrow has not arrived, there is only today, so let's start."
Mother Teresa

We have passed the Covid-19 pandemic for approximately six months since it was announced in early March 2020. Day to day, week to week and month to month, President Joko Widodo and the Ministers are trying to overcome the Covid outbreak from Merauke to Sabang and from Rote to Miangas. The efforts made by the government itself are not enough. The government must be assisted by the community, private and other parties considering that Covid-19 spreads so quickly without knowing time and space.

We must face this epidemic that is coming as fast as the wind in various ways, with the available capabilities and strengths. Keeping your distance, washing your hands, wearing a mask, eating nutritious food, exercising, and getting enough rest are the words we hear every day. The government does not tire of appealing and reminding its citizens what should be done. At the same time, the government is trying to overcome the impact of the Covid-19 outbreak,

especially economic growth which is increasingly pulling us into the brink of recession.

Government assistance to prevent the deterioration of society from their sources of life and to sustain their daily lives continues. The President and his ministers, especially the Minister of Health, as well as the Ministers specially assigned to tackle Covid-19 and the economic downturn, are working day and night to prepare the best steps to deal with Covid-19. All are working hard to adjust the health system and all related systems, along with efforts to find drugs and vaccines for Covid-19.

The Minister of Health together with the Minister of BUMN as Chair of the Implementation Team of the Covid-19 Handling Committee and National Economic Recovery, other Ministers, Heads of BNPB, KSAD, TNI, POLRI and BUMN are working seriously so that Indonesia can get out of the Covid-19 situation and its downturn the economy.

Until today, in this universe, there is no single type of medicine that can cure Covid-19. Likewise, with the Covid-19 Vaccine which is currently still in the third trial phase. This vaccine trial still takes at least six months to be used as an active vaccine ingredient.

Amid all this uncertainty, there is one way of passive immunization that has been tested to cure Covid-19 at moderate, severe and critical levels. This method is called Convalescent Plasma Therapy (CPC). This therapy works by transferring plasma containing antibodies to SARS-CoV-2 from recovered Covid-19

patients to be transfused into patients who are still suffering from Covid-19.

Currently the CPT has been officially implemented in many countries and strengthened by the FDA approval for emergency use of CPT for Covid-19 patients on August 23, 2020. In Indonesia, CPT has begun to be echoed since mid-March 2020 and has begun to be implemented in stages at Government Reference Hospitals. and private hospitals in Java and Bali since April 2020.

Since the beginning, the Ministry of Health has been incredibly supportive of the CPT and established an exceptionally good collaboration with Dr. dr. Theresia Monica Rahardjo, Sp.An., KIC., M.Si., MM., MARS. and team members in this Handbook of Management of Convalescent Plasma Therapy. Currently, RSPAD as the Presidential Hospital is one of the leaders in CPT both in research and services. The Ministry of Health together with all related parties will make every effort to hasten the implementation of CPT throughout Indonesia.

"Yesterday has passed, tomorrow has not arrived, there is only today, so let's start".

Jakarta, September 1, 2020,
Lt. Gen. TNI (Ret.) Dr. dr. Terawan Agus Putranto, Sp.Rad. (K).
Minister of Health of the Republic of Indonesia

FOREWORD

"People who are strong aren't those who always win.
But those who remained strong when they fell".
Khalil Gibran

President Jokowi repeatedly reminded us of the importance of "self-discipline and mutual cooperation" between communities in the face of the Corona Virus Covid-19 pandemic. President Jokowi from the beginning urged the public to do social distancing, physical distancing, wash their hands, at home and finally made it mandatory to wear masks for people who wanted to go outside.

The efforts made by the central government have increased in frequency after the establishment of the Task Force for the Acceleration of Handling Covid-19. Efforts to prevent and deal with the Covid-19 outbreak are increasingly massive when the Large-Scale Health and Social Restrictions (PSBB) Emergency is declared. The government is trying as quickly and best as possible to provide medical personnel with medical devices and medicines and vitamins to prevent and treat the Covid-19.

The impact of the Covid-19 pandemic by itself shook the Indonesian economy, even shook the world economy and 213 countries were exposed to Covid-19. The enactment of a Health Emergency made

President Jokowi prepare 9 Economic Policies amid the Covid-19 pandemic, from cutting the APBN and APBD to subsidizing low-income people. Finally, President Jokowi instructed the allocation of a special fund for handling Covid-19 amounting to IDR 405.1 trillion.

All these efforts involve all parties for prevention and treatment of the Covid-19 pandemic, both the public (including volunteers), the private sector and the competent ministries and government agencies for that. Coordination between institutions, coordination with related ministries, continues to be carried out by President Jokowi almost every day. Some technical coordination was carried out by the Chair of the Covid-19 Handling Acceleration Task Force.

In the Covid-19 treatment process, Indonesia learned from the experiences of countries that have been affected by the Covid-19 pandemic first. One of the countries that started to emerge from the Covid-19 pandemic is China (China). This country performs treatment not only using Avigan and Hydrochloroquine, but also conducting Convalescent Plasma Therapy (CPT). In the city of Jackma, namely Shanghai, China has conducted a trial of Convalescent Plasma Therapy since February 17, 2020. Lu Hongzhou said that "We believe this method can be highly effective in our patients. There is no fully licensed treatment and vaccine against the new Coronavirus, and the process of developing and testing drugs can take months or even years.

What has been done by China, has been followed by several countries such as South Korea, Germany,

America, Britain, and several other countries, including Indonesia.

Convalescent Plasma Therapy (CPT) in Indonesia, has been started since April 11, 2020 by a doctor at the Tanggerang Hospital. A CPT patient recovered on April 22, 2020. This progress was voluntarily followed by several individuals through patient autonomy based on the request and consent of families in several cities and hospitals, using CPT Guidelines prepared by Dr. dr. Theresia Monica Rahardjo Sp.An., KIC., M.Si. with her team members. This therapy is also starting to be carried out by other doctors at referral hospitals and private hospitals.

The progress of Covid-19 treatment through this therapy is a new hope for all of us, especially for those who are positively exposed to Covid-19. The persistence of medical personnel who are fighting at the forefront of handling Covid-19 deserves thumbs up. We really appreciate every effort and determination of medical personnel in fighting for the life of every Indonesian. Medical personnel deserve respect and appreciation for what they do every day, every hour, every minute and every second in saving Indonesian lives. They are heroes of humanity amid the Covid-19 pandemic.

For their duties and responsibilities, medical personnel willingly sacrificed their families at home, leaving their children, husband/wife, parents to fight Covid-19 with what they have, with the equipment available and a heart that longs for home and family.

"They are not strong people who always win. But those who remained strong when they fell (Khalil Gibran)".

Let us support them with "self-discipline and continue to work together" against Covid-19.

Jakarta, April 25, 2020

Lieutenant General TNI DR. (H.C.) Doni Monardo
Head of Indonesian National Board of Disaster Management
Head of National COVID-19 Task Force

FOREWORD

Indonesia continues to deal with the Corona virus until now, just like other countries in the world. The number of Corona virus cases continues to grow with some reporting recoveries, but not a few have died. Coronavirus infection or COVID-19 in humans is considered new because it is usually only known in animals. The new behavior of this virus is it's ability to infect and spread from human to human quickly, causing pneumonia, shortness of breath and death.

In dealing with the Covid-19 pandemic, the government has at least done three things, namely preventive efforts, early diagnosis and curative action. Facing something new in the world of medicine, of course, there are not many references and literature to guide it. For this reason, it is important to make innovations and new breakthroughs in both preventive, curative and rehabilitative efforts.

The Indonesian government (President Jokowi) has taken comprehensive steps in preventive efforts through physical distancing, social distancing, procurement of personal protective equipment (PPE), to large-scale social restrictions. However, the existence of local culture such as homecoming, traditional ceremonies, cultural activities and low discipline are challenges for Indonesia. As an effort to carry out early

detection quickly and widely, of course there are still many limitations because the means of rapid testing and polymerase chain reaction (PCR) examinations for Covid-19 are still very dependent on other countries (imports). In addition, the limited human resources (HR) for the PCR examination laboratory.

The existence of preventive efforts and early detection which still have many limitations, there must be serious efforts and hard work in curative handling, to prevent the increasing number of victims of death. Plasma transfusion therapy for Covid-19 cases is a new breakthrough that has been tried in several countries recently, such as Germany, the United States and China.

It is time for the scientific community of expert professors, academics, clinicians, to put aside their respective egos and work together to explore and test this new method of plasma transfusion. The hope is that this plasma transfusion will not only save many Covid-19 patients but can also be applied for prevention, especially encouraging the immune system of medical workers as the frontline in handling Covid-19.

Jakarta, April 6, 2020

Head of BKKBN RI
Dr. Hasto Wardoyo, Sp.OG.(K).

FOREWORD

Health research has progressed rapidly, therefore the professionalism of health care and its use must be properly understood by researchers as the principle of the welfare of living things is maintained and research procedures can be accounted for so that the data obtained has high validity.

Ethical feasibility in the form of written information for research involving living things must meet certain requirements. In a research, it is necessary to publish national and international scientific journals. All research involving humans must not violate universal ethical standards, but also pay attention to various socio-cultural aspects of the society being studied.

As one of the research objectives conducted by Dr. dr. Theresia Monica Rahardjo, M.Si., Sp.An., KIC., namely convalescent plasma is to maximize the benefits of the research itself for the community.

The Indonesian Advocates Congress (KAI) as an Advocate Organization in Indonesia will provide legal protection to every doctor who conducts clinical research/trials involving humans as subjects, of course, research that can be accounted for and on the research mechanism.

On this occasion I would like to express my deepest gratitude to Dr. dr. Theresia Monica Rahardjo, Sp.An., KIC., M.Si because I personally felt the great benefit of giving convalescent plasma to a disease that I had suffered so that it gave me a continuation of life.

Keep on fighting Dr. dr. Theresia Monica Rahardjo, Sp.An., KIC., M.Si., provide new knowledge that can provide benefits and provide healing for patients who need convalescent plasma.

Jakarta, September 2, 2020

President,
Indonesian Advocate Congress
Adv. H. Tjoetjoe Sandjaja Hernanto, S.H., MH., CLA., CIL., CLI., CRA.
Main Advocate
NIK. 3172061607641001

AUTHOR'S NOTE

Praise the Lord, this Convalescent Plasma Therapy Book for COVID-19 Patients was successfully completed in a short time.

It all started with a call in myself as a doctor to find an alternative way of therapy that would benefit COVID-19 patients. Convalescent Plasma Therapy is a method of therapy that has long been found and is useful in overcoming various viral diseases, but it does not really sound like it is because it is covered by drugs and vaccines. This Convalescent Plasma Therapy has been used to treat previous SARS, Ebola, H1N1 and MERS outbreaks. The studies that have been conducted have shown that Convalescent Plasma Therapy in these diseases gives good results, especially for patients with severe to critical symptoms.

Convalescent Plasma Therapy for COVID-19 sufferers is currently being carried out in China when the outbreak exploded and several early studies have shown that administering Convalescent Plasma from recovered COVID-19 patients can relieve symptoms and accelerate the recovery of patients who are still suffering from the disease. Even the Food and Drug Administration (FDA) in the United States (US) itself has granted permission and issued requirements for convalescent plasma donors and recipients.

Until now, drugs that have been found to be suitable for COVID-19 have not been found, and until the discovery of a vaccine against COVID-19, Convalescent Plasma Therapy is a way to gain direct immunity against this disease. Based on this, I together with my colleagues from various disciplines try to make a book on Convalescent Plasma Therapy for COVID-19 Patients. We all sincerely hope that this inaugural book is especially useful as a guidebook and reference for every education and health service center in Indonesia in implementing Convalescent Plasma Therapy so that it can contribute to reducing morbidity and mortality in COVID-19 patients.

Finally, I would like to express my deepest appreciation and deepest gratitude for the willingness of the professors, seniors, peers and all parties who were spontaneously and enthusiastically willing to immediately join and contribute in the making of this book.

"Time is Life"
Race against time overcoming COVID-19.

Bandung, April 6, 2020

Coordinator of the TPK COVID-19 Team
Dr. dr. Theresia Monica Rahardjo, Sp.An., KIC., M.Si.

Chapter 1

Introduction

COVID-19 has become a global problem at this time and declared as a pandemic by WHO. All countries, including Indonesia, are doing their best to overcome the disease. One promising therapy in the current condition is Convalescent Plasma Therapy (CPT), a therapy that involves giving an antibody contained plasma (CP) from a recovered COVID-19 patient to a COVID-19 patient who is still suffering from the disease.

This modality of treatment already used previously for more than a hundred year ago when the Spain Flu structed worldwide from 1918 to 1920. Since then, CPT has been applied to treat diseases caused by virus including Ebola Virus, which is a recommended therapy by WHO in 2014, this modality of therapy also applied in Hong Kong during the SARS-CoV-1 outbreak in 2003, H1N1 in 2009-2010 and MERS-CoV in 2012.

Initially, CPT has been carried out in Wuhan China as the first country suffered the COVID-19 outbreak followed by many studies among countries worldwide, including research and emergency use carried out in New York, United States (US). The US Food and Drug Administration (FDA) has issued a decision allowing the use of CP as a therapy for people with COVID-19.

This guideline includes several steps needed to obtain and collect CP from recovered COVID-19 patients and give it to COVID-19 patients in need as following:

- Identification of recovered COVID-19 patients as potential donors
- Informed Consent and donor selection
- Blood group identification and screening for infectious infections through blood transfusions
- Blood collection and donor management
- Labelling, storage, and collection of data on blood transfusion services
- Informed Consent of CPT recipients
- Pre-transfusion assessments
- Convalescent plasma storage and transport to the transfusion site
- Selection of COVID-19 patients who will receive CPT
- The process of giving a transfusion
- Collection of data at the transfusion site
- Assessment of the effectiveness of the CPT.

Chapter 2

Guidelines for Donor Selection, Screening, Donations, and Treatment of Convalescent Plasma Donor

2.1. Identification of suitable donor plasma from recovered COVID-19 patients.

The suitable donor must meet the following requirements:

a. Preferably 18 to 60 years old
b. Healthy with no comorbid disease
c. Has a weight > 55 kg
d. Previously, had been diagnosed positive for COVID-19 through the results of PCR.
e. Overall symptom resolution at least 14 days prior to plasma donation.
f. A negative result from either one or if the patient is declared cured by the treating doctor.
g. Donors must be negative for HLA antibodies (if HLA antibody testing not available, CP can be taken from women who have never been pregnant or receive blood transfusion, or male who have never receive blood transfusion).

h. Determine the SARS-CoV-2 neutralizing antibody and antibody titer whenever possible (ideally optimal antibody titer > 1:320 and neutralizing antibody titer > 1:80).

2.2. Information, explanation and donor selection

If someone has been identified as a potential donor, then an explanation must be given about why the plasma is needed to treat people with COVID-19. Prospective donors must be informed that there is no reward or payment for the plasma donations given.

If the prospective donor agrees to give the plasma, the prospective donor must pass a health screening process including general criteria such as weight and height, medical and social history (such as behavioural risk factors), basic physical examination and haemoglobin examination.

Written consent from the donor for the donation of 1 unit of whole blood to be processed into plasma, or 1 unit of plasmapheresis for CPT is done independently without coercion. The process of taking donor blood, testing, processing, and storing is carried out at the Blood Bank. The hospital that previously treated the donor provided data about the potential donors in the form of age, sex, comorbidities, treatment time, clinical history (before therapy, time of discharge, complications, length of stay) and other confidential data related to the Blood Bank for the benefit of donor selection.

2.3. Blood donor classification, infectious infection screening and other tests

Prospective donors who meet the criteria and have given written approval then undergo an examination before donation:

- Identification of ABO and Rhesus (RhD) blood type
- Blood screening for HIV, HBV, HCV, syphilis, and/or other infections deemed necessary using immunoassay methods and/or NAT if possible
- Haemoglobin level examination
- Erythrocyte antibody screening tests.

Depending on the tests to be performed, serum or plasma can be used for this examination. Two blood samples of 5 mL each were taken, one with an EDTA tube for plasma sample and one in a tube without anticoagulant for serum sample. The remainder of the two blood samples are stored in an aliquot for retrospective antibody testing or other tests as needed.

2.4. Blood sampling, plasma processing and donor handling

The selected prospective donors must give negative results to blood-borne infection and meet all donor requirements other. If the time from the pre-donation and donation tests exceeds 48 hours, the blood-borne infection examination must be repeated at the time of donation.

Donations in the form of whole blood should be collected using double blood bags for plasma separation using the centrifugation method. Convalescent plasma can also be taken through the process of plasmapheresis. Plasmapheresis is the method of choice because it allows the collection and storage of larger volumes of plasma so that it can be used for more than 1 patient. In both methods of conventional plasma processing, the use of leukoreduction procedures is strongly recommended. Convalescent plasma treatment to reduce the risk of blood-borne infection through the Pathogen Inactivation procedure is also highly recommended whenever facilities allow.

Donors must be handled properly before, during and after donation. Reactions/side effects that arise in donors must be handled adequately. The minimum interval for donating whole blood for subsequent donors is 60 days for male donors and 90 days for female donors, while the minimum interval for donation of plasmapheresis is 14 days.

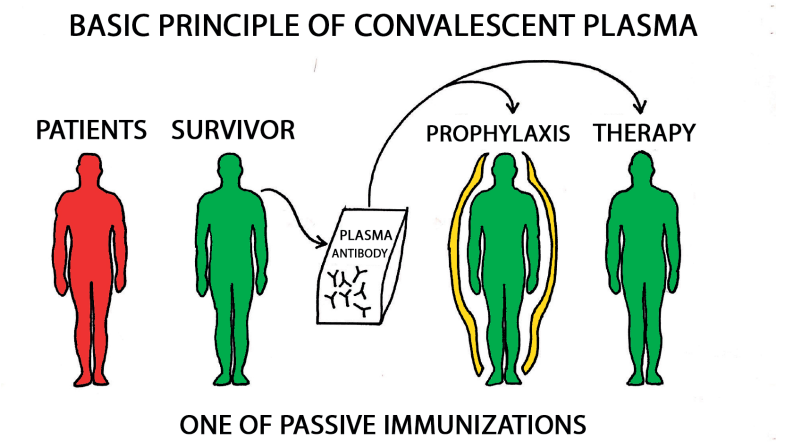
Prospective donors with positive blood-borne infection test results must be handled properly to get further treatment.

2.5. Plasma storage, labelling and transportation

Convalescent plasma whether processed from donated whole blood which then centrifuged or from the plasmapheresis procedure can be stored at 2-6^{0}C in the blood refrigerator for up to 40 days and if stored

at -18^{0}C in the form of Fresh Frozen Plasma (FFP) in the plasma refrigerator can be stored up to 12 months.

Storage is carried out separately with other blood components and labelling by standard must be fulfilled by writing 'COVID 19 CP' and blood groups ABO and RhD, and the time of collection to maintain the safety of convalescent plasma. Plasma transport should be carried out at 2-6^{0}C and recorded as standard.



Picture 1. The basic principle of CPT, used antibody contained plasma from COVID-19 survivor to help recipient immune system eradicate the virus.

Chapter 3

Guidelines for Convalescent Plasma Transfusions

3.1. Selection COVID-19 patients as recipients

COVID-19 patients as plasma recipients or recipients must meet the following requirements:

1. Have a positive laboratory test result for COVID-19 (PCR).
2. Have moderate, severe, or critical COVID-19.
    - Moderate COVID-19; experience at least criteria i and one of criteria ii and iii:
        i. Clinical symptoms of pneumonia, namely cough, fever, shortness of breath, respiratory rate above 20 times per minute.
        ii. Blood oxygen saturation > 92% without oxygen supplementation.
        iii. Blood oxygen saturation > 96% with nasal oxygen supplementation of 2 liters per minute.

    - Severe COVID-19; experienced at least one of the following circumstances:
        i. Shortness of breath.
        ii. Respiratory rate > 30 beats/minute.

iii. Blood oxygen saturation < 91% without oxygen supplementation.
iv. Oxygen saturation > 92% and < 95% with nasal oxygen supplementation of 2 litres per minute.
v. Ratio of arterial oxygen partial pressure to inspired oxygen fraction < 300 and/or
vi. Pulmonary infiltrates > 50% within 24 to 48 hours.

- Critical COVID-19; experienced at least one of the following circumstances:
  i. Respiratory failure (Ratio of arterial oxygen partial pressure to inspired oxygen fraction < 200).
  ii. Requires oxygen supplementation exceeding the nasal cannula 2 litres per minute (simple mask/reservoir mask/CPAP/HFNC) to maintain saturation above 91%.
  iii. Septic shock and/or
  iv. Multiple organ dysfunction or failure

- The distribution of COVID-19 based on oxygen saturation and estimation of arterial oxygen partial pressure can be seen in Table 1.

3. Can be given immediately to treated patients who complain of shortness of breath.
4. Informed Consent.

3.2. Informed Consent

Informed consent for recipients is obtained from the patient himself or the patient's family/guardian according to the patient's condition.

3.3. Collection of patient blood samples for laboratory examination

Patients must be identified precisely. Two vein blood samples of 5 mL each were taken from the patient before transfusion, one stored in the EDTA tube for plasma samples, the other stored in the tube without anticoagulant for serum samples. These two samples were used for ABO and RhD blood groups, cross-matching, and baseline viral load assay.

A sample of 5 mL of blood should be drawn in an empty tube without anticoagulant for serum samples the next day/day after transfusion to determine viral load and for other tests if necessary.

Before the recovered patient goes home, two additional venous blood samples of 5 mL in a plain tube without anticoagulant are required for viral load testing. The remaining serum from the blood sample should be stored in the aliquot for retrospective testing or other tests if necessary.

3.4. Selection of convalescent plasma for transfusion

Selection of convalescent plasma to be used as therapy is carried out by considering the following:

SpO_2	PaO_2	P/F Ratio Room Air	P/F Ratio O2 Nasal 2 lpm	P/F Ratio O2 Mask 6 lpm	P/F Ratio O2 Reservoir Mask 10 lpm
97	110	523,8	366,7	183,3	137,5
96	90	428,6	300,0	150,0	112,5
95	80	381,0	266,7	133,3	100,0
94	73	347,6	243,3	121,7	91,3
93	88	419,0	293,3	146,7	110,0
92	64	304,8	213,3	106,7	80,0
91	60	285,7	200,0	100,0	75,0
90	58	276,2	193,3	96,7	72,5
89	56	266,7	186,7	93,3	70,0
88	54	257,1	180,0	90,0	67,5
87	52	247,6	173,3	86,7	65,0
86	51	242,9	170,0	85,0	63,8
85	50	238,1	166,7	83,3	62,5

Table 1. Estimated P/F ratio and COVID-19 severity based on oxygen saturation (SaO2) and oxygen given.

a. Have the same ABO system blood group, or if this is not possible, use convalescent plasma from a donor with AB blood type.
b. Have screening results for HIV, Hepatitis B, Hepatitis C, and non-reactive syphilis infections.
c. IgM anti SARS CoV-2 negative, IgG anti SARS CoV-2 positive.
d. Preferably (if testing facilities are available) negative erythrocyte antibody screening results.
e. Have compatible (minor) cross-matching results.

3.5. Convalescent plasma transfusions

Convalescent plasma should be transfused into COVID-19 patients using standard transfusion equipment. Adult dose of plasma approximately 3.125 to 5 cc/kg body weight so the first dose is one unit of convalescent plasma (approximately 200 mL total). The second or subsequent dose can be repeated within 48 hours according to the clinical conditions and associated laboratory studies in the adult patient. The paediatric patient was given convalescent plasma at a dose of 10 mL/kg body weight.

Convalescent plasma transfusions are given at a slow rate and the patient should be monitored during plasma administration for early detection of any transfusion reactions or other side effects especially in the first 15-20 minutes. The transfusion process is completed within 1-4 hours.

Before transfusion, convalescent plasma must be

thawed in a water bath with a temperature of 30-37ºC or other standard heating device and transfused immediately after thawing.

Convalescent plasma transfusions can be repeated. The need for subsequent convalescent plasma transfusions is determined according to the recipient's clinical conditions and response, and if possible, from the level of COVID-19 neutralizing antibody in the donor and recipient.

3.6. Monitor the patient

Recipients of convalescent plasma should be closely monitored for any possible unwanted side effects and to assess the effectiveness of therapy. In addition to clinical monitoring, viral load and antibody levels can also be checked if possible.

Chapter 4

Other Considerations

We must ensure the availability of facilities and infrastructure for the application of CPT, including human resources, equipment, infection control procedures and data interpretation.

4.1. Human resources and equipment

The transfusion officer is an officer who is trained and ensures that blood or plasma collection from donors is in accordance with applicable regulations. Equipment for the collection of blood or plasma donor, convalescent plasma processing, storage and transport of plasma should be considered.

4.2. Prevention of infection

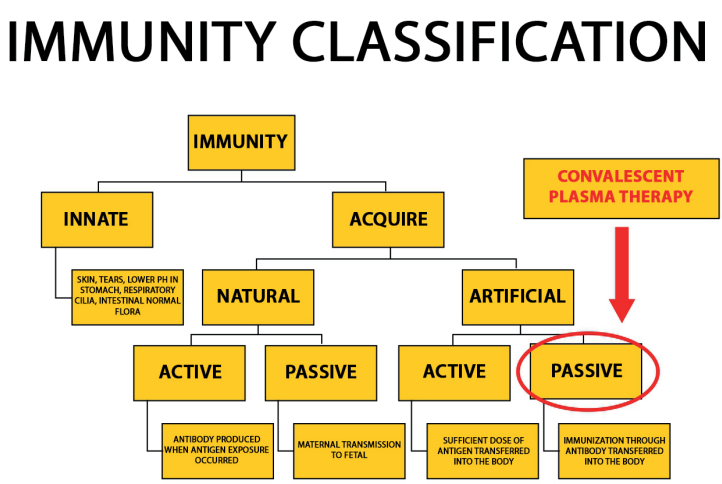
Convalescent plasma must be treated in accordance with the stated conditions, starting from the identification of ABO and RhD blood groups, and blood-borne infection examination.

4.3. Collection, analysis, and interpretation of data

Donor and recipient data should be collected using

the data collection form in Annex 3 primarily for the purpose of health statistics and the assessment of recipient response without delaying the timing of therapy.

Donor can donate the plasma every 14 days or two times in a month. Donors with sufficient level of antibody usually can donate 4 to 6 times, few donors can donate more than 6 times, according to the antibody level.



Picture 2. The simple classification of human immune system.

Chapter 5

How to Apply Convalescent Plasma Therapy Effectively?

Theresia Monica Rahardjo, Teguh Triyono,
Patra Rijalul Harly

5.1. Introduction

Convalescent plasma therapy (CPT) can be traced back more than a hundred years ago when the Spain flu structed worldwide between 1918 to 1920 and shown a clinically significant decline in the risk of fatality if it given in the first 48 hours since symptoms occurred. It followed by CPT used in Ebola, SARS, H1N1 and MERS. Early CPT with sufficient antibody level is the important key to increase the recovery rate and reduce the morbidity and mortality rate.

5.2. Current Pandemic Situation

The corona virus disease, officially named COVID-19 by the World Health Organization is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has already become a global pandemic at the present time, with a staggering case of more than 169 million, and death of more than 3,5 million

worldwide. This virus has a huge impact, first to the health system and second to the global economy. The health impact including the morbidity and mortality rates which caused an overload of the health care systems related components. The failing health system will affect and restrict economic activities in both production and consumption.[1]

The first two cases in Indonesia were confirmed on March 2, 2020 and since then has risen into more than a million confirmed positive cases, with 883,682 recovered and 30,277 death in 34 provinces recently in early 2021 and still increasing. The CPT in Indonesia started by a team of doctor who made a book called CPT Guidelines for COVID-19 Patient at March 2020. Followed by a journey culminated in a National convalescent plasma donor movement on January 18, 2021, in attempt to apply CPT wider in Indonesia especially provinces with high positive rate. This movement is corresponding to main goals of Indonesian government in COVID-19 management which is to increase recovery rate and reduce morbidity and mortality rate.[2]

Until present time, there is no definitive therapy to COVID-19, the drugs and treatment available today more towards palliative therapy to reduce the viral effect to the body. The only definitive causal therapy towards SARS-CoV-2 is CPT, which uses the plasma from recovered COVID-19 patient to treat active COVID-19 patient who still suffered from the disease. This classic adaptive immunotherapy has been applied

to the prevention and treatment many infectious diseases for more than one century.[3]

5.3. The Bright Side of Convalescent Plasma Previous Studies

The first well recorded research of convalescent plasma (CP) utilization was on September 28, 1918 at U.S. Naval Hospital to treat influenza cases complicated with pneumonia named Spanish Flu, and spans from 1918 to 1925 with 1,703 patients treated with influenza-convalescent human blood products. The result has shown a clinically significant decline in the risk of fatality. Each patient has given 300 ml of serum once daily for two succesive days. The most beneficial result occured after applying the convalescent serum within the first 48 hours of the pneumonia complication. The serum therapy shortened the course of the disease and decreased the fatality rate. Risk of fatality absolute decrease range from 18.66% to 21.60% in different studies.[4]

Effectiveness of CPT and hyperimmune Ig for Severe Acute Respiratory Infection (SARI) treatment with viral etiology also showed a statistically significant reduction of 75% in mortality rate, among SARI patients treated by this method compared to placebo or no therapy.[5] A meta analysis of 32 trials of SARS-CoV infection and severe influenza showed a statistically significant decline in the pooled odds of fatality in subjects given CPT against placebo or no therapy (odds ratio: 0.25; 95% CI, 0.14–0.45). The absolute decrease in

the risk of death varied from 7% to 23% (95% CI, 5.59–42.02) in two studies of SARS-CoV infection. Subgroup assessments has indicated that CPT given early in the course of the disease increase benefit of CPT. Discharge from the hospital by day 22 was 54% higher after CPT as compared to placebo or no therapy (77% vs. 23%). Multicenter study in Iran reported CPT can decrease the total mortality rate by 40%.[4]

5.4. The Key towards Effective Convalescent Plasma Therapy

Based on previous studies, the effect of CPT could be optimally achieved based on three factors. First, how much CP can be given. Second, sufficient antibody level on the convalescent plasma given. Third, on which stage of the disease the plasma was given.[6]

Some studies suggest the dose of CP is 3.125 to 5 ml/kg BW for adult and 10 ml/kg BW for children. The recommended antibody level in CP is 1:320 to 1:640. Some studies even use plasma with 1:1280 antibody level but there are also other studies using lower level of antibody.[3-6]

The US FDA (2021) mentioned that plasma donations must be tested by registered or licensed blood establishments for anti-SARS-CoV-2 antibodies as a manufacturing step to determine suitability before release using one of the tests listed below.[7]

The first dose of convalescent plasma is 200 ml or one bag and can be repeated within 48 hours based

Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma			
Manufacturer (listed alphabetically)	**Assay**	**Qualifying Result**	**Date of Listing under this EUA**
Abbott	SARS-CoV-2 IgG (ARCHITECT and Alinity i)	Index (S/C) ≥ 4.5	February 4, 2021
Abbott	AdviseDx SARS-CoV-2 IgG II (ARCHITECT and Alinity i)	≥ 840 AU/mL	March 9, 2021
Beckman Coulter	Access SARS-CoV-2 IgG	S/CO ≥ 3.3	February 4, 2021
EUROIMMUN	Anti-SARS-CoV-2 ELISA (IgG)	Ratio ≥ 3.5	February 4, 2021
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 68%	February 4, 2021
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL	February 4, 2021
Mount Sinai	COVID-19 ELISA IgG	Spike ELISA titer ≥ 1:2880	November 30, 2020
Ortho	VITROS Anti-SARS-CoV-2 IgG	S/C ≥ 9.5	August 23, 2020[11]
Roche	Elecsys Anti-SARS-CoV-2	COI ≥ 109	February 23, 2021
Roche	Elecsys Anti-SARS-CoV-2 S	≥ 132 U/mL	February 4, 2021
Siemens	ADVIA Centaur SARS-CoV-2 IgG (COV2G)	Index ≥ 4.8	February 4, 2021

Table 2. Tests acceptable for high titer COVID-19 Convalescent Plasma.

on clinical condition and improvement. Repeated dose is usually needed in a more severe disease, the more severe the more plasma needed. Generally intermediate

stage of COVID-19 needs 2 bags of plasma, severe stage needs 3-4 bags of plasma and critical stage needs 5-6 bags of plasma. The largest quantity of CP applied for COVID-19 patient ever documented was in a study from China, described eight times convalescent plasma application for one patient, from 200-400 mL for each application with total plasma more than 2 liter.[6,8,9]

Timing is the next important factor because CPT should be given in the right time to give optimal effectiveness. Based on previous studies, early CPT in the course of the disease, within 2 weeks since the first onset of symptoms, gave better outcome as compared to CPT in critical condition. A multicenter RCT study in Spain has shown that CPT is superior to standard of care in avoiding progression to mechanical ventilation or death in hospitalized patients with COVID-19 (0% vs 14%, 0% VS 9.3%), respectively. The latest RCT study in Argentina said early administration of high antibody titer CP within 72 hours after the onset of mild COVID-19 in elderly can reduced the progression of the disease (RR, 0.52; 95% CI; 0.29 to 0.94; P = 0.03). A meta-analysis from Indonesia also stated CPT can reduce mortality rate (RR, 0.57 [95% CI; 0.43, 0.76]; P < 0.001) and higher number of discharged patients (RR, 2.53 [95% CI; 1,72, 3,72]; P < 0.001).[10]

The success of CPT can be monitored from the negative conversion rate, beside the clinical and laboratory improvement. One study found 72 hours

negative conversion rate as high as 87.2% on the CPT group, as compared to 37.5% on placebo, in the critically ill (OR, 11.39 [95% CI, 3.91-33.18]; P < 0.001). Clinical improvement occurred within 72 hours, including febrile reduction. Laboratory result and respiratory parameters improving within 1 to 2 weeks.[8,11,12,13]

Based on the evidence above, the effectiveness or success of CPT can be maximized by administering early in the course of the disease. The logic behind this approach is, antibody contained in CP is highly effective in eliminating SARS-CoV-2, but not to repair organ damage resulted from the disease process or cytokine storm. The best time to give CPT is before the organ failure or cytokine storm occurred. Should organ failure and cytokine storm has occurred, the complexity of treating the patients is way higher.

The viral load and viral shedding will also reduced with early CPT administration. A study showed the viral load in mild disease will be reduced in 14 days but on the contrary the viral load is still large or even increasing on severe disease. Early administration of CP will reduce the viral load and shorten the viral shedding. Reduction of viral load will prevent and reduce the occurrence of cytokine storm.[14]

Furthermore, CPT is potentially beneficial to hasten the recovery and negative conversion in asymptomatic patients or even for preemptive measure in healthy subjects. Early administration of CPT not only reduces the morbidity and mortality rate but also relieves the

workload of doctor and other medical employees. Subsequently it will reduce the use of ventilator and ICU. This will impact to the economy side of health system. In the end, CPT and vaccination will work side by side, vaccine will prevent disease contraction and CPT will help to cure the disease. This is the reason why further wider and broader systematic well designed researchs are needed to conclude the value of CPT in Covid-19 management.

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Chapter 6

Important Things to Remember in Convalescent Plasma Therapy

Theresia Monica Rahardjo

1. The Basic Principle of Convalescent Plasma Therapy (CPT)

   Antibody contained in Convalescent Plasma (CP) has a main function to eliminate the virus not to repair organ damaged.

2. The Best Time for CPT
   - Early application is a must.
   - In the first week of febrile.
   - In the first 72 hours since short of breath occurred.
   - Especially in patient with comorbid.
   - Can be started in moderate stage of disease.
   - Before cytokine storm occurred or at least in the early phase of inflammatory response phase.
   - Before organ damage occurred.

3. What is Comorbid?
   - Comorbid is a condition or disease which can aggravate the disease.
   - Comorbid also can make patient more vulnerable

to the disease because some comorbidities can cause a disorder of the immune system.

- Comorbidities are age, obesity, hypertension, diabetes mellitus, hyperlipidemia, heart and vascular disease, renal disease, lung disease, autoimmune disease and cancer.

4. How to know the CPT given is eradicating the virus?
   - Clinical condition of the patient.
   - Laboratory and radiology parameter.
   - CT Value

     Based on the basic principle of CPT, antibody contained in the CP has the main function to eliminate the virus, it means the conversion rate from positive to negative in PCR swab is one of the indications that CPT is working effectively.

5. Cycle Threshold Value (CT Value)
   - Give a description of viral load in the body.
   - Higher value means lesser virus and vice versa.
   - Can be used to predict the progression and prognosis of the disease.

6. Can CPT still be given if there is an inflammatory reaction?
   - Antibody contained in the CP has the main function to eradicate the virus so CPT can be given as long as the PCR swab give a positive result, means the virus still exist inside the body.

- If the patient already suffered cytokine storm, CPT must be combined with other treatments to overcome the inflammatory response and hypercoagulable state, in this case like interleukin inhibitor or corticosteroid and anticoagulant, beside other supportive treatments like ventilator and organ support.

7. Three Important Factors in CPT
   - Dose
   - Antibody level
   - Timing of CPT

8. Three Principle of Treatment in COVID-19
   - Eliminate the virus.
   - Treat the inflammatory response.
   - Treat the hypercoagulable state.

9. Why there are still differences in study result of CPT?
   - Based on explanation before, CPT should be given regard to three factors namely dose, antibody level and timing of CPT.
   - Based on the stage of the disease, CPT has to combined with other treatment when cytokine storm and hypercoagulable state occurred.
   - The problems now are study design, donor and recipient criteria, cooperation, collaboration and funding. Those problems will influence the study design and later the result of the study.

- The resolution can be achieved with the integration of the three important factors, dose, antibody level and timing, in the study design and to make an "apple to apple" comparison in every stage of disease. Studies that integrate those 3 factors showed significant value in lower mortality rate compared to studies that do not specifically include those factors and generalized CP administration for all stages of the disease.
- Each stage of disease has own characteristic and different need of CPT amount based on viral load. Higher antibody level and early administration of CPT yields a better study result. The better the study design, the better result will be.

10. How to Get Convalescent Plasma (CP)?
    - Doctor in charge makes a CP request letter to Indonesian Red Cross (PMI).
    - Suitable CP will be provided by PMI.
    - CPT can be done in hospital to the patient.

11. The Benefit of being a CP Donor
    - Medical screening.
    - Infectious disease screening.
    - Donor with multiple plasma donations tends to have longer duration of higher antibody.

12. Who can become a CP donor?
    - Every COVID-19 survivor can become a donor as long as the antibody level is adequate.

- A COVID-19 survivor who received CPT can become a donor in the next 3 months.
- A COVID-19 survivor who has been vaccinated can give the plasma 6 weeks after the second vaccine.
- Despite the opinion differences, the person who has been vaccinated but not COVID-19 survivor has a possibility to become a CP donor. The antibody produced depend on the type of the vaccine, whether it is a whole virus of a part of the virus. Further data is needed to confirm this possibility.

Chapter 7

After Convalescent Plasma, What Is Next?

Theresia Monica Rahardjo, Teguh Triyono, Patra Rijalul Hardy

7.1. Introduction

Convalescent Plasma Therapy (CPT) is one of the treatment modalities for COVID-19 patient which is applied widely in Indonesia. Recently, more than 37,000 bags of Convalescent Plasma (CP) already distributed by Indonesian Red Cross (PMI) and Government Hospital based Blood Establishments to all regions in Indonesia, especially in Java and Bali. Majority of CPT applied to COVID-19 patient through autonomic way when the reminders through research. Plasma regiment used in Indonesia is a whole plasma, taken from COVID-19 survivor before given to COVID-19 patient. Specific antibody to SARS-CoV-2 contained by the plasma will boost the immunity of COVID-19 patient to eradicate the virus and speed up recovery process.

As the process goes along the way and the CPT already spread within the country, what will happen next? Whether to stop at CPT using whole plasma

or are there further steps that can be done? The answer is yes! Attemps to purify COVID-19 and other virus antibody are the next step after CPT based on effectivity, efficiency and value integration. All those goals can be achieved through the process called Plasma fractionation.

7.2. Definition

Basically, fractionation comes from word fraction and fractionation is a division process of a particular substance including gas, solid, liquid, suspension or isotop, into components or fractions with variable composition according to each gradient and characteristic. Fractionation allows to isolate more than two components from one solution with only one process.

Fractionation often used in many science and technology. Liquid and gas can be separated using fraction distillation based on difference in boiling point. Component fractionation also be done during colum chromatography based on difference in affinity between stationary and mobile phase. In fractional crystallization and freezing, chemical substance fractionated according to differences in solubility at a certain temperature. In cell fractionation, cell components divided based on mass difference.

7.3. Plasma Fractionation

Plasma fractionation basically has the same principle

with blood fractionation. Plasma fractionation yields components contained within the plasma including immunoglobulin, albumin and coagulation factors. These components mainly used as treatment to many conditions and diseases in human.

7.4. Plasma-Derived Therapy (PDT)

Protein produced by fractionation process has many clinical indications.[1] The benefits described as following:

1. Coagulation factors

   Factor VIII (FVIII), FIX, and the prothrombin complex (a complex fraction comprising FII, FIX, FX, and for some preparations FVII, as well as protein C and protein S) are coagulation factors contained in plasma. Other limited coagulation factor include fibrinogen, von Willebrand factor, FV, FVII, FXI, FX, or FXIII. Majority of these proteins are used for replacement therapy in proteins insufficiency or loss in the blood circulation. One of the products is Fibrin sealant (fibrin glue) built from a double component protein preparation including a concentrate of fibrinogen (possibly containing fibronectin and von Willebrand factor among other proteins) and thrombin, when the two components mixed, they form a fibrin-rich surgical clot used for topical applications, tissue hemostasis, or tissue sealing and healing.
2. Important protease inhibitor or anticoagulant concentrates

These include antithrombin, alpha 1-antitrypsin (alpha 1-protease inhibitor), a protein with potent anti-elastase activity and C1-esterase inhibitor (C1-inhibitor).

3. Major plasma protein
   Polyvalent normal immunoglobulin (IgG) is the main plasma protein, related to clinical applications and therapeutic importance. The term polyvalent means it contains millions of antibodies reflecting the immunization profile of the donor population to multiple antigens from their living environment. Polyvalent IgG donors are not selected for having a high titer in a particular antibody. This type of IgG is an essential therapeutic product for primary immune deficiencies or with secondary immune deficiencies resulting from disease or disease therapy. They are also used widely for their immunomodulatory properties in treating inflammatory and autoimmune diseases, and other immunological alterations. Normal polyvalent IgG are administered intravenously, intramuscularly, or subcutaneously depending upon patients, specific pathological characteristics, the clinical setting, and the regulatory condition.
4. Hyperimmune IgG
   This product is made from the plasma of donors, typically vaccinated, identified to express high titer in neutralizing antibodies directed against various antigens such as the D red blood cell antigen, hepatitis B, tetanus, rabies, hepatitis A, or cytomegalovirus.

5. Albumin remains as important protein produced from plasma fractionation and the first protein to have been extracted from human plasma. It is used clinically related to its oncotic as well as detoxification capacity.

7.5. How COVID-19 affects PDT

The coronavirus disease 2019 (COVID-19) gives additional stress on the plasma supply. Convalescent plasma becomes one of treatment modalities for this new disease. A year after the first broke out in China, CPT already applied in many countries worldwide and take the PDT into the new level.

The safety of CPT is not become a main problem again because many studies found this treatment is relatively safe. The major focus now is the effectivity of the therapy. There is still a contradiction of results from many studies but generally most of them still requires more in-depth exploration, especially in the research design in **"dose", "antibody level"** and **"application time"**. These three factors already described in the previous chapter.

Likewise, **"hyperimmune globulins derived from convalescent plasma"** have been produced for research use in clinical trials. The CoVIg-19 Plasma Alliance is an active group of manufacturers (CSL, Takeda, Octapharma and others) already combined efforts to collect convalescent plasma and to produce an unbranded hyperimmune globulin. Another manufacturer, Grifols, is developing hyperimmune

globulin in collaboration with the US Food and Drug Administration (FDA), the Biomedical Advanced Research Development Authority, and the National Institutes of Health.[2]

7.6. Plasma Fractionation Market

Plasma fractionation can be used in many conditions and diseases including hematology, hemato-oncology, rheumatology, immunology and emergency condition with coagulation factors or thrombocyte component needed. Plasma demands increase gradually during COVID-19 pandemic. Furthermore, plasma fractionation will become one of the main needs in research or treatment especially to viral or autoimmune diseases. Plasma will be increasingly valuable from the process of manufacture to distribution.

As described above, polyvalent IgG is the main product of protein produced by fractionation plasma. It was first developed in the 1950s to treat patients with primary immune deficiencies (PID) via intramuscular application. In the 1980s, the technology to purify fully intact IgG had advanced enough to allow intravenous administration, significantly enhancing its efficacy and convenience. The IgG market increased immediately once it was discovered that the protein could be used to treat other disease besides PID.[3]

Since early 1990s, IgG became the most important protein from a commercial perspective in the global plasma fractionation industry. It rises from time to time, about 20% in 1984, 24% in 1996, and 46%

in 2008. In 2016, intravenous and subcutaneous polyvalent IgG, represented 47% of the global plasma protein market. This growth was primarily attributed to product usage to treat conditions established for years, including PID, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Guillain-Barré syndrome (GBS). This market increased furthermore with COVID-19 as one of main contributors in plasma demand.[3]

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Chapter 8

Convalescent Plasma Donor in Indonesia

8.1. The History of CPT in Indonesia

The story dated back to March 18, 2021, when a doctor sent a letter to Indonesian President suggested government to accommodate CPT as one of alternative treatment for COVID-19. Two weeks after the letter, she has been invited to do a zoom meeting by a health team headed by chairman of BKKBN on April 2, 2020.

In the next few days, she and her team published the first version of CPT Guidelines book on April 6, 2020 in e-pdf form and the book got the copyright on August 6, 2022. She awarded by Indonesian Record Museum as The Initiator of Convalescent Plasma Therapy in Indonesia on June 2, 2020. The hardcopy of the CPT Guidelines was published on September 28, 2020, supported by Indonesia Belajar and attended by 880 participants online.

The CPT in Indonesia is implemented in two ways, first by research and second by patient autonomy as one of Bioethics Values, both had validity in law. Autonomy way already helped a lot of people

during the pandemic in Indonesia and supported by community organizations with a purpose to help COVID-19 patients who need convalescent plasma.

During the period from April to December 2020, the collaboration network started to grow and take shape gradually between the initiator and team, Indonesian Red Cross (PMI), and Indonesian COVID-19 Task Force (BNPB). The culmination of this collaboration was the declaration of national Convalescent Plasma Donor Movement on January 18, 2021.

Since then, the numbers of donors are increasing rapidly and starting to offset the huge demand for convalescent plasma in Indonesia. Today, more than 33.000 bag of CP from more than 13.000 donors already distributed by PMI to all over region in Indonesia.

8.2. The Declaration of a National Convalescent Plasma Donor

This event was inaugurated by Vice President of Indonesia, Prof. Dr. (H.C.) K.H. Ma'ruf Amin, Chairman of PMI, Dr. (H.C.) Drs. H. M. Jusuf Kalla, Coordinating Minister for Human Development and Cultural Affairs, Prof. Dr. Muhadjir Effendy, M.A.P., Minister of Research and Technology, Prof. Bambang Brodjonegoro, S.E., M.U.P., Ph.D., representatives of Indonesian Board for Disaster Management (BNPB), and representatives of Health Ministry, on PMI Head Quarter Jakarta. In this event, Chairman of Indonesia Legislative, Dr. (H.C.) Ir. Airlangga Hartarto, M.B.A., M.M.T., IPU as a COVID-19 survivor also donated his plasma.

Picture 3. The Declaration of a National Convalescent Plasma Donor (private collection).

8.3. Convalescent Plasma Donor in BNPB and PMI

Helpline 117 extention 5 is a line formed by BNPB and PMI to speed up the donor screening and

Picture 4. Convalescent Plasma Donor at PMI Jakarta (with permission from Restu Saraswati, usually called Mak Centong).

selection process and provides the information for plasma recipient, in this case COVID-19 patients and their family whose looking for CP.

8.4. Convalescent Plasma Donor in BUMN

BUMN plasma donor program launched at February 8, 2021 in 15 provinces of Indonesia and watched online in 34 provinces of Indonesia.

8.5. Convalescent Plasma Donor in Primaya Hospital

Primaya Hospital is the first hospital incorporated CPT in its procedure and treat severe patients with CP. Based on data, more than 90 patients received CPT with successful rate more than 90%. This hospital also has its own donor program earlier and now collaborating with PMI to speed up the program.

Picture 5. Convalescent Plasma Donation (with permission from Primaya Hospital Tangerang).

8.6. Convalescent Plasma Donor in Society

a. Plasma Hero

Plasma Hero is a community organization founded by dr. Ariani, Sp.A.(K)., as a place to gather CP donors, to facilitate the connection between patient relative with donor and help PMI to fulfil the increasing demand for CP.

Picture 6. Plasma Hero (with permission from dr. Ariani, Sp.A.(K)., founder of Plasma Hero).

b. **Akdoplak**

Aksi Donor Plasma (Akdoplak) is an application built by dr. Khoirul, Sp.KK. as an expression of gratitude for being healed from COVID-19 by CPT.

Picture 7. Aksi Donor Plasma Konvalesen (with permission from dr. Khoirul, Sp.KK., founder of Akdoplak).

Chapter 9

International Webinar of Convalescent Plasma Therapy

Special Addition

International Webinar of Convalescent Plasma Therapy was held on the May 21, 2021 as a continuation of The National Convalescent Plasma Donor Movement on January 18, 2021. Faculty of Medicine, Maranatha Christian University (MCU) is the main organizer of this webinar supported by competent parties.

The specialty of this webinar is in the speakers invited. Apart from two speakers from Indonesia, Dr. dr. Theresia Monica Rahardjo, Sp.An., KIC., M.Si., MM., MARS. from MCU and Dr. dr. Ria Syafitri Evi Gantini, M.Biomed. from PMI, this webinar also invited three speakers from United States of America who are expert in CPT.

The three distinguished speakers are:

1. **Professor Michael J. Joyner, M.D.**
   Institution: Mayo Clinic

   Professor Joyner is a leader of a National Program sponsored by the U.S. Government to coordinate

the collection and distribution of COVID-19 convalescent plasma treatment for individuals with severe or life-threatening disease. He is a principal investigator, Expanded Access to convalescent Plasma for the Treatment of Patients With COVID-19, FDA, 2020. He also a consultant at Department of Anesthesiology and Perioperative Medicine. He is Vice Chair for research, Department of Anesthesiology and Perioperative Medicine. He received many Honors and Awards, and his scientific publications are numerous.
(Source: www.mayo.edu)

2. Professor Arturo Casadevall, M.D., M.S., Ph.D.
Institution: Johns Hopkins Bloomberg School & Public Health

Professor Casadevall is a professor of medicine at the Johns Hopkins School of Medicine. He holds a joint appointment in molecular and immunology at the Johns Hopkins Bloomberg School of Public Health. His research focuses on how microbes cause disease and how the immune system defends itself. His scientific publications are amazingly numerous. He received many Honors and Awards. He is one of the major researchers in convalescent plasma in USA and worldwide.
(Source: www.jhsph.ed)

3. **Professor Liise-anne Pirofski, M.D.**
Institution: Albert Einstein College of Medicine

Professor Pirofski is a physician-scientist, and her research programs focus on immunity to encapsulated pathogens and antibody mediated immunity to infectious diseases. She is chief of the Division of Infectious Disease and the Jacques and Selma Mitrani Chair in Biomedical Research at Albert Einstein College of Medicine and Montefiore Medical Center. Her publications also numerous and she is deeply devoted to biomedical education and mentoring for which she has receiving numerous Awards.
(Source: einsteinmed.org)

4. **Dr. dr. Theresia Monica Rahardjo, Sp.An., KIC., M.Si., MM., MARS.**
Institution: Faculty of Medicine, MCU

She is well known as the initiator of Convalescent Plasma Therapy for COVID-19 in Indonesia. She is also a lecturer of Faculty of Medicine, MCU and a Chairman of Development, Innovation and Cooperation (PPIDK) of Medical Faculty, MCU. She also a head of anesthesia installation of Maranatha maxillofacial Hospital.
(Source: MCU)

5. **Dr. dr. Ria Syafitri Evi Gantini, M.Biomed. from PMI.**

She is the head of the central Blood Transfusion Service and has a wide range of teaching experience in Tranfusion and Quality Management training. She is a member of International Society of Blood Transfusion (ISBT) and International Plasma Fractionation Association (IPFA). She is one of the central persons in convalescent plasma screening, store and distribution to all region of Indonesia. *(Source: PMI)*

Picture 8. International Webinar Convalescent Plasma Therapy (private collection).

Appendix 1

Convalescent Plasma Donation Consent Form for COVID-19 Patients

1. General Information

Currently COVID-19 is a disease that is becoming an epidemic in the world, including in Indonesia. This disease is transmitted by a virus through saliva splashes and attacks the airways and lungs. People with strong immune system can recover without symptoms or experience only mild symptoms, but people with not/less optimal immune system can fall into severe and critical conditions.

Until now, there is no therapy or vaccine to treat and prevent this disease. People with good immunity like relatives who have recovered from COVID-19 certainly have immunity (antibodies) to the virus. These antibodies are found in a component of your blood called plasma. Plasma that contains these antibodies can help other people whose immune systems are not strong enough to fight the disease so that the person is likely to recover or can alleviate the symptoms they are experiencing so that the possibility of recovery is greater.

If you are willing to be a plasma donor, we will ask you to be willing to undergo the necessary procedures so that your plasma can be given to people in need.

2. Examination that you will undergo when you are ready to be a plasma donor.

a. Blood type testing
   Ten ml of your blood will be taken to determine the ABO and RhD blood type as well as screening for other diseases and hemoglobin levels in your blood. If all the tests are within normal limits, then you will be a plasma donor.
b. Blood donation
   Blood bank personel will draw your blood through the veins on the inside of your elbow after previously cleaning the area with an alcohol swab. The volume of blood drawn ranges from 350-450 ml and generally the process takes about 10-12 minutes to obtain 1 blood bag.

   If you donate plasma through a special machine (apheresis machine), a trained personel will place a needle in your arm which will be connected to the machine that will ONLY take your blood plasma, while your red blood cells will be returned to your body. The attendant will take about 500 mL of plasma and the process takes 45-60 minutes.

   After the procedure, you are asked to rest for 15-30 minutes, after which you can return to your activities. Avoid activities that exert a lot

of energy and you have to drink a lot to replace the fluids that are taken. The body will replace these fluids within 24-36 hours.

c. What's next?
The blood drawn will be processed and stored in a special storage area labeled with a code without any sibling's name on it.

3. Discomfort and risks that may occur

The procedure can cause bruising, minor pain or discomfort, infection is very rare. We will take all preventive measures to minimize risks.

4. Confidentiality

All information and results of your tests will be kept confidential. The officer who checks your blood will inform you of your test results and provide suggestions according to the test results.

5. Will I know who will receive my plasma?

No, you will not know who will receive your plasma.

6. Does the recipient or recipient know my identity?

The recipient or recipients of your plasma will not know your identity.

7. Fees and payments

You do not need to pay and are not paid in this plasma donation process.

8. Participation and cancellation of donations

You are free to decide whether to donate or not.

9. Who can I contact if I have something to ask?

If you want to ask something, please contact .....

Signature as a sign you are ready to be a plasma donor

Donor Signature	Name	Date

Appendix 2

Consent Form to Undergo Convalescent Plasma Therapy

1. General Information

Siblings/siblings/family members are currently diagnosed with COVID-19 and the results of laboratory tests are positive for COVID-19. Until now, there is no therapy or vaccine to treat and prevent this disease. But there are people with good immunity who have recovered from COVID-19 and of course have immunity (antibodies) against the virus. These antibodies are found in a component of blood called plasma. The plasma that contains these antibodies may help you to fight the disease so that you are more likely to recover.

If you are willing to become a recipient or recipient of a plasma donor, we will ask you to be willing to undergo the necessary procedures so that you can receive plasma according to your condition.

2. What we expect from you?

We ask for your willingness to accept convalescent plasma from donors who have recovered from

COVID-19. Donor plasma contains immunity (antibodies) which can help your body's resistance to fight COVID-19 so that it can increase your chances of recovery.

However, everyone reacts differently, and we cannot confirm that this therapy will give the desired results. This therapy has been done in several countries and the results are promising.

3. If you are willing to accept the convalescent plasma, what should you do?

You will be given 200-500 ml of plasma fluid through a tube that is inserted into your vein on the inside of your arm. Your clinical condition will determine whether this therapy will be repeated or not.

4. Can I change my mind?

Yes, you can change your mind from not agreeing to receive plasma therapy to agreeing or otherwise.

5. What are the risks of this plasma therapy?

Blood plasma has been used before in a variety of conditions and is generally very safe. Side effects that may occur, although rarely are allergic reactions, generally in the form of redness and itching of the skin or fever. The risk of transmitting infectious diseases through blood transfusions has

been minimized because every blood bag to be transfused has gone through strict screening for the disease. However, you will be closely monitored during the plasma transfusion procedure to minimize any possible transfusion reactions.

6. Do I have to pay for this therapy?

You don't have to pay for this therapy

7. Is confidentiality guaranteed?

Yes, your confidentiality as a plasma recipient is guaranteed

8. Who can I contact if I have something to ask?

If you want to ask something please contact .....

The signature as a sign of agreement to be a plasma recipient

Recipient	Name	Date

If the patient is unable to provide informed consent:

Signature relatives	Name	Relationship with patients	Date

If the patient is underaged:

Signature of parent/ guardian	Name	Relationship with patients	Date
Child signature	**Name**		**Date**

I, the undersigned, have thoroughly explained the relevant information of convalescent plasma therapy to the brother named above and will provide him with a copy of this file.

Physician	Name	Date

If the person giving the consent is illiterate, the witness must be present and sign the following:

I am with the patient throughout the Informed Consent process. This file is read accurately to the patient and all patient questions have been answered and the patient has agreed to undertake conventional plasma therapy.

Witness	Name	Date

THE EDITORS

Dr. dr. Theresia Monica Rahardjo, Sp.An., KIC., M.Si., MM., MARS. showed her medical soul in the middle of COVID-19 pandemic which is already cause many victims including medical personils. In the midst of polemic awaits arrival of a definite vaccine and a variety of drugs believed can cure the disease, Doc Mo, as she used to call, initiate Convalescent Plasma Therapy (CPT) for COVID-19 patient. Even though there are still opinion and study result differences of CPT effectivity, not all medical personnels agree and many of them also reject it.

Doc Mo fights to socialize CPT to many hospitals and colleagues with one mission: save lives of COVID-19 patients. This earned her MURI award as The Initiator of CPT Guidelines for COVID-19 in Indonesia on June 2, 2020.

The row of tittles she is wearing shows Doc Mo is a long live learner, no wonder she achieved The Best Graduate Medical Doctor in 2006/2007 academic year at Faculty of Medicine, Maranatha Christian University,

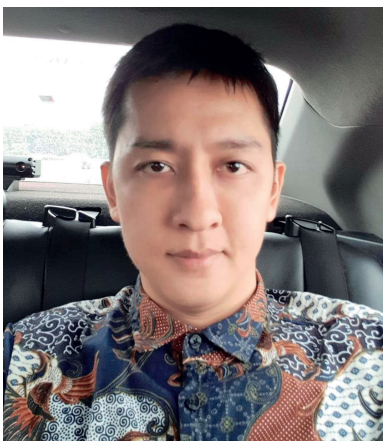
Highest GPA of Specialist Graduates at Faculty of Medicine, Padjadjaran University in 2012, and Summa Cum Laude on Doctoral Program in 2016. Uniquely, in her extraordinary busyness, she still can express her love for art and design, combine with her passion to science, make her won Best Poster at Free Paper Poster Presenter pada acara ISNACC (Indonesian Society of Neuro-Anesthesia and Critical Care) ke-11 dan Second Winner at Free Paper Presentation pada National Congress of ISICM ke-5.

As a doctor and lecturer, Doc Mo also contribute to academic and research world through her writing in scientific journal in national and International. Now, she is a chairman of Development, Innovation and Collaboration Center (PPDIK), Faculty of Medicine, Maranatha Christian University. Her social interest applies through community service in Maxillofacial Hospital, Faculty of Dental, Maranatha Christian University.

Dr. dr. Teguh Triyono, M.Kes., Sp.PK.(K). graduated from Faculty of Medicine, Gadjah Mada University in 1993 and joint the Clinical Pathology Department and Laboratory Medicine in 1999. Dr. Teguh finished his master's degree in

2001 and doctoral degree in 2016 in the same university. Since 2008, he becomes Clinical Pathology Department Dr. Sardjito General Hospital after became Clinical Pathology Specialist. He becomes the consultant of Blood Bank and Transfusion Medicine at Dr. Sardjito General Hospital since 2009.

Dr. Teguh is a founder of Blood Transfusion Service Unit at Dr. Sardjito General Hospital which is recently grows into distinguished Blood Transfusion Service Unit and Center of Excellence with blood donation service and therapeutic service based on apheresis, screening and antibody detection, and National Hemovigillance Center. He has active role in development process of Transfusion Medicine, National (National Blood Service Committee) and International (WHO).



dr. Patra R Harly, Sp.An., KIC. was born in Bandung on November 11, 1981. When he was ten, he moved to Bali, and lived in Denpasar with his family. He finished his elementary and high school in Denpasar. After graduation, he continued his study at Faculty of Medicine, Udayana University and finished his Bachelor of

Medicine in 2004 the finished his medicine profession in 2006.

He stayed from 2007 to 2008 at Puskesmas Uitao, Semau Island, Kupang, Nusa Tenggara Timur. Then he took Anesthesiology Specialist Program at Faculty of Medicine, Airlangga University/Dr. Soetomo General Hospital, Surabaya and finished the program on 2013 in 4 years 11 months.

He starts his work as Anesthesiologist at Siloam Hospitals Jambi. During this time, he accepted to continue studying in Intensive Care Consultant Program, Faculty of Medicine, Padjadjaran University/ RSUP Hasan Sadikin Bandung during year 2014 and finished it in 1 year and 6 months. He officially has a degree of Intensive Care Consultant on May 2017.

He already has a family with two daugthers and live in Jambi. He also actively become a member of Indonesia Intensive Care Society (PERDICI).