



(REVIEW ARTICLE)



The immune system's fight against the Coronavirus; convalescent plasma from Covid-19 survivors may be used to treat patients and protect those at risk

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Abstract

Severe Acute Respiratory Syndrome (SARS) and Coronavirus (Covid-19) outbreak are creating emergency in public health sector. Using antiviral, antimalarial and vaccine are still under investigations, so Convalescent plasma therapy for Covid-19 is a current option because it has been succeeded in other Coronaviruses before. This work will discuss what is the Covid-19? What is the source of Covid-19? Is it transmitted from animal to human? And will discuss the convalescent plasma (CP) as a therapy for Covid-19.

Keywords: SARS; COVID-19; Convalescent Plasma Therapy; SARS-CoV-2; Neutralizing antibodies; ACE-2 receptor; Coronavirus

1. Introduction

Coronaviruses have been founded in many hosts in mammals such as cats, mice, dog, camels, etc. some of coronaviruses are pathogenic to human but produce mild symptoms, but lately there are two lethal viruses; Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) they showed severe fever. In December 2019, a new member founded in Wuhan , China, patients show some symptoms such as SARS and MERS, it called 2019-novel Coronavirus (2019-nCoV) [1].

World Health Organization (WHO) mentioned that Covid-19 management will be by prevention of the infection, monitoring and detection of cases, till now there is no specific treatment for Covid-19 because there is no evidence [2]. On 11 March 2020, WHO characterized Covid-19 as pandemic, On 12 March, 80,980 confirmed cases with no specific antiviral as a treatment for this virus [3].

Covid-19 named newly by the international committee on taxonomy of viruses as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), some pneumonia patients showing symptoms such as cough, dyspnea from unknown sources at the beginning. The virus was assumed to be zoonotic as it has been discovered in market in Wuhan where they were selling live animals or in patients who had traveled to Wuhan, March 2020, covid-19 has reached to 199 countries and caused more than 27000 deaths, Covid-19 is one of β -coronavirus family so it has a single strand RNA, positive-sense with about 30 kb nucleotides encoding 4 main structural proteins, nucleocapsid protein (N), Spike protein (S), Envelop protein (E) and Membrane protein (M), the most important one is the spike protein (S) protein because it is club-shaped glycoprotein which gives the virus its crown-like appearance [4].

The spike protein of coronavirus uses angiotensin-converting enzyme 2 (ACE 2) as a receptor of the host cell. Some researchers in China (Guangzhou) proposed that pangolins animals are the source for covid-19 outbreak. Covid-19 has been in types; S and L types, S is the older type and less infectious, L discovered later and has high rate of spread and aggressive [5].

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The respiratory epithelial cells that are infected with coronavirus have become vacuolated and its cilia have been damaged so lead to local inflammation and increase nasal secretions. People with weak immune system show many complications if they suffer from Covid-19 [5].

2. Convalescent plasma (CP) is considered as a therapy for COVID-19

Plasma from patients who have recovered from coronavirus contains neutralizing antibodies for Coronavirus; FDA has mentioned that convalescent plasma has studied before in other viruses such as SARS, MERS and H1N1 influenza [6].

Convalescent plasma (CP) therapy is considered as passive immunity that was used in the past for coronaviruses from Spanish influenza to these days for SARS-cov-2, it shows to reduce mortality. Figure 1 shows convalescent plasma in patients with respiratory infection by Coronaviruses (SARS, MERS, and COVID-19) [1].

FDA approved using convalescent plasma to treat patients of coronavirus, some patient who recovered from covid-19 volunteered (donors) to donate blood, to use their convalescent plasma to treat patients in severe condition. Volunteer patients (donors) should show no symptoms for 14 days, and show negative result of covid-19 test which is determined by nasopharyngeal swap or PCR or antibody based assay [6].

Donors and between 18 and 65 years old, obtaining Plasma by Apheresis by centrifugation of the blood from the donor. To get neutralizing antibodies, there are other proteins should be obtained such as anti-inflammatory cytokines, natural antibodies, clotting factors, defensins, pentraxins and other undefined proteins [1].

Convalescent Plasma (CP) therapy "Immunotherapy" carried out by using IgG (from the plasma of the recovered patient) combines with anti-viral drugs that used in prevent and strengthen immunity against the virus. IgG antibody consist of two major parts; F(ab')₂ part for recognition of the antigens, (Fc) part for immune response activation and complement activation for microorganism clearance. Intravenous Immunoglobulin (IVIg) is used as anti-infectious agent for bacteria, fungi, and viruses [5].

Antibodies (IgG) are collected from donors (recovered patients from covid-19) and studies prefer to be collected from recovered patients from the same city or surrounding area, IgG that are collected from patients in different countries different than others because they are different in diet, lifestyle and the environment, removal of any pathogens or infection from the plasma of the recovered patient (donor). Sacco University hospital in Milan, Italy, reported that they isolated a new strain of coronavirus from an Italian patient that mutated and different from the original one that isolated in China [5].

There are some studies in Japan support that coronavirus can cause reinfection of recovered patients [7].

3. Convalescent Plasma (CP) has many advantages

Using convalescent plasma (CP) approach in SARS-CoV decreases the days that patients stay in the hospital, as well as has a role in respiratory tract that reduce the viral load. Using convalescent plasma for COVID-19 has a good role to decrease the viral load as well as clinical condition improvements [1].

There are no adverse effects of using CP administration in Influenza A (H1N1), SARS-CoV and MERS-CoV, in Ebola case shows mild adverse, such as nausea, fever and skin erythema, in COVID-19 studies show that it is safe. Figure 2 shows the associated adverse events to convalescent Plasma in different epidemics [1].

The dose of transfusion of CP is not standard, in some studies administration dose for CP between 200 to 500mL, current studies suggest administration of 3mL/Kg per dose in 2 days [1].

Composition of Convalescent Plasma (CP) includes many of blood drive components, Plasma includes inorganic salts mixture, water, complements, coagulation and antithrombotic factors, immunoglobulins and albumin.(Fig. 1) [1].

Table 1 Convalescent plasma in patients with respiratory infection by Coronaviruses (SARS, MERS, and COVID-19)

Country	Study design	Viral Etiology	Diagnosis	Individuals included	Non-CP treatment	Previous clinical state CP	Dose protocol CP	Intervention	Outcome	Mortality
China	Case series	COVID-19	RT-PCR	Intervention: 4	Lopinavir/ Ritonavir, Interferon alpha-2b, oseltamivir, Ribavirin	Clinical deterioration	Unknown	200-400mL in one or two consecutive transfusions. A patient received 2,400 mL divided in eight consecutive transfusions	Clinical recovery and discharge from hospital	0% intervention group
China	Case series	COVID-19	RT-PCR	Intervention: 5	All patients received antiviral management during treatment.	Clinical deterioration	CP from the same donor	CP 200-250 mL two consecutive transfusions CP 200 mL single dose	Improvement in viral load and increase in antibodies	0% intervention group
China	Clinical trial	COVID-19	RT-PCR	Intervention: 19	Ribavirin, Cefoperazone, Levofloxacin, Methylprednisolone, Interferon, peramivir, Caspofungin.	Clinical deterioration	CP from the same donor	CP 200 mL single dose	Viral load improvement and lung imaging	Reduction of viral load and improvement in lung images
China	Case series	COVID-19	RT-PCR	Intervention: 6	Not reported	Clinical deterioration	Unknown	CP 200-250 mL two consecutive transfusions.	Reduction of viral load and increase of SARS-CoV IgG and IgM antibodies	0% intervention group
South Korea	Case report	COVID-19	RT-PCR	Intervention: 2	Lopinavir/ Ritonavir, hydroxychloroquine and empirical antibodies	Clinical deterioration	unknown	unknown	Reduction of viral load and increase of SARS-CoV IgG and IgM antibodies	0% intervention group

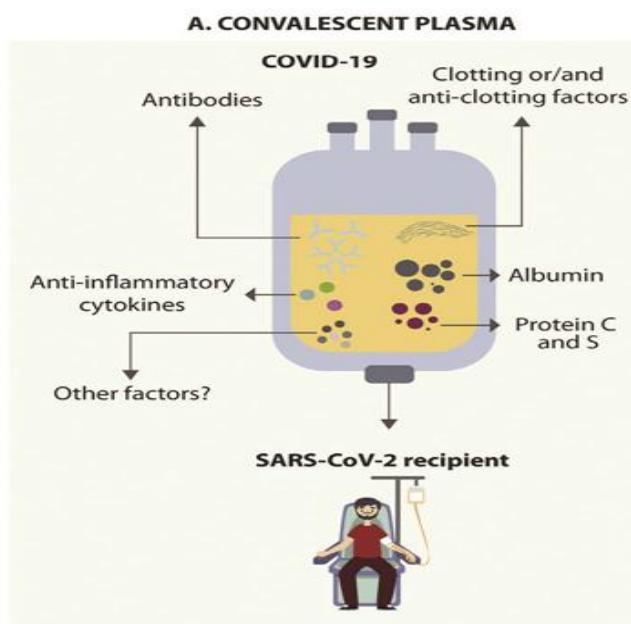
China	Retrospective comparison of cases	SARS-CoV	CDC case definition	Intervention: 19, control: 21	Intervention group: Ribavirin, 3 doses Methylprednisolone (1.5 g) Control group: Ribavirin, 4 or more doses of Methylprednisolone (1.5 g)	Clinical deterioration	Unknown	CP 200-400 mL days 11 and 42 after the onset of symptoms	Mortality, length of hospital stay, adverse events	23% reduction ($P=.03$)
China	Case series	SARS-CoV	CDC case definition and serology	Intervention: 80	Unknown	Clinical deterioration	Unknown	CP 279 mL per day 14	Mortality, length of hospital stay	12.5% intervention group
China	Case series	SARS-CoV	unknown	Intervention: 40	Unknown	Unknown	Unknown	CP unknown dose	Mortality	0% intervention group
Taiwan	Case series	SARS-CoV	serology	Intervention: 3	Ribavirin, Moxifloxacin, Methylprednisolone	Clinical deterioration	Unknown	CP unknown dose on day 11 of symptoms onset	Mortality, antibodies, viral load, adverse events	0% intervention group
China	Case series	SARS-CoV	CDC case definition	Intervention: 1, control: 28	All patients received Ribavirin, Azithromycin, Levofloxacin, Steroids, Mechanical ventilation	Vulnerable or comorbid older adults	Unknown	CP 50 mL single dose on day 17 of symptom onset	Mortality, length of hospital stay	7% reduction ($P=.93$)
China (Hong Kong)	Case report	SARS-CoV	Clinical diagnosis	Intervention: 1	Antiviral, Steroids, Ventilation	Clinical deterioration	CP from the same donor	CP 250 mL 2 doses day 7 of the onset of symptoms	Mortality	0% intervention group
China (Hong Kong)	Case report	SARS-CoV	WHO case definition	Intervention: 1	Ribavirin, Oseltamivir, Cefotaxime, Levofloxacin	Clinical deterioration	CP from the same donor	200 mL CP on day 14 of symptom onset	Mortality	0% intervention group
South Korea	Case series	MERS-CoV	RT-PCR	Intervention: 3	Steroids	Clinical deterioration	Unknown	CP unspecified dose	Antibody titers	0% intervention group

Source: [1]

Table 2 Associated adverse events to convalescent Plasma in different epidemics

Country	Viral etiology	Adverse events
China	COVID-19	None
China	COVID-19	None
China	COVID-19	Self-limited facial erythema in 2/10 patients. No major adverse events.
China	COVID-19	None
South Korea	COVID-19	None
China	SARS-CoV	None
China	SARS-CoV	None
China	SARS-CoV	None
Taiwan	SARS-CoV	None
China	SARS-CoV	None
China	SARS-CoV	None
China	SARS-CoV	None
South Korea	MERS-CoV	None
Guinea	Ebola	Nausea, skin erythema, fever. No major adverse events.
China	Influenza A(H1N1)	None
China	Influenza A(H1N1)	None
China	Influenza A(H5N1)	None
China	Influenza A(H5N1)	None

Source: [1]

**Figure 1** Composition of Convalescent Plasma [1]

4. The neutralizing antibodies have role in viral removal

Neutralizing antibodies have role in the viral removal (Neutralization) and their efficiency depends on their concentrations in the plasma and prevent virus from entrance to host cell, CR3022 antibody binds with COVID-19 RBD and shows no competition to binding to angiotensin-converting enzyme 2 (ACE-2) for the binding to COVID-19 RBD so COVID-19 can't bind to ACE2 receptor of the host cell. There are other antibodies, immunoglobulin IgG and IgM that bind to the virus don't change its replicate but have role in prophylaxis and improvement of recovery. (Fig. 2) [1, 8].

Competition of the neutralizing antibody with the receptor (ACE2) for binding to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. The protruding portion (violet) of RBD is both the ACE2 receptor-binding site and the antibody epitope (Figure 3) [1, 8].

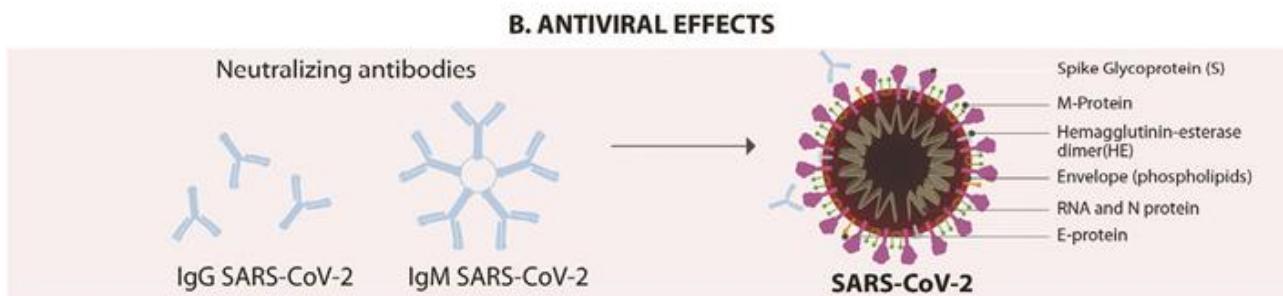


Figure 2 Antiviral effect [1]

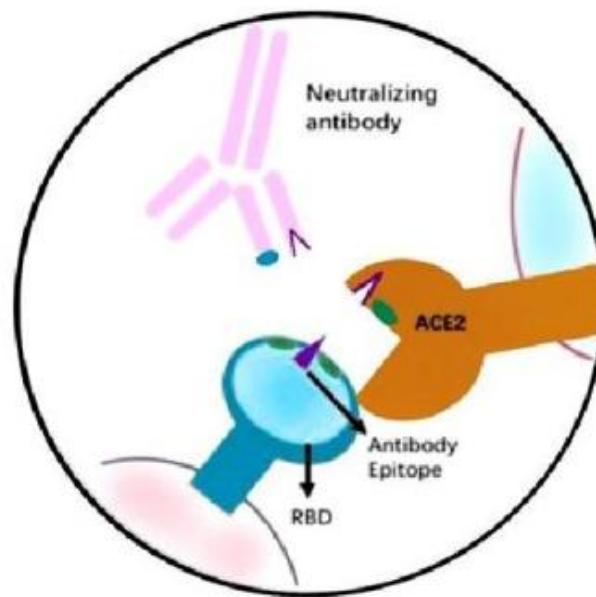


Figure 3 Schematic mechanism of neutralizing antibodies [8]

After infection of Covid-19, IgM is the first antibody which is produced by day 7 and can be determined in serum till day 21, then IgG antibody is produced at around day 14 and continue for long time. (Fig. 4) In Convalescent Plasma (CP) therapy, plasma with rich IgG is collected after 14 day from recovery date, the high antibody in the plasma of recovered patient on the 21st day [8].

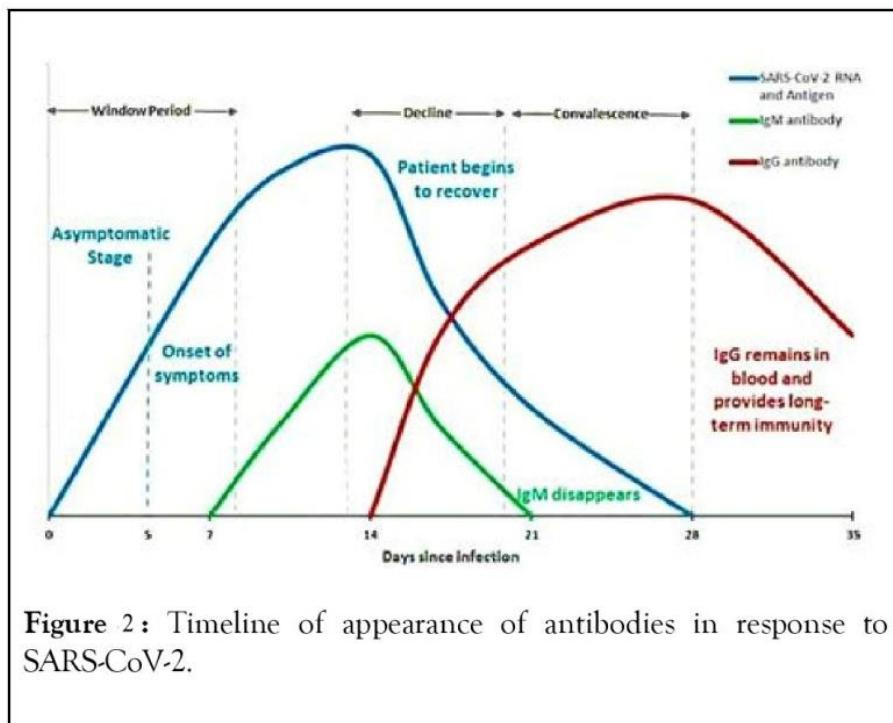


Figure 4 Timeline of appearance of antibodies in response to SARS-CoV-2[8]

5. Conclusion

Physical and social distance, washing hands, quarantine and sanitizing habits have been good approaches for slowing down the spread of the virus. Using Lopinavir/Ritonavir has no good effect to reduce the number of death, Hydroxychloroquine causes reduction of the temperature, but it's not effective for covid-19 management. Convalescent Plasma (CP) is effective and safe.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest.

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