

Plasma Therapy: An Effective Treatment for Infections from Microbes with Special Reference to Coronavirus Disease 2019

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Sainani *et al.*: Effectiveness of Plasma Therapy

Infections hold a major place in the global disease burden. About thousands of different microbial species invade human body thereby leading to complications in the physiology of a particular system or the body as a whole. While the world has tried to combat the microbial infections through various natural and synthetic chemical constituents and certain additional medical aids, we still lack effective treatment against all kinds of microorganisms especially, the evolving new microbial species. Currently, as the world is suffering from a major pandemic spread of infection caused by severe acute respiratory syndrome coronavirus 2, scientists all over the world are trying to produce an effective prophylaxis as well as treatment to fight the viral attack. Amongst different trials going on, this review focuses on the effectiveness of plasma therapy, its mechanism and its applications in various infections so far and it's possible role to treat coronavirus disease 2019.

Key words: Infections, microorganisms, severe acute respiratory syndrome coronavirus 2, plasma therapy, prophylaxis, coronavirus

Infections are sufferings caused by microorganisms. They occur when the microbes enter the body of the host and start disturbing the normal physiology in many ways. Their attack might be systemic or on a particular organ/organ system. Since ages, mankind has suffered from infections caused by innumerable microbes, bacteria, viruses, or fungi. They are considered foreign to the body since they are not normal residents and therefore not a part of normal physiological actions in the body.

This is the reason they cause serious problems, exaggerating symptoms that are sometimes tolerable while some others are quite dangerous. As known by all, there are millions of different species of microbes that lead to infections, hence we also have countless drugs that are used to either kill (microbial) or stop the growth (micro static) of these attackers. Researchers and Mother Nature have blessed us with so many synthetic and natural substances that act against the microorganisms. But unfortunately, there are certain infections where these substances are not effectively enough to nullify the infection thereby deteriorating the condition of the body or may be even causing death. Therefore, these infectious agents still pose a quite risk to mankind.

Apart from synthetic and natural chemical constituents

used as therapy, there are proteins called antibodies synthesized by the immune system of the host body in response to the attacking microbe called as antigen. This is the reason human body is tolerable to certain kind of bacteria wherein the antibodies produced by the immune cells destroy them thereby eliminating the infection. Considering the usefulness of antibodies, one such therapy that is used to treat infectious diseases is the plasma therapy. It is a kind of treatment wherein the blood plasma of a person cured from the infection is transfused into a suffering patient.

This is because plasma of the cured person consists of specific antibodies against the causative agents which might also fight the antigen (microbe) in the body of plasma receiving patient. Therefore plasma therapy has served and can serve as an efficient treatment for various infections caused by bacteria, viruses and fungi. Infections from viruses originate from the proliferation of harmful viruses inside the body. Viruses require assistance of host to replicate themselves^[1]. Viruses infect host cells by injecting their genetic material and

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by hijacking host's internal cell machinery to make more viral particles by the process of replication^[2]. There are so many viruses which can infect animals as well as human beings and can be life threatening. According to the structure and genetic makeup of viruses, researchers have developed better treatment options available to save the life of patients.

Infection from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has increased a global concern and challenges for the researchers to develop a better treatment option^[3]. This infection starts with viral entry and recognition of host cell receptors which is mediated by corona virus spike (S) protein as shown in fig. 1. As it acts as a major binding site, it is a new valuable target for the researchers to develop effective therapy against SARS-CoV-2^[4,5]. In case of corona virus family a receptor binding domain is poorly conserved, hence it is difficult to identify receptor binding domain

for SARS-CoV-2^[6].

In one study, Angiotensin-Converting-Enzyme-2 (ACE2) has been found as a receptor for SARS-CoV-2^[7]. In normal individual, ACE2 is expressed in type I and II alveolar cells in the lungs. As compared to the females, males have more ACE2 expression in their alveolar cells. Damages to alveolar cells lead to series of systematic reactions, difficulties in breathing, lung injury and even death^[8]. People infected with SARS-CoV-2 virus show fever and cough as most common symptoms followed by diarrhea and vomiting^[9]. As of 30th April 2020, there is no vaccine available for Coronavirus Disease-19 (COVID-19) and prevention of this disease is an important step to decrease its rate of transmission^[10]. Use of drugs like hydroxychloroquine and plasma therapy can give a ray of hope to fight against COVID-19^[11].



Fig. 1: Mechanism of plasma therapy

While the world is suffering from a serious pandemic spread of SARS-CoV-2 infection which damagingly affects the respiratory system of the host, this review attempts to explain the effectiveness of plasma therapy in general and to highlight its probable importance in COVID-19.

BLOOD PLASMA: SOURCE OF FIGHTER IMMUNOGLOBULINS

About 55 % of blood is plasma which is a watery straw colored liquid consisting of 92 % water, 8 % of plasma proteins and trace amount of other constituents. Hence basically, blood is formed from 2 major components; blood cells and blood plasma. We already know how important blood (cells and plasma) is for survival of a human being. Each component has its own function, failure of which, leads to serious disorders. The blood cells include erythrocytes, leucocytes and platelets. Talking about the composition of plasma, it includes various kinds of proteins, with variety of crucial functions; nutrients that are circulated throughout the body to reach different cells and waste products that should be removed through a proper route by a specific organ or medium.

Proteins present in plasma include fibrinogen and clotting factors which are vital for blood clotting mechanism; albumin is a carrier or transport protein, which is mainly responsible for maintenance of osmotic pressure of blood and for transfer of many substances from one region to the other. This occurs by binding of the substance (hormones, vitamins, enzymes, cations and drugs) to albumin. Due to this binding, albumin is also known to manage the levels of the substrate bound to it.

It is a major protein constituting about 50 % of all plasma proteins. Plasma also consists of globulins which have an immune function to fight against the foreign bodies that damage the host cells. Apart from these constituents, there is a collection of regulatory substances in the plasma which includes exocrine and endocrine hormones that act on their specific targets; enzymes and co-factors which are crucial for all biochemical reactions occurring in the body; and electrolytes (salts, acids, bases, ions) which are important for maintaining physiological parameters like pH, osmotic pressure, electrolyte balance; contraction and relaxation, which is the basis of functioning of every organ system. Apart from these substances, plasma also contains nutrients absorbed from the intestine to reach

various cells for Adenosine 5'-Triphosphate (ATP) production and waste products given by different cells to be eliminated out of the body through appropriate medium^[12].

Of all the above mentioned components of blood plasma, we are concerned with globulins/immunoglobulins in case of a bacterial or viral infection, since this review attempts to focus on the importance of immunoglobulins to get rid of an infection. Immunoglobulins, also called as antibodies, are specific glycoproteins produced by B cells^[13]. Whenever an antigen (microbe) enters the body, it is taken inside a B cell where it is broken down into fragments which are combined with Major Histocompatibility Complex (MHC) proteins. This combination is identified by T cells to activate B cells^[12]. On activation, B cells produce plasma cells and memory B cells. It is the plasma cell which proliferate and produce millions of antibodies that travel along the plasma to arrive at the site of infection^[14].

Once they reach the required site, the antibodies fight the infection through various mechanisms like breaking up the bacterial toxins^[15], preventing the attachment of virus to the plasma membrane of the cell^[16], damaging the motility of microbe to limit its spread^[17], cross-linking of microbes with each other rendering them inactive resulting in a clump or precipitate, by stimulating phagocytosis i.e engulfment and degradation of the pathogen and by activating complement system which is a collection of proteins produced by liver that functions to breakdown and engulf the foreign material as that of antibodies, but with different mechanism^[18]. Also, the memory B cells store the information of the antigen so that if there are recurrent attacks by the same antigens, the cells can be immediately proliferated and specific antibodies can be synthesized^[19].

Hence antibodies are outstanding fighters of our immune system which show their action through various ways to throw out the micro-organism from the body. There are millions of bacteria and viruses against which our body produces antibodies and we are saved from a rigorous damage to the tissues and organs. The effects of an infection may be mild to moderate which are manageable but sometimes it might be quite severe and non-curable. If there is a new variety of antigen attacking the body, until our immune system designs antibody against it, there is a lot of damage either systemically or on a specific organ system, especially in case of viruses. This damage is so rigorous that it

might permanently affect functions of vital organs such as respiration, pumping of heart, control of organs by brain, digestion and metabolism, fluid and electrolyte balance and excretion of wastes or it may also be fatal.

To treat infections by bacteria, viruses and fungi, researchers and scientists have discovered innumerable drugs like antibiotics, antivirals, antifungals, natural oils etc. which may be synthetic or natural^[20]. But unfortunately, these agents are not efficient against certain type of pathogens. In addition to drugs used to kill the microbes, use of immunomodulators^[21], operative drainage and plasma therapy^[22-24] have also been found to tackle the infectious diseases.

USE OF BLOOD PLASMA AGAINST INFECTION: PLASMA THERAPY

Plasma therapy is an approach to treat infectious diseases by the use of plasma, serum or antibodies from an infection survived individual. An attempt to study this approach was first made in animals in the early 20th century considering the fact that 26 patients were cured of poliomyelitis infection when they were infused with serum of poliomyelitis survivors. Cure of an infection due to serum from disease survivors indicates that there are immune rich contents in the serum which might destroy the pathogen.

One of the pathogen fighting substances produced by immune system are antibodies that breakdown the infectious agent. These antibodies were found to circulate in the blood plasma and became the basis of plasma therapy wherein the plasma from a patient who has survived from the infection is used as a source of antibodies in the suffering patient. Once, transfused into a new patient, the antibodies present in the donor's plasma will fight against the antigen present in the receiver's body as shown in fig. 1. It might also trigger the synthesis of the antibodies by the receiver's immune system.

Apart from transfusion of plasma, sometimes, particular antibodies might be isolated and injected into the patient. Hence plasma therapy serves as an efficient approach to fight infectious diseases provided the donor's antibodies are found to be active and efficacious inside the receiver's body and if they are stable while isolation, transfusion and other steps performed in the therapy.

APPLICATIONS OF PLASMA THERAPY TILL DATE

Probably, an immunoglobulin in the form of diphtheria antitoxins is the first therapeutic product developed from plasma. It was also observed that fresh plasma is also responsible to correct clotting time in hemophilia patients^[25]. Therapeutically useful immunoglobulins and fibrinogen can be extracted from plasma which can be useful in treatment of various infectious disease conditions. As the blood plasma of patient recovered from any infection has developed immunity against it, the immunoglobulins present in that plasma can be therapeutically effective for treatment in other infected individuals.

During pandemic infection of H1N1 Virus in 2009, a cohort study was conducted in which significant reduction in respiratory tract viral load, serum cytokine response and relative risk of mortality were observed in the patients treated with convalescent plasma^[26]. In subgroup analysis reduction in the viral load was observed in Intensive Care Unit (ICU). No adverse effects were found in patient treated with plasma therapy^[27]. Antibodies from convalescent plasma might be suppressing viraemia. Schoofs and colleagues reported that 3BNC117-mediated immunotherapy, a broad neutralizing antibody to Human Immunodeficiency Virus-1 (HIV-1) enhances immunity of host as well as it helps in blocking new infection and clearing infected cells^[27].

In 2014, use of convalescent plasma collected from patient recovered from Ebola virus disease was suggested by World Health Organization (WHO) as a treatment^[28]. Convalescent plasma from recovered patients helps in viral clearance on one hand and increased sustainability of protective neutralizing antibodies on the other hand, when used in infected patients. Also plan was made to prepare IV immunoglobins which can be utilized in treatment of further new cases^[29]. In another case treatment of argentine hemorrhagic fever, caused by an arenavirus (Junin virus), in which patients were shown to be benefited from immune serum administered within 1 w after symptoms began^[30]. In patients infected from Chikunguniya Virus (CHIKV), it was observed that administration of CHIKV immunoglobins extracted from plasma of recovered patients show safety as well as prevention of infection in individuals who are at risk of severe infection^[31].

In case of measles, it was observed that the adults who had got infected in childhood have developed immunity in them but the concentration was low. The immunity can be transferred from the mother to child through plasma transfusion which can protect the child from many infections. The use of convalescent serum from the patients who recovered from the infection showed significantly effective results. It can be used to develop passive immunity if injected after 3 to 5 d of exposure to the pathogen. With the increasing disease exposure, larger dose had to be used to develop immunity^[32].

In 2015, protocol was established stating use of convalescent plasma therapy in patients suffering from infection caused by Middle East Respiratory Syndrome (MERS) related corona virus (EMC/2012)^[27]. In order to evaluate the efficacy of convalescent plasma therapy in the treatment of patients with SARS, administration of plasma on 14th d of infection had shown a positive response and on 22nd d of infection many patients were discharged from the hospital after the therapy^[33].

The result from 10 adult cases showed that 200 ml dose of convalescent plasma was well tolerated and maintained the neutralizing power of antibodies at high level leading to improvement in symptoms within 3 d and cure of infection within 7 d of treatment^[34]. From above studies we can conclude that convalescent plasma therapy has shown positive response to cure various infectious diseases.

PLASMA THERAPY IN COVID-19

According to WHO, no specific treatment is recommended for COVID-19 disease because of lack of evidences. But some evidence shows that convalescent plasma from the patient recovered from viral infections can be utilized for treatment without occurrence of any adverse effect^[27]. The novel corona virus ("SARS-Cov-2") outbreak has created a sense of global panic and to treat the COVID-19, currently no specific antiviral drug is approved^[35]. The increasing mortality rate challenges researchers to investigate new antiviral drug to save the lives of people across the globe. The search for the effective treatment is underway with multiple investigations across the globe^[36]. However various studies conducted in China reported that plasma therapy in COVID-19 can benefit the infected patients. When infected patient receives plasma from the survivors of illness, it benefits patients by producing protective antibodies^[37]. Though plasma exchange is

not a novel treatment but therapeutic plasma exchange can be a possible treatment for COVID-19.

Plasma therapy is a classic immunotherapy and has been used for the prevention and treatment of various infectious diseases for more than a century. According to the researchers, from past two decades it has been used for the treatment of MERS, SARS and H1N1 pandemic with satisfactory safety and efficacy reports^[23,26,33,38]. A meta-analysis was carried out in which 32 patients infected from SARS-CoV-2 receiving plasma therapy were studied and statistically significant reduction in mortality rate was observed^[39]. As, SARS and MERS show similar clinical and virological characteristics, plasma therapy might be a promising treatment option for COVID-19 rescue^[36].

A pilot study was conducted to explore feasibility of plasma therapy on 10 severe COVID-19 patients from 3 different hospitals receiving one dose of 200 ml plasma transfusion. The dose was well tolerated by the patients with significant improvement in clinical symptoms. Also, the increase in oxyhaemoglobin saturation accompanied by rapid neutralization of viremia and decreased lymphocyte count in peripheral blood were reported. In addition, plasma therapy is reported to be effective in temperature normalization, relief of dyspnoea, normalization in oxygen saturation and radiological improvement in the patients^[34]. In New Delhi, India, a 49 y old male patient who was treated with plasma therapy has shown positive result and also weaned off ventilator support on 4 d of plasma transfusion. And also the two consecutive tests were found negative for infection^[40].

As plasma therapy is an effective treatment for various infectious diseases, with safety and efficacy studies, it can be a better treatment option for COVID-19. The various research challenges in the development of specific anti-viral drug or vaccine for COVID-19 and gradually increasing mortality rates lead to increased global panic. But administration of plasma therapy is not only found to be useful in reducing clinical symptoms but also decreased the duration of hospitalization of patients. Table 1^[41-50] highlight some of the important works where convalescent plasma transfusion was used as treatment option in COVID-19 patients and results of certain works indicate that plasma therapy can be an effective treatment in reducing the suffering period and saving the life of patient in COVID-19 pandemic.

TABLE 1: FEW IMPORTANT WORKS HIGHLIGHTING THE USE OF PLASMA THERAPY IN COVID-19 PATIENTS

Sr. No.	Title	Country	Authors	Dosage	No. of patients in the study	Patient details (age, gender, co-morbid conditions, etc)	Adverse effects	Results
1	Treatment with convalescent plasma for COVID-19 patients in Wuhan, China ^[41]	China	Mingxiang Ye <i>et al.</i>	200 ml	6	Age: 28-75 y Gender: 3 males, 3 females	Nil	Resolution of Ground Glass Opacities (CGOs) in 5 patients. Immediate increase in anti-SARS-CoV-2 antibodies in 2 patients
2	Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial ^[42]	China	Ling Li <i>et al.</i>	4-13 ml/kg body weight	103	All patients had chest abnormalities confirmed from CT scan Median age: 70 Gender: 60 subjects were male and 43 were female Patients with conditions like hypertension, diabetes, cardiovascular disease, cancer etc were included All patients showed symptoms suggesting severe or life-threatening COVID-19 disease All patients showed pneumonia confirmed by chest imaging	2 patients showed severe transfusion related adverse events One patient reported chills and rashes within 2 h of transfusion but recovered with appropriate treatment One patient reported shortness of breath, cyanosis and severe dyspnoea within 6 h of transfusion	The plasma therapy along with standard treatment was compared to standard treatment alone in this study. Convalescent plasma therapy did not result in a statistically significant improvement in patients suffering from severe and life-threatening COVID-19

			1776	Age: 60 y	Reduction in ICU stays period
3	Conalescent plasma therapy in patients with COVID-19 ^[43]	Turkey Fevzi Altuntas <i>et al.</i>	(Test: 888, Control: 888)	Gender: 1250 male and 526 females All patients were severely and critically ill Most of the patients had co-morbid conditions like hypertension, diabetes, respiratory system diseases, chronic liver and renal diseases and cancer	Reduction in mechanical ventilation support
4	Treatment of 5 critically ill patients With COVID-19 with convalescent plasma ^[44] .	China Chenguang Shen <i>et al.</i>	5 2 cycles of 200-250 ml	Age: 30-70 y Gender: 3 male and 2 female All patients Reported ARDS Required mechanical ventilation	Plasma therapy showed improvement in clinical status of patients but the subjects were also on other medications
5	Treatment of COVID-19 patients with convalescent plasma in Houston, Texas ^[45]	Texas, US Eric Salazar <i>et al.</i>	25 300 ml	Age: 19-77 y Gender: 11 male and 14 female All patients were required to have severe or critical COVID-19 disease to be included in the study All patients were on oxygen support and received anti-viral and anti-inflammatory treatment Around 65 % of subjects had one or more co-morbid conditions like diabetes, hypertension etc	76 % of patients showed improvement in clinical status and 44 % of patients were discharged after 14 d of plasma transfusion indicating plasma therapy as a safe treatment option in severely ill COVID-19 patients

1101	6	Effect of convalescent plasma therapy on viral shedding and Survival in COVID-19 patients ⁽⁴⁶⁾	China Qing Lei Zeng <i>et al.</i>	300 ml	21 (only 6 of them received plasma due to availability and compatibility) breath and fatigue. They were also confirmed of having pneumonia	Age: Around 60 y Gender: 5 male, 1 female	Nil	Convalescent plasma therapy decreased viral load and contributed to longer survival duration in COVID-19 patients with respiratory failure
Indian Journal of Pharmaceutical Sciences	7	Convalescent plasma therapy in the management of COVID-19 patients-The newer dimensions ⁽⁴⁷⁾	India Mahapatra S <i>et al.</i>	200-250 ml	All patients had respiratory failure.	Age: 18-85 y	Improvement in recovery rate	It did not reduce mortality in critically end-stage patients
September-October 2022	8	Convalescent plasma therapy in patients with moderate-to-severe COVID-19: A study from Indonesia for clinical research in low- and middle-income countries ⁽⁴⁸⁾	Indonesia Marliana S. Rejeki <i>et al.</i>	3 doses of 3 ml/kg	230 subjects were grouped under critical group among the test subjects.	Age: 48-75 y Gender: 5 males and 5 females	Not reported	Early discharge from hospital Convalescent plasma with neutralizing antibody titer of more than 1:160 showed complete recovery and decreased mortality Good clinical improvement in all patients with moderate disease and 2 patients with severe disease

High rate of clinical improvement	Age: 45-60 y	Gender: 105 males and 35 females.					Reduced mortality rate In case of severely ill patients, plasma therapy showed clinical improvement in 7 d when compared to control group who showed improvement in 15 d
		All subjects were either moderately (symptoms and pneumonia) or severely (Oxygen saturation less than 90, more than 30 breath/minute, admitted to ICU) ill				Sondas Alsharidah <i>et al.</i>	Oxygen saturation improved within 3 d of transfusion
		Around 45 % of patients were diabetic and hypertensive					Lymphocyte count decreased within 7 d and 11 d of transfusion in moderately and severely ill patients respectively
		Age: 40-75 y	385 patients were moderately ill while 694 were severely ill	1079		Sandeep Budhiraja <i>et al.</i>	C-reactive protein reduced in 14 d of plasma transfusion
		All patients who were severely ill had one or more co-morbid conditions like hypertension, diabetes, Coronary Artery Disease (CAD) and were admitted to ICU		(Test: 393, Control: 686)			Convalescent plasma transfusion showed significant reduction in mortality in patients admitted to ICU, particularly in females and especially in patients with one co-morbid condition

CONCLUSION

The SARS-CoV-2 infection affects one of the most vital systems of the body, i.e respiratory system. Its incursion on the respiratory cells (alveoli) leads to difficulty in breathing and insufficient supply of oxygen to the body. This in turn leads to serious complications like multiple organ failure and death if there is no timely cure of the infection. Therefore, targeting the foreign body itself would serve the purpose. Antibodies are the major fighters produced by the immune system to degenerate and eliminate the microbes from the body. But if the immune system fails to produce appropriate and adequate antibodies against the virus, plasma therapy, involving transfusion of plasma containing antibodies from a disease survived patient can be a ray of hope. Considering this phenomenon, the trials of plasma therapy in COVID-19 patients have been started. Hence, plasma therapy can be an effective treatment to cure people from COVID-19.

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Conflict of interest:

The authors declare that there is no conflict of interest in the present study.

REFERENCES

- Den Boon JA, Diaz A, Ahlquist P. Cytoplasmic viral replication complexes. *Cell Host Microbe* 2010;8(1):77-85.
- Gelbart WM, Knobler CM. Pressurized viruses. *Science* 2009;323(5922):1682-3.
- Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents* 2020;55(3):105924.
- Belouzard S, Madu I, Whittaker GR. Elastase-mediated activation of the severe acute respiratory syndrome coronavirus spike protein at discrete sites within the S2 domain. *J Biol Chem* 2010;285(30):22758-63.
- Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 2005;309(5742):1864-8.
- Graham RL, Donaldson EF, Baric RS. A decade after SARS: Strategies for controlling emerging coronaviruses. *Nat Rev Microbiol* 2013;11(12):836-48.
- Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *Biorxiv* 2020;26(1):919985.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506.
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708-20.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA* 2020;323(13):1239-42.
- Zhou D, Dai SM, Tong Q. COVID-19: A recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother* 2020;75(7):1667-70.
- Tortora GJ, Derrickson B. Principles of anatomy and physiology; 2009.
- Schroeder Jr HW, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol* 2010;125(2):S41-52.
- Buttram HE. Current childhood vaccine programs: An overview with emphasis on the measles-mumps-rubella (MMR) vaccine and of its compromising of the mucosal immune system. *MedVeritas* 2008;5(2):1820-7.
- Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. *Curr Opin HIV AIDS* 2015;10(3):129-34.
- Murin CD, Wilson IA, Ward AB. Antibody responses to viral infections: A structural perspective across three different enveloped viruses. *Nat Microbiol* 2019;4(5):734-47.
- Cullender TC, Chassaing B, Janson A, Kumar K, Muller CE, Werner JJ, *et al.* Innate and adaptive immunity interact to quench microbiome flagellar motility in the gut. *Cell Host Microbe* 2013;14(5):571-81.
- Noris M, Remuzzi G. Overview of complement activation and regulation. *Semin Nephrol* 2013;33(6):479-92.
- Seifert M, Küppers R. Human memory B cells. *Leukemia* 2016;30(12):2283-92.
- Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clin Proc* 2011;86(2):156-67.
- Masihi KN. Fighting infection using immunomodulatory agents. *Expert Opin Biol Ther* 2001;1(4):641-53.
- Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, *et al.* Convalescent plasma: New evidence for an old therapeutic tool? *Blood Transfus* 2016;14(2):152.
- Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. *N Engl J Med* 2007;357(14):1450-1.
- Wong HK, Lee CK. Pivotal role of convalescent plasma in managing emerging infectious diseases. *Vox Sang* 2020;115(7):545-7.
- Farinacci M, Krahn T, Dinh W, Volk HD, Dungen HD, Wagner J, *et al.* Circulating endothelial cells as biomarker for cardiovascular diseases. *Res Pract Thromb Haemost* 2019;3(1):49-58.
- Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, *et al.* Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011;52(4):447-56.
- Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis* 2020;20(4):398-400.
- Winkler AM, Koepsell SA. The use of convalescent plasma to treat emerging infectious diseases: Focus on Ebola virus disease. *Curr Opin Hematol* 2015;22(6):521-6.

29. Wilkinson DE, Hassall M, Mattiuzzo G, Stone L, Atkinson E, Hockley J, *et al.* WHO collaborative study to assess the suitability of the 1st International Standard and the 1st International Reference Panel for antibodies to Ebola virus; 2017.
30. Enria DA, Briggiler AM, Sánchez Z. Treatment of Argentine hemorrhagic fever. *Antiviral Res* 2008;78(1):132-9.
31. Couderc T, Khandoudi N, Grandadam M, Visse C, Gangneux N, Bagot S, *et al.* Prophylaxis and therapy for Chikungunya virus infection. *J Infect Dis* 2009;200(4):516-23.
32. Zingher A. Convalescent whole blood, plasma and serum in prophylaxis of measles. *J Am Med Assoc* 1924;82(15):1180-7.
33. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, *et al.* Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005;24(1):44-6.
34. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, *et al.* Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci* 2020;117(17):9490-6.
35. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579(7798):270-3.
36. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020;395(10223):507-13.
37. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: An argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Crit Care* 2020;24(1):1-3.
38. Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, *et al.* Challenges of convalescent plasma infusion therapy in middle east respiratory coronavirus infection: A single centre experience. *Antivir Ther* 2018;23(7):617-22.
39. Walter ND. *Ce Pt Cr Ipt Us Cr*; 2015. p. 1-9.
40. Plasma therapy on Delhi coronavirus patient shows promise; 2020.
41. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, *et al.* Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* 2020;92(10):1890-901.
42. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, *et al.* Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. *JAMA* 2020;324(5):460-70.
43. Altuntas F, Ata N, Yigenoglu TN, Bascı S, Dal MS, Korkmaz S, *et al.* Convalescent plasma therapy in patients with COVID-19. *Transfus Apher Sci* 2021;60(1):102955.
44. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, *et al.* Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020;323(16):1582-9.
45. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, *et al.* Treatment of COVID-19 patients with convalescent plasma in Houston, Texas. *Am J Pathol* 2020;190(8):1680-90.
46. Zeng QL, Yu ZJ, Gou JJ, Li GM, Ma SH, Zhang GF, *et al.* Effect of convalescent plasma therapy on viral shedding and survival in patients with coronavirus disease 2019. *J Infect Dis* 2020;222(1):38-43.
47. Mahapatra S, Rattan R, Mohanty CB. Convalescent plasma therapy in the management of COVID-19 patients-The newer dimensions. *Transfus Clin Biol* 2021;28(3):246-53.
48. Rejeki MS, Sarnadi N, Wihastuti R, Fazharyasti V, Samin WY, Yudhaputri FA, *et al.* Convalescent plasma therapy in patients with moderate-to-severe COVID-19: A study from Indonesia for clinical research in low and middle-income countries. *E Clin Med* 2021;36:100931.
49. Alsharidah S, Ayed M, Ameen RM, Alhuraish F, Rouheldeen NA, Alshammari FR, *et al.* COVID-19 convalescent plasma treatment of moderate and severe cases of SARS-CoV-2 infection: A multicenter interventional study. *Int J Infect Dis* 2021;103:439-46.
50. Budhiraja S, Dewan A, Aggarwal R, Singh O, Juneja D, Pathak S, *et al.* Effectiveness of convalescent plasma in Indian patients with COVID-19. *Blood Cells Mol Dis* 2021;88:102548.