

## The Effect of Convalescent Plasma in Patients With Covid-19 in Intensive Care Unit

ALINA BEREANU<sup>1,2</sup>, OVIDIU CRISAN<sup>3</sup>, ANNE-MARIE CONSTANTIN<sup>4</sup>, SIMONA CAINAP<sup>4</sup>, CALIN CAINAP<sup>4</sup>,  
RALUCA DRAGULESCU<sup>2</sup>, RARES BEREANU<sup>1</sup>, BOGDAN VINTILA<sup>1</sup>, CORINA ROMAN<sup>1,2</sup> and MIHAI SAVA<sup>1,2</sup>

<sup>1</sup>Faculty of Medicine, "Lucian Blaga" University of Sibiu, Sibiu, Romania;

<sup>2</sup>County Clinical Emergency Hospital of Sibiu, Sibiu, Romania;

<sup>3</sup>Faculty of Pharmacy, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania;

<sup>4</sup>Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

**Abstract.** Background/Aim: Convalescent plasma collected from COVID-19 survivors contains antibodies against receptor binding domains with potent antiviral activity. The use of this therapy for COVID-19 is still under investigation, as the pathophysiological and immunological mechanisms responsible for the evolution of the disease have not been fully identified. Patients and Methods: In this retrospective observational study, we included all patients with a confirmed SARS-Cov-2 infection based on positive RT-PCR testing, who received convalescent plasma treatment in addition to standard therapy, between 17.05.2020 and 27.11.2020, following hospitalization in the Anaesthesia and Intensive Care Unit of the Sibiu County Emergency Clinical Hospital, Romania. Results: Convalescent plasma therapy of patients with SARS-Cov-2 infection and severe forms of the disease (requiring only high-flow oxygen therapy or non-invasive ventilation) significantly improved inflammatory markers (CRP, fibrinogen) and ventilatory parameters (SaO<sub>2</sub>, paO<sub>2</sub>, paO<sub>2</sub>/FiO<sub>2</sub>) reducing the need of supplemental oxygen delivery ( $p < 0.05$ ). Other factors that had a significant influence on the outcome were age and comorbidity. Conclusion: Inflammatory markers and ventilatory parameters were significantly improved and the

need of supplemental oxygen delivery was reduced in COVID-19 patients treated with convalescent plasma.

The new SARS-Cov-2 coronavirus causes COVID-19 disease leading to high morbidity and mortality. The mortality rate of COVID-19 patients in intensive care has been declining very slowly since the beginning of the pandemic, however, still remains high (from 60% in March 2020 and 46% in May to 36% in October 2020) (1-5).

Although most people infected with the new SARS-CoV2 coronavirus develop mild forms of the disease, some patients develop severe disease, with acute respiratory distress syndrome and systemic inflammatory response, and even multiple organ dysfunction syndrome. As a result of an inadequate response of the host to infection, COVID-19 may become a systemic disease with endothelial damage resulting in generalized thrombotic microangiopathy (6). Today, there is unanimous agreement on the need to provide early and individualized treatment. Treatment with convalescent plasma (CP) is of particular interest in the management of this disease.

Studies have suggested that CP collected from COVID-19 survivors contains antibodies against receptor binding domains (RBD) with potent antiviral activity. The use of CP has been approved in both the USA and Europe and is included in the FDA and European Commission recommendations. In Romania, treatment with CP is instructed by a Ministerial Order (6, 7).

The eligibility criteria included the following: patients with COVID-19 admitted to the ICU who have a rapid progression of severe pneumonia/pulmonary infiltrates ( $>50\%$  in 24-48 h), PaO<sub>2</sub>/FiO<sub>2</sub>  $<300$ , patients mechanically ventilated for less than 10 days or on the threshold of intubation and mechanical ventilation, severe dyspnoea with less than 6 l O<sub>2</sub>/min, respiratory rate  $>30$ /min, SpO<sub>2</sub>  $<93\%$ , PaCO<sub>2</sub>  $>55$  mmHg in patients without chronic obstructive pulmonary disease (COPD).

Correspondence to: Calin Cainap, MD, Ph.D., Department of Oncology, Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Republicii street 34-36, 40015, Cluj-Napoca, Cluj, Romania. Tel: +40 740256076, e-mail: calincainap2015@gmail.com

**Key Words:** Covid-19, SARS-Cov-2, convalescent plasma, hyperimmune plasma.



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (<https://creativecommons.org/licenses/by-nc-nd/4.0>).

The use of CP required the following: the presence of anti-SARS-CoV-2 antibodies in sufficient titer (FDA recommends a neutralizing antibody titer of at least 1/160), and a donor that meets blood donation criteria (8, 9). The optimal time of harvest would be in the first 2-3 months after healing (10, 11).

In this retrospective observational study, we present the results of the use of CP on the evolution of critically ill patients with severe forms of COVID-19.

## Patients and Methods

In this retrospective observational study, we included all patients with confirmed SARS-Cov-2 infection, who received CP treatment in addition to standard therapy, between 17.05.2020 and 27.11.2020, following hospitalization in the Anaesthesia and Intensive Care ward of the Sibiu County Emergency Clinical Hospital, Romania. This study was performed with the approval of the Ethics Commission of the Sibiu County Clinical Hospital. The study included 23 patients with a severe form of COVID-19. Informed consent was obtained from a legal representative of the patient (the patients included in the study receiving high-flow oxygen therapy, ventilation, sedation), by telephone, for biosecurity reasons. The recommendation of CP administration was made by the intensive care physician according to the national and international guidelines for COVID-19.

The administration of CP was performed according to one of the recommended regimens, namely a single administration of a volume of 600 ml of plasma (3 units of CP of 200 ml each). Neutralizing antibody titer was over 1:160 in most patients and at least 1:80 in two patients. The rate of administration was 100-250 ml plasma per hour. The time of administration was in the first 14 days of illness. No severe adverse effects were observed.

Patients with severe form of the disease were considered as those who had at least one of the following: respiratory rate  $>30/\text{min}$ ,  $\text{SaO}_2 \leq 93\%$ ,  $\text{PaO}_2/\text{FiO}_2 < 300$ , pulmonary infiltrates that increased by more than 50% in 24-48 h. Critical patients were considered as those with at least one of the following: acute respiratory distress ( $\text{paO}_2/\text{FiO}_2$  ratio  $< 200$ , requiring orotracheal intubation), sepsis, impaired consciousness, multiple systems organ failure (MSOF) (6, 7).

Standard treatment administered in the intensive care unit (ICU) included high-flow oxygen therapy, non-invasive mechanical ventilation, invasive mechanical ventilation, antivirals (hydroxychloroquine, lopinavir/ritonavir, remdesivir), anticoagulants (heparin fractionated in therapeutic doses), antibiotic therapy (azithromycin or meropenem in combination with linezolid), tocilizumab, depending on the clinical condition and paraclinical parameters of each patient.

**Data analysis.** Data were collected from patient observation sheets and analysed using Microsoft Excel programme.  $p$ -Values  $< 0.05$  were considered statistically significant. The primary outcome was the evolution of the patients, namely the survival rate. We used descriptive analysis and  $t$ -test for analysing two samples assuming equal variances. We recorded or assayed for the following: the ventilatory parameters,  $\text{SaO}_2$ ,  $\text{paO}_2$ ,  $\text{paO}_2/\text{FiO}_2$  ratio, markers of inflammation, PCR, fibrinogen, ferritin, leukocytes, lymphocytes, the evolution of D-dimers. We used the average values of these parameters. SARS-Cov-2 extraction was performed using an automatic extractor certified and validated CFX96 real-time PCR

Table I. Patients' comorbidities.

Comorbidities	No. of patients
Obesity	11 (47.82%)
Hypertension	13 (56.52%)
Coronary heart disease	6 (26.08%)
Diabetes mellitus	4 (17.39%)
Hypothyroidism	2 (8.69%)
Chronic hepatopathy	3 (13.04%)
Chronic kidney disease	2 (8.69%)
Chronic respiratory disease	2 (8.69%)
Heart failure	2 (8.69%)
Thrombophilia	1 (4.34%)
Chronic digestive disease	2 (8.69%)

Detection System (Bio-Rad). The CFX96 Touch System is a precise real-time PCR detection System. This six-channel real-time PCR instrument is used by Laboratory Department of the Sibiu County Emergency Clinical Hospital, Romania and combine advanced optical technology with precise thermal control.

## Results

In total, 23 patients with severe COVID-19 who received CP treatment, were included in the study. Of these, 8 were women and 15 men, aged between 35 and 70 years, respectively. All patients in the study had comorbidities. The frequency of comorbidities in patients treated with CP hospitalized in the ICU, are summarized in Table I. Of the 23 patients who received CP, 14 died (60.86%) and 9 (39.13%) showed improvement in symptoms and were transferred to the Infectious Diseases ward, where they were subsequently discharged from.

Regarding pulmonary computed tomography imaging at admission, 16 patients presented with severe bilateral interstitial pneumonia (more than 50% damage of the lung parenchyma) 6 patients presented with a moderate form of the disease (25-50% damage of lung parenchyma) and 1 patient presented with a mild form ( $< 25\%$  damage of lung parenchyma).

Of the 23 patients with severe COVID-19 included in this study, 16 were critically ill patients at admission to the ICU. Depending on the severity of the disease, patients required high-flow oxygen therapy (5 patients), non-invasive ventilation (7 patients), or invasive ventilation with orotracheal intubation (11 patients). The average duration of hospitalization was  $19.28 \pm 10.85$  days, ranging from 3 to 46 days.

To determine the response of patients to treatment, we followed the ventilatory parameters ( $\text{SaO}_2$ ,  $\text{paO}_2$ ,  $\text{paO}_2/\text{FiO}_2$  ratio), markers of inflammation (PCR, fibrinogen, ferritin), leukocytes, lymphocytes, and the evolution of D-dimers (Table II). The most important

Table II. *Biological parameters at admission to ICU.*

Parameter	Patients with favourable evolution (9) (mean value)	Deceased patients (14) (mean value)
SaO <sub>2</sub> (NV 95-100%)	84.5%	79.2%
paO <sub>2</sub> (NV>80 mmHg)	72.91 mmHg	68.87 mmHg
PaO <sub>2</sub> /FiO <sub>2</sub> (NV≥400)	<200	<100
PCR (NV<0.5 mg/dl)	35.95 mg/l	200.77mg/l
Fibrinogen (NV 2.0-4.0 g/l)	658.1mg/dl	538.7mg/dl
Ferritin (NV male 12-300 ng/l, female 12-150 ng/l)	831.03 ng/ml	1,158.05 ng/ml
Leukocytes (3.5-10.5×10 <sup>9</sup> /l)	11,430×1,000/ml	13,922×1,000/ml
Lymphocytes (NV 800-5,000/μl)	1,022.31/μl	902.4/μl
D-dimers (NV 100-250 ng/ml)	3,338.99 ng/ml	1,772.07 ng/ml

CRP: C reactive protein; SaO<sub>2</sub>: blood oxygen level; paO<sub>2</sub>: partial pressure of oxygen in the arterial blood; ICU: Intensive Care Unit; NV: normal value.

correlations with favourable outcome were the values of the partial pressure of oxygen in the arterial blood, oxygen saturation, the ratio PaO<sub>2</sub>/FiO<sub>2</sub>, and the values of fibrinogen and PCR, with a statistical *p*-value <0.05 (Table III).

Our results indicated that CP therapy of patients with SARS-Cov-2 infection presenting with severe forms of the disease but requiring only high-flow oxygen therapy or non-invasive ventilation could significantly reduce inflammatory markers (CRP, fibrinogen) and ventilatory parameters (SaO<sub>2</sub>, paO<sub>2</sub>, paO<sub>2</sub>/FiO<sub>2</sub>), reducing the need of supplemental oxygen administration (*p*<0.05).

The majority of patients (75%) who were not intubated at the time of CP administration but were only treated with high-flow oxygen or non-invasive ventilation, had a favourable evolution unlike intubated and mechanically ventilated critically ill patients who showed an unfavourable evolution and death (*p*<0.05). Most of the patients who died were intubated at the time of plasma therapy [11 patients out of 14 (78.57%)] (Table IV).

In terms of age, patients with good evolution were significantly younger 52.37±6.62 years, in comparison to those with an unfavourable outcome 67.8±8.08 (*p*<0.005) (Figure 1). The factors that influenced the outcome were: age, comorbidities, and the severity of disease. All patients had comorbidities; however, those with a single comorbidity had a more favourable outcome than those with more comorbidities.

Most patients (86.95%) had more than one associated comorbidity (Table V). The most common comorbidities encountered were hypertension (56.52%) and obesity (47.82%). The most common association of comorbidities was between hypertension and obesity (43.47%). In patients with unfavourable outcome, hypertension was more frequently associated with the pathological antecedents

Table III. *Biological parameters at admission to ICU.*

Parameter	Patients with favourable outcome ( <i>p</i> -Value)	Deceased patients
SaO <sub>2</sub>	↑1.3×IMV (<0.005)	↓1.1×IMV (<0.09)
PaO <sub>2</sub>	↑1.4×IMV (<0.005)	↓1.2×IMV (<0.03)
PaO <sub>2</sub> /FiO <sub>2</sub>	↑1.5×IMV (<0.001)	↓1.9×IMV (<0.02)
Fibrinogen	↓1.9×IMV (<0.05)	↓1.7×IMV (<0.42)
PCR	↓3.6×IMV (<0.02)	↓1.6×IMV (<0.25)
Leukocytes	↓1.1×IMV (<0.29)	↑2.4×IMV (<0.32)
Lymphocytes	↑1.5×IMV (<0.18)	↓1.03×IMV (<0.29)
Ferritin	↑1.3×IMV (<0.25)	↓1.06×IMV (<0.43)
D-dimers	↓1.24×IMV (<0.33)	↑4.65×IMV (<0.09)

IMV: Initial mean value; CRP: C reactive protein; SaO<sub>2</sub>: blood oxygen level; paO<sub>2</sub>: partial pressure of oxygen in the arterial blood.

(71.42%) compared to patients with favourable outcome (44.44%). Among the patients with favourable outcome, 33.33% presented a single associated comorbidity *versus* 7.14% of the patients with an unfavourable outcome; the rest had two or more associated comorbidities.

## Discussion

The use of CP, also called hyperimmune plasma, has an historical value; it was used in the late nineteenth century for the treatment of diphtheria. In the pre-vaccine era, CP was used for the treatment of viral diseases such as polio, measles, mumps, influenza, and Ebola with varying degrees of success (12-15). The principle of the treatment is based on the action of neutralizing antibodies present in the CP against the virus (16).

Severe COVID-19 occurs in the first 7 to 10 days after infection (17-20). Understanding the evolution of the adaptive immune response mediated by B and T cells after SARS-Cov-2 infection is essential in the prognosis of COVID-19 disease and in the development of treatment strategies.

Early in the infection, there is an expansion of B cells with memory and plasmablasts, and IgM and IgA antibodies are detected from day 5 to 7 after infection. IgG appear on the 7th-10th day after the onset of symptoms. Serum IgM and IgA levels decrease after approximately 28 days and IgG titer reaches a peak after 49 days. At the same time, SARS-Cov-2 activates T cells in the first week of infection (CD4 T cells with specific viral memory and CD8 T cells), which reach a peak at 2 weeks (Figure 2) (17, 18, 21, 22). The magnitude of IgG RBD antibody titers, which recognize the receptor binding domain, are strongly correlated with viral neutralization (17-20).

Antibody levels decrease over time. Gaebler *et al.* conducted a study on the humoral response with memory on a cohort of 87 individuals and found that IgM and IgG levels

Table IV. Evolution of patients according to respiratory status at the time of convalescent plasma administration.

Respiratory status at the time of convalescent plasma administration	No. of patients with favourable evolution	No of patients who died	Mortality
Patients with high-flow oxygen therapy or non-invasive ventilation	9	3	25%
Patients intubated and mechanically ventilated	11	11	100%

against the viral spike protein binding domain of SARS-Cov-2 decreased drastically over time, whereas IgA levels were less affected (23).

Other immune mechanisms such as cell-mediated cytotoxicity, complement activation, or phagocytosis are possible mechanisms by which CP may exert its therapeutic effect in patients with COVID-19. In addition, anti-inflammatory cytokines, defensins, pentraxins, and other immunomodulatory proteins may have a role in ameliorating the systemic inflammatory response syndrome, the main pathophysiological basis for acute respiratory distress syndrome and mortality from COVID-19 pneumonia (24). However, the effective titrations of neutralizing antibodies in CP, the optimal time for plasma donation, the optimal time for plasma treatment and the severity of the disease of the patient receiving CP remain unclear (16).

In our study, the majority of patients with SARS-Cov-2 infection who received CP had severe forms of the disease, requiring high-flow oxygen therapy or non-invasive ventilation, showed improvement, were cured from the disease and were subsequently discharged, unlike critically ill intubated patients with SARS-Cov-2 in whom no improvement in clinical, paraclinical and laboratory parameters was observed after plasma administration and who showed an unfavourable outcome with acute respiratory distress syndrome (ARDS), MSOF and death. There are studies that show improved prognosis and increased survival after treatment with CP. Thus, Murphy *et al.* published a literature review on the administration of CP in COVID-19 patients. They identified over 60 studies from 22 countries and reported a 10% decrease in mortality in patients receiving CP treatment (25). Also, Sun *et al.* performed a meta-analysis and highlighted a number of favourable effects and favourable clinical implications of CP treatment in COVID-19 patients (26). Zhang *et al.* conducted a study on the impact of CP treatment on the clinical prognosis of

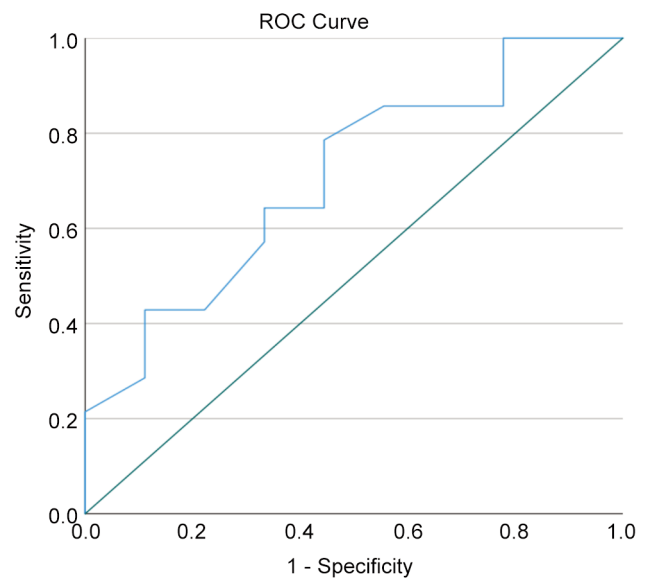


Figure 1. ROC curve for the association between age and COVID-19 outcome (AUC 0.706, cut-off 58 years). ROC: Receiver operating characteristic; AUC: area under the ROC curve.

Table V. No. of associated comorbidities.

No. of comorbidities	No. of patients
1 comorbidity	3 (13.04%)
>1 comorbidity	20 (86.95%)

COVID-19 patients and reported decreases in viremia from 55 105 copies/ml to 180 copies/ml in 5 days after CP treatment. On the other hand, negative RT-PCR tests were reported 10 days after initiation of CP treatment and patients were discharged in an improved condition (27). A similar study was performed by Shen *et al.* who reported decreases in viremia in patients receiving CP 2-3 days after plasma administration (28).

In contrast, the largest multicenter PLACID study conducted in India in October 2020 involving more than 400 patients concluded that there were no differences in the progression to severe form of the disease and in mortality between the group of patients receiving plasma and the group not receiving. One of the strengths of the study is that it enrolled patients without comorbidities (16).

Unlike other studies, we conducted our study only in patients with severe and critical forms of COVID-19, hospitalized in the ICU, this also being the particularity of the study. All patients in our study had one or more comorbidities, hypertension being the most frequently associated with the unfavourable outcome of the patient.

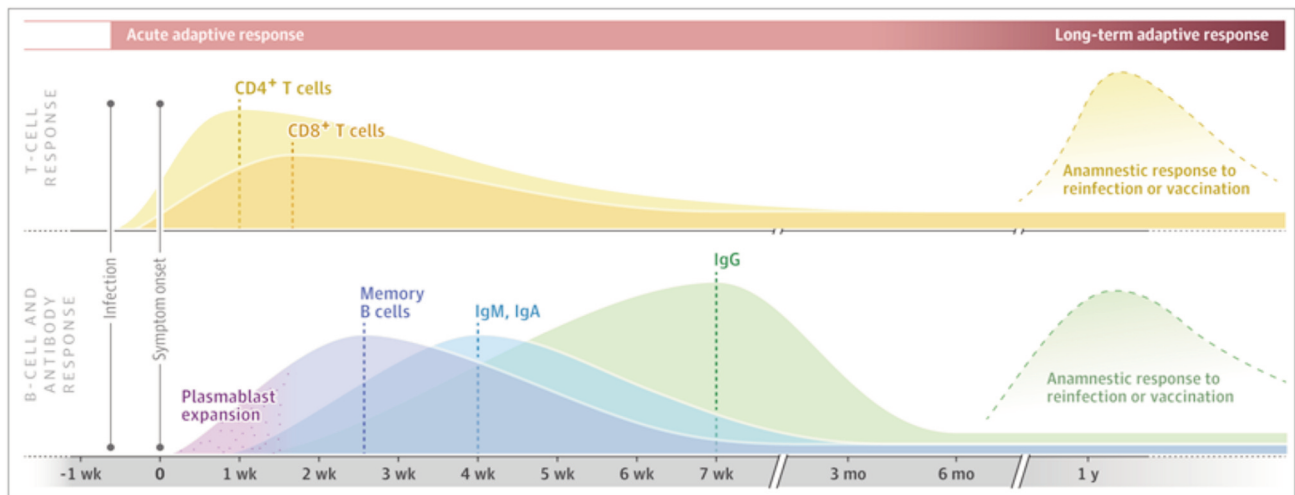


Figure 2. Adaptive immune response to SARS-CoV-2 (17).

Why is plasma rich in anti-SARS-CoV-2 antibodies not effective? A possible explanation is that in addition to immune components, plasma also contains many molecules and components with prothrombotic effect and plasma can have a direct effect on endothelial damage (which, incidentally, is the epicenter of inflammatory mechanisms in this disease). In addition, antibodies against interferon may be present in the donor's plasma and thus the recipient's immune response may be affected (29-31).

A more recent randomized clinical trial conducted by Bandopadhyay *et al.*, concludes that CP also has an anti-inflammatory effect independent of the level of neutralizing antibodies against SARS-CoV-2. This study found that, as a result of CP treatment, neutralizing antibodies as well as reductions in circulating interleukin 6 and interferon gamma-induced protein 10 contributed to the rapid and significant reduction of hypoxia (32).

Why don't we know if CP is effective? The key could be the inclusion criteria, optimal dose, and time point. However, the data on the efficacy and risks of CP are contradictory and do not allow clear recommendations to be made. Despite the controversies, CP has therapeutic application in severe or critical forms of COVID-19, being included in the administration protocols in our country and elsewhere (6, 7).

## Conclusion

In our study, patients with severe forms of COVID-19 (requiring only high-flow oxygen therapy or non-invasive ventilation) who received CP, showed, in most cases (75%), improvement and were cured from the disease. In contrast, critically ill patients who were intubated at the time of

plasma administration had no improvement in clinical, paraclinical, and laboratory parameters after plasma administration. They also showed an unfavourable course with ARDS and MSOF, and eventually died (100%). Our results indicate that CP therapy of patients with severe forms of Covid-19 disease could significantly reduce inflammatory markers (CRP, fibrinogen) and ventilatory parameters (SaO<sub>2</sub>, paO<sub>2</sub>, paO<sub>2</sub>/FiO<sub>2</sub>), reducing the need of supplemental oxygen delivery. Other factors that had a significant influence on the outcome were age and comorbidity.

## Conflicts of Interest

There are no conflicts of interest related to this study.

## Authors' Contributions

The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for using the COVID-19 convalescent plasma for the treatment of certain hospitalized patients with COVID-19. The finding on our study can be useful for selecting the hospitalized patients who require high-flow oxygen therapy or non-invasive ventilation for the treatment of patients with COVID-19 that can benefit from CP therapy.

## References

- 1 Worldometer. Available at: <https://www.worldometers.info/coronavirus> [Last accessed on July 20, 2021]
- 2 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S and Shang Y: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 8(5): 475-481, 2020. PMID: 32105632. DOI: 10.1016/S2213-2600(20)30079-5

- 3 Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention: [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi* 41(2): 145-151, 2020. PMID: 32064853. DOI: 10.3760/cma.j.issn.0254-6450.2020.02.003
- 4 Armstrong RA, Kane AD and Cook TM: Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. *Anaesthesia* 75(10): 1340-1349, 2020. PMID: 32602561. DOI: 10.1111/anae.15201
- 5 Armstrong RA, Kane AD, Kursumovic E, Oglesby FC and Cook TM: Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies. *Anaesthesia* 76(4): 537-548, 2021. PMID: 33525063. DOI: 10.1111/anae.15425
- 6 Filipescu D, Grigoraş I, Grinţescu I, Tomescu D, Bubenek-Turconi ŞI, Săndesc D, Popescu M and Bălan C: Terapie intensivă a pacientului critic cu boală Covid-19 în secţiile ATI. Ghid SRATI Ediţia şi Revizia 2/2, Noiembrie 2020. Available at: [https://www.srati.ro/public/data\\_files/content-static/ghid-covid-19-editia-2.pdf](https://www.srati.ro/public/data_files/content-static/ghid-covid-19-editia-2.pdf) [Last accessed on February 19, 2022]
- 7 Ordin nr. 2054\_27.11.2020 (1) Protocol de tratament pentru SARS-Cov-2. Publicat în Monitorul Oficial nr. 1167 din 3 Decembrie 2020. Available at: <https://legislatie.just.ro/Public/DetaliuDocument/234074> [Last accessed on February 19, 2022]
- 8 Salazar E, Kuchipudi SV, Christensen PA, Eagar TN, Yi X, Zhao P, Jin Z, Long SW, Olsen RJ, Chen J, Castillo B, Leveque C, Towers DM, Lavinder J, Gollihar JD, Cardona J, Ippolito GC, Nissly RH, Bird IM, Greenawalt D, Rossi RM, Gontu A, Srinivasan S, Poojary IB, Cattadori IM, Hudson PJ, Joselyn N, Prugar L, Huie K, Herbert A, Bernard DW, Dye J, Kapur V and Musser JM: Relationship between anti-spike protein antibody titers and SARS-CoV-2 *in vitro* virus neutralization in convalescent plasma. *bioRxiv*, 2020. PMID: 32577662. DOI: 10.1101/2020.06.08.138990
- 9 Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JR, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MN, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Van Buskirk CM, Winters JL, Stubbs JR, Paneth NS, Verdun NC, Marks P and Casadevall A: Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 130(9): 4791-4797, 2020. PMID: 32525844. DOI: 10.1172/JCI140200
- 10 Du Z, Zhu F, Guo F, Yang B and Wang T: Detection of antibodies against SARS-CoV-2 in patients with COVID-19. *J Med Virol* 92(10): 1735-1738, 2020. PMID: 32243608. DOI: 10.1002/jmv.25820
- 11 Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, Hu JL, Xu W, Zhang Y, Lv FJ, Su K, Zhang F, Gong J, Wu B, Liu XM, Li JJ, Qiu JF, Chen J and Huang AL: Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 26(8): 1200-1204, 2020. PMID: 32555424. DOI: 10.1038/s41591-020-0965-6
- 12 Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH and Burgess TH: Hark back: passive immunotherapy for influenza and other serious infections. *Crit Care Med* 38(4 Suppl): e66-e73, 2010. PMID: 20154602. DOI: 10.1097/CCM.0b013e3181d44c1e
- 13 van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, Horby PW, Raoul H, Magassouba N, Antierens A, Lomas C, Faye O, Sall AA, Fransen K, Buyze J, Ravinetto R, Tiberghien P, Claeyss Y, De Crop M, Lynen L, Bah EI, Smith PG, Delamou A, De Weggheleire A, Haba N and Ebola-Tx Consortium: Evaluation of convalescent plasma for Ebola virus disease in Guinea. *N Engl J Med* 374(1): 33-42, 2016. PMID: 26735992. DOI: 10.1056/NEJMoa1511812
- 14 Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, Chan P, Wong KC, Leung CB and Cheng G: Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 24(1): 44-46, 2005. PMID: 15616839. DOI: 10.1007/s10096-004-1271-9
- 15 Devasenapathy N, Ye Z, Loeb M, Fang F, Najafabadi BT, Xiao Y, Couban R, Bégin P and Guyatt G: Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. *CMAJ* 192(27): E745-E755, 2020. PMID: 32444482. DOI: 10.1503/cmaj.200642
- 16 Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P and PLACID Trial Collaborators: Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 371: m3939, 2020. PMID: 33093056. DOI: 10.1136/bmj.m3939
- 17 Stephens DS and McElrath MJ: COVID-19 and the path to immunity. *JAMA* 324(13): 1279-1281, 2020. PMID: 32915201. DOI: 10.1001/jama.2020.16656
- 18 Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, Rawlings SA, Sutherland A, Premkumar L, Jodi RS, Marrama D, de Silva AM, Frazier A, Carlin AF, Greenbaum JA, Peters B, Krammer F, Smith DM, Crotty S and Sette A: Targets of T cell responses to SARS-CoV-2 Coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* 181(7): 1489-1501.e15, 2020. PMID: 32473127. DOI: 10.1016/j.cell.2020.05.015
- 19 Suthar MS, Zimmerman MG, Kauffman RC, Mantus G, Linderman SL, Hudson WH, Vanderheiden A, Nyhoff L, Davis CW, Adekunle O, Affer M, Sherman M, Reynolds S, Verkerke HP, Alter DN, Guarner J, Bryksin J, Horwath MC, Arthur CM, Saakadze N, Smith GH, Edupuganti S, Scherer EM, Hellmeier K, Cheng A, Morales JA, Neish AS, Stowell SR, Frank F, Ortlund E, Anderson EJ, Menachery VD, Roupahel N, Mehta AK, Stephens DS, Ahmed R, Roback JD and Wrammert J: Rapid generation of neutralizing antibody responses in COVID-19 patients. *Cell Rep Med* 1(3): 100040, 2020. PMID: 32835303. DOI: 10.1016/j.xcrm.2020.100040
- 20 Murphy M, Estcourt L, Grant-Casey J and Dziki S: International survey of trials of convalescent plasma to treat COVID-19 infection. *Transfus Med Rev* 34(3): 151-157, 2020. PMID: 32703664. DOI: 10.1016/j.tmr.2020.06.003
- 21 Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, Chng MHY, Lin M, Tan N, Linster M, Chia WN, Chen MI, Wang LF, Ooi EE, Kalimuddin S, Tambyah PA, Low JG, Tan YJ and Bertoletti A: SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* 584(7821): 457-462, 2020. PMID: 32668444. DOI: 10.1038/s41586-020-2550-z
- 22 Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, Hippenstiel S, Dingeldey M, Kruse B, Fauchere F, Baysal E,

- Mangold M, Henze L, Lauster R, Mall MA, Beyer K, Röhm J, Voigt S, Schmitz J, Miltenyi S, Demuth I, Müller MA, Hocke A, Witzenth M, Suttorp N, Kern F, Reimer U, Wenschuh H, Drosten C, Corman VM, Giesecke-Thiel C, Sander LE and Thiel A: SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature* 587(7833): 270-274, 2020. PMID: 32726801. DOI: 10.1038/s41586-020-2598-9
- 23 Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, Cho A, Jankovic M, Schaefer-Babajew D, Oliveira TY, Cipolla M, Viant C, Barnes CO, Bram Y, Breton G, Hägglöf T, Mendoza P, Hurley A, Turroja M, Gordon K, Millard KG, Ramos V, Schmidt F, Weisblum Y, Jha D, Tankelevich M, Martinez-Delgado G, Yee J, Patel R, Dizon J, Unson-O'Brien C, Shimeliovich I, Robbiani DF, Zhao Z, Gazumyan A, Schwartz RE, Hatzioannou T, Bjorkman PJ, Mehndru S, Bieniasz PD, Caskey M and Nussenzweig MC: Evolution of antibody immunity to SARS-CoV-2. *Nature* 591(7851): 639-644, 2021. PMID: 33461210. DOI: 10.1038/s41586-021-03207-w
  - 24 Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, Rojas-Villarraga A, Ramírez-Santana C, Díaz-Coronado JC, Manrique R, Mantilla RD, Shoenfeld Y and Anaya JM: Convalescent plasma in Covid-19: Possible mechanisms of action. *Autoimmun Rev* 19(7): 102554, 2020. PMID: 32380316. DOI: 10.1016/j.autrev.2020.102554
  - 25 Murphy M, Estcourt L, Grant-Casey J and Dzik S: International survey of trials of convalescent plasma to treat COVID-19 infection. *Transfus Med Rev* 34(3): 151-157, 2020. PMID: 32703664. DOI: 10.1016/j.tmr.2020.06.003
  - 26 Sun M, Xu Y, He H, Zhang L, Wang X, Qiu Q, Sun C, Guo Y, Qiu S and Ma K: A potentially effective treatment for COVID-19: A systematic review and meta-analysis of convalescent plasma therapy in treating severe infectious disease. *Int J Infect Dis* 98: 334-346, 2020. PMID: 32634589. DOI: 10.1016/j.ijid.2020.06.107
  - 27 Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, Chen Q, Zhang L, Zhong Q, Zhang X, Zou Y and Zhang S: Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome Coronavirus 2 infection. *Chest* 158(1): e9-e13, 2020. PMID: 32243945. DOI: 10.1016/j.chest.2020.03.039
  - 28 Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y and Liu L: Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 323(16): 1582-1589, 2020. PMID: 32219428. DOI: 10.1001/jama.2020.4783
  - 29 Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Béziat V, Manry J, Shaw E, Haljasmägi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Le Pen J, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, Abers MS, Aiuti A, Casari G, Lampasona V, Piemonti L, Ciceri F, Bilguvar K, Lifton RP, Vasse M, Smadja DM, Migaud M, Hadjadj J, Terrier B, Duffy D, Quintana-Murci L, van de Beek D, Roussel L, Vinh DC, Tangye SG, Haerynck F, Dalmau D, Martinez-Picado J, Brodin P, Nussenzweig MC, Boisson-Dupuis S, Rodríguez-Gallego C, Vogt G, Mogensen TH, Oler AJ, Gu J, Burbelo PD, Cohen JJ, Biondi A, Bettini LR, D'Angio M, Bonfanti P, Rossignol P, Mayaux J, Rieux-Laucat F, Husebye ES, Fusco F, Ursini MV, Imberti L, Sottini A, Paghera S, Quiros-Roldan E, Rossi C, Castagnoli R, Montagna D, Licari A, Marseglia GL, Duval X, Ghosn J, HGID Lab, NIAID-USUHS Immune Response to COVID Group, COVID Clinicians, COVID-STORM Clinicians, Imagine COVID Group, French COVID Cohort Study Group, Milieu Intérieur Consortium, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, Tsang JS, Goldbach-Mansky R, Kisand K, Lionakis MS, Puel A, Zhang SY, Holland SM, Gorochov G, Jouanguy E, Rice CM, Cobat A, Notarangelo LD, Abel L, Su HC and Casanova JL: Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 370(6515): eabd4585, 2020. PMID: 32972996. DOI: 10.1126/science.abd4585
  - 30 Roman-Filip C, Catană MG, Bereanu A, Lăzăroae A, Gligor F and Sava M: Therapeutic plasma exchange and double filtration plasmapheresis in severe neuroimmune disorders. *Acta Clin Croat* 58(4): 621-626, 2019. PMID: 32595246. DOI: 10.20471/acc.2019.58.04.08
  - 31 Sava M, Catană M and Roman-Filip C: The importance of early neurorehabilitation in the recovery of post-vaccination Guillain-Barre syndrome - a case report. *Balneo Research Journal* 10(10.2): 98-102, 2019. DOI: 10.12680/balneo.2019.246
  - 32 Bandopadhyay P, D'Rozario R, Lahiri A, Sarif J, Ray Y, Paul SR, Roy R, Maiti R, Chaudhuri K, Bagchi S, Maiti A, Perwez MM, Sarkar BS, Roy D, Chakraborty R, Vasudevan JS, Sharma S, Biswas D, Maiti C, Saha B, Bhattacharya P, Pandey R, Chatterjee S, Paul S and Ganguly D: Nature and dimensions of systemic hyperinflammation and its attenuation by convalescent plasma in severe COVID-19. *J Infect Dis* 224(4): 565-574, 2021. PMID: 34398242. DOI: 10.1093/infdis/jiab010

Received January 26, 2022

Revised February 18, 2022

Accepted February 22, 2022