

Coronavirus Pandemic

A practical approach for the compassionate use of convalescent plasma in patients with severe COVID-19 in developing countries

Brenner Elías Sabando Vélez¹, Carlos Plaza Meneses^{1,2}, Miguel Felix^{3,4}, Emanuel Vanegas^{3,4}, Valeria L Mata^{3,4}, Horacio Romero Castillo⁵, Jorge W Oliveros Alvear¹, Enrique Boloña², María Alejandra Posligua¹, Luis Renato Layedra Bardi¹, Carlos Vera Paz^{3,4}, Ivan Cherez-Ojeda^{3,4}

¹ *Departamento de Hematología, Hospital Luis Vernaza, Guayaquil, Ecuador*

² *Clinica Guayaquil, Guayaquil, Ecuador*

³ *Universidad Espíritu Santo, Samborondón, Ecuador*

⁴ *Respiralab Research Group, Respiralab, Guayaquil, Ecuador*

⁵ *Icahn School of Medicine at Mount Sinai, New York, NY, United States*

Abstract

The COVID-19 pandemic has affected 187 countries, representing a global public health problem. The increasing number of critically ill patients and deaths have fueled a desperate search for treatments that can halt the course of the disease. Currently, there are several experimental therapies with demonstrated in vitro activity against COVID-19 used in clinical practice, including hydroxychloroquine, remdesivir, interleukin-6 pathway inhibitors, and convalescent plasma; however, to date no agent has proven efficacy against COVID-19. In the case of convalescent plasma, this therapy consists in obtaining neutralizing antibodies from previously infected individuals by plasmapheresis and administering them to patients with severe disease. Recently, the use of convalescent plasma has shown promising results in preliminary studies, with case series reporting a decrease in temperature, and viral load, as well as improvement in clinical parameters among patients receiving this treatment. However, there are still unmet needs regarding the safety profile, tolerability, dosage, and timing this therapy should be given. Based on this, the objective of our study was to develop and propose a practical approach for the compassionate use of convalescent plasma for the treatment of patients with severe COVID-19, given the constraints and limitations of developing countries. We encourage health professionals in developing countries to use the current evidence and approaches to experimental treatments for patients with COVID-19, adapting them to their conditions, and always based on a thorough risk-benefit evaluation for each patient, and whenever possible to design and promote the much needed research in this field.

Key words: coronavirus; COVID-19; developing countries; plasmapheresis; convalescent plasma.

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Introduction

At the end of 2019, a cluster of pneumonia cases of unknown origin were reported in the city of Wuhan, China, with a seafood market identified as the potential initial source for this outbreak [1,2]. After several days of research, the entire genome of the virus called SARS-CoV-2 was identified, promptly initiating the production of diagnostic tests [3,4]. At the same time the virus was reported in several nearby countries, leading to the WHO (World Health Organization) to declare the current outbreak, COVID-19, as a public health emergency of international concern. Unfortunately, due to its epidemiological and biological characteristics which make it highly contagious, along with the clinical severity developed by some patients, COVID-19 was officially named as a pandemic around mid-March of 2020 [2,5].

Clinical symptoms and severity are varied, but affected patients mainly present with fever, cough, shortness of breath, diarrhea, and confusion [5,6]. The spectrum of symptomatic infection ranges from mild to critical, with roughly 80% of symptomatic patients presenting with mild disease [7]. However, several studies suggest that older patients, with associated comorbidities such as cardiovascular disease, type 2 diabetes, chronic kidney and lung disease, and cancer, are at higher risk for severe and life-threatening disease [7–10]. At the time of writing, there are 187 countries affected worldwide, with almost 4 million confirmed cases and over 280,000 deaths attributable to the virus [11].

The increasing number of critically ill patients and deaths has fueled a desperate search for potential treatments, including the use of experimental agents,

Table 1. Suggested criteria for plasma donor selection.

Requirements
1. Pre-diagnosis of COVID-19 documented by laboratory tests.
2. If possible, a negative nasopharyngeal swab and blood sample PCR. Otherwise, a documented evidence of complete resolution of symptoms of at least 14 days before donation [27,28].
3. If possible, the measurement of neutralizing antibodies should be at least 1:160 [22], and optimally > 1:320 [29]
4. Compatible ABO donors with negative anti-HLA antibodies, preferably male.
5. Hematocrit > 36% at the time of donation.

investigation of targeted therapies, and the development of vaccines [6,12]. Currently, there are several agents with demonstrated in vitro activity against COVID-19 used in clinical practice, including hydroxychloroquine, remdesivir, interleukin-6 pathway inhibitors, and convalescent plasma; however, to date no agent has proven efficacy against COVID-19 [13]. In the case of convalescent plasma, preliminary studies have shown a decrease in body temperature, decrease in viral load, and clinical improvement among patients receiving this therapy [12,14–16]. Furthermore, there is previous evidence and experience with the use of convalescent plasma for other viral diseases, such as Ebola, MERS, SARS, and H1N1 influenza [17,18].

The application of convalescent plasma in patients with severe COVID-19 disease is an experimental treatment, consisting of acquiring neutralizing antibodies by plasmapheresis from previously infected individuals, and administering them to patients with severe disease. Although it has a theoretical basis, to date the evidence is limited [16]. However, the health crisis in which we find ourselves demands an additional effort to seek treatments that can reduce mortality from COVID-19, and that are economically and technically applicable in our setting. Based on these findings, the

objective of this letter to the Editor is to propose a practical approach for the compassionate use of convalescent plasma in patients with severe COVID-19 in developing countries.

Methodology

For the application of convalescent plasma, we suggest the fulfillment of three requirements: i) adequate selection of the donor, ii) adequate selection of the patient receiving treatment, iii) availability of equipment and procedural norms.

Suggested criteria for donor selection

The selection of the donor is of vital importance, as is the selection of the candidates to receive the treatment. We suggest the following criteria (Table 1).

Criteria for choosing candidates to receive convalescent plasma

Due to the lack of a validated severity scale for patients with COVID-19, and the limited evidence surrounding this treatment, we suggest limiting the use of convalescent plasma to patients who have risk factors for severe disease (Table 2).

Table 2. Suggested risk factors for severe COVID-19 disease.

Parameter	Descriptor
Epidemiological	- Age >55 years - Pre-existing lung disease - Chronic kidney disease - Pre-existing cardiovascular disease (including hypertension) - Transplant history, use of immunosuppressive treatment, or uncontrolled HIV
Clinical	- Respiratory rate > 24 - Oxygen saturation < 90% at room air - Heart rate > 125 beats per minute - PaFi ≤ 300 - Pulmonary infiltrates >50% in 24-48 hours
Laboratory	- D-dimer > 1000 ng/mL - CPK > double the limit of normal - CRP > 100 - Lymphocyte count < 0.8 10 ⁹ /L at admission - LDH > 245 U/L - Elevated troponin - Ferritin > 300 ug/L

HIV: human immunodeficiency virus; CPK: creatine phosphokinase; CRP: C-reactive protein; LDH: lactate dehydrogenase; References: [7,8,30–33].

Availability of equipment and procedural rules

Once the ideal candidates to donate and receive plasma have been identified, and the relevant clinical assessments performed for each; the risks and benefits of the intervention should be explained to both parties, and an informed consent should be obtained before starting the procedures.

To obtain the donor plasma, we suggest the application of productive plasmapheresis following the most recent guidelines [19,20], in which at least 4 test tubes are obtained, consisting of 3 dry tubes, one tube with EDTA, as well as 600-800 cc of plasma per donor:

- a) The dry tubes will be sent to undergo the usual serology procedures in blood banks (hepatitis B and C, HIV, syphilis, Chagas, etc.) [20].
- b) The EDTA tube will be used to determine group, factor, and Coombs test.
- c) The plasma obtained will be stored in a freezer at a temperature between -20 to -40 degrees Celsius.
- d) If possible, all blood products should undergo a pathogen reduction technique [21].
- e) The personnel who carry out these procedures must comply with all biosafety measures.

For the transfusion of convalescent plasma, we suggest the following:

- a) The transfusion should only be performed once the donor's serology tests results are obtained and the ABO compatibility with the recipient has been confirmed.
- b) Although there is still no consensus on the optimal dose, consider administering 200 to 600 mL of plasma (corresponding to roughly 8-10 ml/kg, with a maximum dose of 600 mL) once per day, and up to three consecutive doses [22].
- c) The intravenous infusion must be slow while monitoring the patient to detect any type of acute transfusion reaction, particularly during the first 15 to 20 minutes.
- d) The transfusion should be completed within 1 to 4 hours from the start of monitoring and recording of vital signs.

Monitoring and follow-up of patients receiving treatment

There is no definitive consensus on the parameters for the prospective evaluation of this treatment. However, we suggest monitoring the clinical and laboratory parameters indicated in Table 2.

Discussion

The objective of this letter to the Editor was to propose a practical approach, based on the limited

evidence available, for the compassionate use of convalescent plasma in patients with severe COVID-19 in developing countries. The effect of this pandemic on healthcare systems worldwide is staggering, and we hypothesize this to be even more severe in low-resource settings and developing countries. For instance, Ecuador has been one of the countries in Latin America most affected by COVID-19, registering to this date almost 30,000 confirmed cases and 2127 deaths [23]. Certain impediments, such as inability to meet demand for confirmatory COVID-19 testing, and a complete saturation of the public healthcare system, leads to an underestimation of the real number of cases and deaths related to the virus [24]. Even though the Ecuadorian government has taken rigorous mobilization measures, such as air restrictions and a national quarantine, cases and fatalities continue to increase exponentially. This, combined with the fact that almost half of confirmed cases have been diagnosed among healthcare workers, further decreases the capacity of the healthcare system to respond to the pandemic [25].

In a recent study by Duan and colleagues, patients with COVID-19 who received one dose of convalescent plasma were found to have an improvement in clinical symptoms within 3 days, as well as the disappearance of viremia in 7 days, and an increase in the titers of neutralizing antibodies [26]. In another case series of 5 critically ill patients receiving this therapy, body temperature normalization, improvement in Sequential Organ Failure Assessment (SOFA) scores, and increase in Pao₂/Fio₂ were found following the plasma transfusion [16]. Despite the current limited evidence, there are still unmet needs regarding the use of convalescent plasma for patients with severe COVID-19, in particular the need to determine the safety profile, tolerability, and possible mortality reduction. Furthermore, there is no clear consensus on the dosage, and timing this therapy should be given.

Because of the speed with which the virus has spread worldwide, collaboration between academic and government institutions is necessary to facilitate research and to find solutions to reduce the morbidity and mortality of this condition. In the case of the United States, regulatory agents, including the Food and Drug Administration (FDA), have already published guidelines for various experimental treatments, and the consensus to this date is to refer whenever possible affected patients for clinical trials [27]. These conditions, however, are difficult to comply with in developing countries, where the lack of funding for research, as well as technical and procedural limitations, constrain the capacity to conduct large and

complex research projects. Despite these limitations, we encourage health professionals in developing countries to use the current evidence and approaches to experimental treatments for patients with COVID-19, adapting them to their conditions, and always based on a thorough risk-benefit evaluation for each patient, and whenever possible to design and promote the much needed research in this field.

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Corresponding author

Iván Chérrez-Ojeda
Universidad Espíritu Santo
Km. 2.5 Vía La Puntilla
0901-952 Samborondón
Ecuador.
Phone: +5934511455
Email: ivancherrez@gmail.com

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