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REVIEW ARTICLE

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Indications and contraindications for convalescent plasma therapy in COVID-19 — a mini-review

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ABSTRACT

Introduction: Convalescent plasma (CP), containing neutralizing antibodies (NAbs), is considered to be potential COVID-19 therapy. Favorable effects of passive administration of NAbs were already demonstrated for other viruses, including SARS and MERS viruses belonging to the Coronaviridae family.

Aim of the study: This review aims to present and systematize current indications and contraindications for COVID-19 CP therapy.

Material and methods: A systematic review of the literature was conducted using Pubmed, Wiley Online Library, Science Direct, and Medline databases.

Results: At present, there is no strong evidence from randomized clinical trials to create universal eligibility criteria for CP treatment. Based on conducted studies and expert opinions, it is considered reasonable to administer CP to patients with a severe course of infection or with a risk of such a course, in the early stages of infection, optimally during 72h from symptom onset. Regarding contraindications to CP therapy, to a large extent, they are the same as commonly known and accepted contraindications for transfusion of routinely obtained plasma. Additionally, CP donations are subjected to obligatory pathogen reduction (PR). The exposure to photosensitizing substances, remaining in the CP following PR, might be associated with adverse effects.

Conclusions: CP transfusion should not be a stand-alone treatment but should be used in clinical trials as a complement to other available COVID-19 therapies if possible. Patients should be informed that the effectiveness of CP has not been sufficiently proven, and that therapy is dependent on the physician's decision and the availability of CP.

Key words: convalescent plasma, COVID-19, pathogen reduction, IgG, SARS-CoV-2

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Introduction

Currently, intensive research is being carried out around the world to develop an effective and safe method of treating patients diagnosed with COVID-19. One potential therapy is the transfusion of plasma from convalescents who were infected with the SARS-CoV-2 virus and developed virus-neutralizing antibodies (NAbs) [1–3]. Favorable effects of passive administration of immune antibodies were demonstrated in relation to other viruses which were etiological factors of the biggest pandemics of recent years, including Ebola [4], SARS [5, 6], and MERS [7] viruses belonging to the Coronaviridae family, and influenza viruses A H1N1 [8] and A H5N1 [9].

The basis of the therapeutic effect of convalescent plasma (CP) transfusion is the ability of antibodies to neutralize the virus. The essence of neutralization is the attachment of antibodies to specific epitopes present on the surface of viral particles, which disrupts the replication cycle and thus reduces the infectivity of the virus. However, it has not been proven whether the antibody's binding to any viral epitope is sufficient to prevent infection, or whether neutralization occurs only

after the antibody has attached to a specific site on the viral surface [10]. In addition, antibodies can exhibit the ability to bind to viral receptors present on the surface of cells of an infected organism. This stops the penetration of the virus into the cell but does not neutralize the virus itself which remains fully functional [11]. Research on the molecular structure of SARS-CoV-2 further indicates the presence of multiple genotypes, primarily of types 1 and 2 [12]. Therefore, from a clinical point of view, NAbs capable of recognizing epitopes present on different viral genotypes seem to be the most desirable. The results of analyses conducted during the Ebola virus pandemic showed that the effectiveness of therapy with CP was related to the concentration of antibodies in plasma obtained from the donors [13]. Therefore, it is recommended to use COVID-19 CP with a high NAbs titer, most often defined as a level above 1:160 [14, 15]. Since the determination of NAbs titer is laborious, technically difficult, and requires an III-degree biosafety laboratory, enzyme immunoassays are commonly used, whose results seem to correlate well with the NAbs titer [16, 17]. The significance of titer and the role of NAb formed in response to a SARS-CoV-2 virus infection remains a subject of further research and scientific reports [18, 19].

Therefore, in the face of the global COVID-19 pandemic, the transfusion of CP containing the appropriate titer of anti-SARS-CoV-2 antibodies, administered at the optimal dose and stage of disease, may have a beneficial therapeutic effect in patients diagnosed with COVID-19, both in an early phase and at an advanced stage of the disease [20, 21].

Leading global health agencies, including the U.S. Food and Drug Administration (FDA) and the European Commission, have issued recommendations indicating an urgent need for further research and clinical trials using CP to obtain information to help determine the therapeutic indications and safety profile of this blood component. Clinical centers from all over the world, including European centers (e.g. in the Netherlands, Spain, and France), are responding to this call and are designing and implementing clinical trials involving the collection and clinical use of CP (a complete list of clinical trials with the use of convalescent plasma, updated by the NIH, is available at the website https://clinicaltrials.gov/ct2/home).

This review aims to present and systematize current indications and contraindications for CP therapy.

Material and methods

A systematic review of scientific reports was conducted using Pubmed, Wiley Online Library, Science Direct, and Medline databases. The bibliography of individual publications included in this study was also analyzed. Additionally, the positions of societies and opinions of experts dealing with clinical transfusion medicine were taken into account.

Indications for convalescent plasma therapy

At present, there are no universal eligibility criteria for convalescent plasma treatment. Based on information from existing studies and expert opinions, it is considered reasonable to administer plasma containing anti-SARS-CoV-2 antibodies to COVID-19 patients with a severe course or with a risk of a severe course of the disease, or in life-threatening conditions [3, 20–22]. The conducted studies indicate that the effectiveness of CP therapy, both in inpatient and outpatient settings, largely depends on the time of transfusion in relation to the duration of symptoms and should be initiated within the first 9 days of the onset of symptoms, ideally within 72 hours [23–25]. The criteria recommended for the assessment of clinical status of a patient diagnosed with COVID-19 as a basis for initiating convalescent plasma therapy are summarized in Table 1. Additional criteria recommended when qualifying patients for convalescent plasma therapy are summarized in Table 2.

Plasma containing anti-SARS-CoV-2 antibodies should not be used in COVID-19 patients with a disease duration of more than 3 weeks. An exception to this rule are patients with an impaired immune response due to concomitant lymphopenia, identified in observational study reports as a risk factor for prolonged hospitalization and increased mortality [26]. This leads us to believe that convalescent plasma therapy may be of clinical benefit in this group of patients. Table 3 presents criteria helpful in deciding whether to initiate therapy in patients with prolonged SARS-CoV-2 infections.

Table 1. Assessment of clinical status during qualification for therapy

Severe health condition*	Life-threatening health condition*
Dyspnea	Respiratory failure
Respiratory rate ≥ 30/min	Septic shock
Blood saturation ≤ 93%	Multi-organ failure
PaO2/FiO2 < 300	
Lung infiltration > 50% in 24 to 48 hours	

*at least one of the specified criteria is required. FiO2 — fraction of inspired oxygen; PaO2 — partial pressure of oxygen

Table 2. Additional criteria recommended when qualifying for the therapy

Hospitalization due to a severe course of the disease or risk of such course
Hospitalization without a severe or critical course of COVID-19 if: • the patient remains in a state of immunosuppression • rapid progression of lung lesions is observed
Providing informed consent for the administration of plasma with anti-SARS-CoV-2 antibodies
Laboratory-confirmed diagnosis of COVID-19: • the RT-PCR assay remains the recommended diagnostic test • nasopharyngeal swab remains the recommended biological material for testing • alternative materials include throat swab, nasal cavity swab, nasal vestibule swab, nasopharyngeal lavage/aspirate • in patients on mechanical ventilation, bronchoalveolar lavage or brush swabs taken during bronchial fibroscopy may be of diagnostic value

RT-PCR — reverse transcription polymerase chain reaction

Table 3. Criteria for initiating therapy in patients with prolonged COVID-19

Duration of illness exceeding 3 weeks
Persistent positive results of tests for the presence of SARS-CoV-2 genetic material
Low titer of SARS-CoV-2 virus-neutralizing antibodies (or specific IgG antibodies) in quantitative assays

Table 4. Contraindications to plasma transfusions

Absolute contraindications	**Relative contraindications**
Congenital severe IgA deficiency* (risk of anaphylactic shock)	Isolated IgA deficiency** • not fulfilling the criteria for severe IgA deficiency*** • in the course of autoimmune diseases***
Previous history of severe allergic reactions related to plasma transfusion (anaphylactic shock)	Previous history of mild post-transfusion allergic reactions associated with plasma transfusion
	History of allergic reactions to plasma proteins or sodium citrate
	Prophylactic plasma transfusion in acute liver failure to supplement coagulation factors,
	Prophylactic plasma transfusion before liver biopsy, paracentesis, thoracic puncture, or central venous line insertion in patients with liver failure
	Disseminated intravascular coagulation without coagulopathy and/or without bleeding
	Volumetric substitution
	Parenteral nutrition
	Hypoproteinaemia
	Correction of congenital or acquired coagulation factor deficiencies in the absence of symptomatic bleeding

*Severe deficiency defined as serum IgA levels < 0.05 mg/dL in patients over 4 years of age with normal serum IgG and IgM levels, and after excluding other (e.g. drug-induced, post-infectious, neoplastic) causes of hypogammaglobulinemia (25)
**A deficiency defined as a serum IgA level < 7 mg/dL in patients over 4 years of age with normal serum IgG and IgM levels, and after excluding other (e.g. drug-induced, post-infectious, neoplastic) causes of hypogammaglobulinemia (e.g. drug-induced, post-infectious, neoplastic) (26)
***A decision on plasma therapy should be made individually for each patient following an analysis of potential benefits and risks

Contraindications and adverse effects of convalescent plasma therapy

Contraindications and adverse effects of convalescent plasma therapy are, to a large extent, the same as commonly known and accepted contraindications to transfusion of routinely obtained plasma. It is, therefore, very important that clinicians who make transfusion decisions are reminded and aware of relevant contraindications to avoid adverse effects of planned therapy. Contraindications to plasma transfusion are presented in Table 4.

Currently, plasma donations from convalescents are subjected to obligatory reduction of pathogens, usually using photochemical and photodynamic inactivation methods. After the inactivation process, filters are used

Table 5. Contraindications and adverse effects associated with pathogen reduction of plasma

Photosensitising substance	Contraindications and possible adverse effects
Methylene blue	• History of sensitization reactions to methylene blue • Patients with diagnosed/suspected glucose-6-phosphate dehydrogenase deficiency (impaired ability to metabolize methylene blue)
Amotosalen	• History of allergic reactions to amotosalen or other compounds of the psoralen group • Neonates undergoing phototherapy (risk of skin erythema)
Riboflavin	• History of allergic reactions to riboflavin (very rare)

Table 6. Contraindications to plasma transfusion specific to convalescent plasma

Concomitant bacterial infection
Active thrombosis
Short expected survival time
Multi-organ damage
Lack of informed consent by the patient

to remove methylene blue and amotosalen, but small amounts of these substances remain in the final product for clinical use. Riboflavin, a physiologically occurring compound, does not need to be removed from the final product (it is associated with a characteristic yellow coloration of the plasma, not affecting the course and the safety of a transfusion). Exposure to photosensitizing substances remaining in the plasma is associated with potentially adverse effects. Contraindications and adverse effects associated with plasma inactivation are summarized in Table 5. Additionally, there are specific contraindications to convalescent plasma transfusion related to comorbid conditions or legal considerations related to experimental therapy. These are summarized in Table 6.

Conclusions

This review summarizes indications and contraindications for COVID-19 CP therapy. Convalescent plasma transfusion should not be a stand-alone treatment, but complementary to other COVID-19 therapies. Patients should be informed that the efficacy of this treatment method has not been sufficiently proven and that the use of convalescent plasma will depend on the physician's decision and the availability of plasma. It is recommended to use plasma with anti-SARS-CoV-2 antibodies as part of prospective (preferably randomized) clinical trials to closely monitor the patients and to provide data on the use and effects of plasma treatment to the blood donation center from which the transfused plasma originated.

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