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An EU programme of COVID-19 convalescent plasma collection and transfusion

Guidance on collection, testing, processing, storage, distribution and monitored use

This document has been endorsed by the Competent Authorities for Substance of Human Origin Expert Group (CASoHO E01718) following consultation of the competent authorities for blood and blood components and by the European Centre for Disease Prevention and Control. While this document is not legally binding, it aims to facilitate a common approach across EU Member States to the donation, collection, testing, processing, storage, distribution and monitoring of convalescent plasma for the treatment of COVID-19. This document is without prejudice to the requirements of the Union blood legislation, any more stringent national measures in place at Member State level and national requirements on the use of this treatment, all of which continue to apply. This guidance is updated as needed, in line with scientific developments. **19 June 2020**
Version 2.0

Background

Plasma collected from patients that have recovered from an infectious disease has been transfused over many decades for the prophylaxis and/or treatment of various infectious diseases although the evidence of its effectiveness and safety is mostly limited to empirical reports. Referred to as convalescent plasma, it can also be used to manufacture immune globulin concentrates (plasma-derived medicinal products). During a rapidly expanding outbreak of a viral infection, large populations of susceptible persons may become ill early in the event, prior to availability of effective vaccines and antiviral therapies. As highlighted by the WHO Blood Regulators Network[1], an organised programme to collect convalescent plasma or serum from disease survivors could provide a

[1] WHO Blood Regulators Network, Position Paper on Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus September 2017

potentially valuable empirical intervention while data on effectiveness and safety of its use are being gathered through structured clinical trials.

The COVID-19 pandemic is a clear situation where plasma from recovered patients might be a valuable resource to support the disease treatment within randomised or case-control clinical trials or observational studies of plasma transfusion and in the development of a plasma-derived medicinal products. The use of convalescent plasma for prophylactic treatment of 'at-risk' population groups is also a possibility in the future but is not addressed in this document.

The first version of this document, published on 8 April 2020 recommended that transfusion of COVID-19 convalescent plasma, as an immediately available experimental therapy with low risk, should be considered as an urgent priority and its outcome monitored. This was based on data from the SARS outbreak[2], and preliminary data from China for COVID-19[3],[4],[5],[6] suggesting that the treatment might be useful, particularly while effective medicinal products or vaccines are still under development and testing, although robust scientific evidence and solid haemovigilance data were still lacking. This recommendation is now reinforced by early data from 5000 transfusions in the USA, in the FDA 'expanded access' framework, confirming that that these transfusions in hospitalized patients with COVID-19 have a high level of safety[7] and a preliminary report in a group of 39 patients compared with case controls in Mount Sinai Hospital, New York, that indicates clinical effectiveness in non-intubated patients[8]. In the first publication of a randomised controlled trial of transfusion in severely or critically ill patients in China, treatment did not significantly improve the time to clinical improvement within 28 days, although the trial was terminated early and may have been underpowered to detect a statistically significant difference[9].

The effectiveness of convalescent plasma transfusion should continue to be tested, ideally in randomised case-control clinical trials; enrolment of patients in those trials should be favoured when they meet eligibility criteria. Several clinical studies, including randomised trials, are ongoing or have been approved in the EU and the USA. During the current COVID-19 crisis, given that randomised clinical trials will take significant time to produce results and will not be available for participation to all hospitals, it is proposed that monitored use in observational studies should also proceed in parallel. The evidence of safety justifies the use in emergency/compassionate situations, although it is recommended that outcome monitoring is performed for all patients treated in all contexts.

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[2] Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-46.

[3] Chen et al. Convalescent plasma as a potential therapy for COVID-19 Lancet Infect Dis Online Feb 27, 2020

[4] Duan et al. The feasibility of convalescent plasma therapy in severe COVID19 patients: a pilot study PNAS April 28, 2020 117 (17) 9490-9496; first published April 6, 2020.

[5] Shen et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. JAMA March 27, 2020.

[6] Editorial Roback and Guarner, Convalescent Plasma to Treat COVID-19 Possibilities and Challenges JAMA, March 27, 2020.

[7] Joyner M, Wright RS, Fairweather D, Senefeld J, Bruno K, Klassen S, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. medRxiv. 2020:2020.05.12.20099879.

[8] Liu STH, Lin H-M, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe COVID-19: A matched control study. medRxiv. 2020:2020.05.20.20102236

[9] Ling L 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 published online June 3 2020.

Objectives, scope and EU added value

This document proposes to bring together the resources of the EU competent authorities for blood and blood components, the European Centre for Disease Prevention and Control, EU blood establishments and the European Commission to face the challenge of responding to the COVID-19 crisis by supporting the development of antibody-based treatment options. It aims to launch a coordinated and effective approach to the collection of convalescent plasma across the EU, supporting the possibilities for the treatment of acutely ill patients (or patients at risk of becoming acutely ill) with the plasma within observational studies, in randomised and case-controlled clinical trials and for emergency use, and in the longer term, for the development of immune globulin concentrates by industry.

EU-wide collaboration on establishing common protocols for donor recruitment, donation and gathering outcome data on a large scale will support the demonstration of safety and quality of convalescent plasma for transfusion. Current provisions and standards for the collection, testing, processing, storage and distribution of blood and blood components should be applied in these circumstances, including the application of the principle of voluntary unpaid donation, in addition to the technical guidance defined in this document and any more stringent requirements defined at the Member State level.

Authorisation of convalescent plasma collection, testing, processing, storage and distribution

Blood establishments complying with the criteria described below for **donation, collection, processing and testing** should be authorised by their competent authority to proceed, unless the Member State has put more stringent requirements in place or their existing authorisation already covers these activities for any plasma for transfusion, including convalescent plasma. This will allow the rapid creation of national and EU inventories of convalescent COVID-19 plasma. Authorisation should specify the intended use (therapeutic use in an approved study protocol (clinical trial, monitored access use or emergency use) or as a source material for production of specific immune-globulin concentrates). Quality and safety requirements for convalescent plasma are regulated by the competent authority for blood and blood components in the Member State.

Blood establishments that have been authorised for donation, collection, processing and testing that have also put in place systems for gathering outcome data to demonstrate safety and quality, as defined below, should also be authorised for convalescent plasma distribution for transfusion, unless the Member State has put more stringent requirements in place or their existing authorisation already covers this activity for any plasma for transfusion, including convalescent plasma.

Donor eligibility

Convalescent plasma donors should be recruited directly by the use of national registries of patients that were infected with COVID-19 and recovered, wherever such registries are in place. Alternatively, potential donors should be identified through collaboration with public health bodies or treating hospitals or through targeted donor recruitment strategies including, but not restricted to, (social) media calls. Personal data sharing strategies must comply with national and EU data protection rules. Blood establishments should approach potential convalescent plasma donors according to nationally agreed procedures. In addition to standard donor criteria for blood or plasma donation, the following criteria should be applied:

1. A prior diagnosis of COVID-19 documented by a positive RT-PCR or a positive test for anti-SARS-CoV-2 antibodies, whether the individual had symptoms or not. NAT and serology tests should be CE marked. Individuals that have not been tested but have a clear history of COVID-19 symptoms may also donate.
2. In general, 28 days should have passed since full recovery, or the end of preventive isolation, before donation proceeds.
3. A deferral period of 14 days could be applied in these circumstances:
   - after full recovery or preventive isolation if pathogen reduction of plasma will be applied during processing;
   - after laboratory evidence of viral RNA clearance from the upper respiratory tract (negative RT-PCR);
   - after a positive serology test for anti-SARS-CoV-2 antibodies in donors that never developed symptoms and never had a negative RT-PCR test result.
4. These deferral period recommendations can be adjusted in the light of accumulating evidence for the clinical significance of viral shedding beyond 14 days from recovery[10].
5. Donors without a history of blood transfusion and female donors who have never been pregnant or are tested and found negative for anti-HLA antibodies using a validated assay.
6. Informed consent in line with national/local policies and preferably addressing the existing uncertainties in the antibody level dynamics in convalescent plasma donors.

Collection, processing and storage

Donors will ideally donate plasma by plasmapheresis, but where that is not possible, whole blood can also be collected, with plasma separation in the blood establishment. The normal donation procedure should be followed including normal donation intervals for those donating more than once. For donors that donate more than once, antibody titres should generally be measured at every donation and donors should be deferred if there is evidence of potentially detrimental antibody depletion. If performing antibody titres is not possible, and until the evidence of antibody level dynamics in COVID-19 convalescent plasma donors is better understood, limiting repeat donations to a 3 month period after the first donation[11] would be a prudent precautionary intervention that may protect donors from the theoretical risk of reinfection.

Plasma obtained by plasmapheresis should be split before freezing into 2-3 separate units (e.g. 3x200 ml). Final products destined transfusion as convalescent plasma or for manufacture of a COVID-19 immunoglobulin product should be specifically labelled as COVID-19 Convalescent Plasma/Blood (or similar description)[12] and stored in a dedicated location. The processing that is routinely applied in the country or blood establishment for the preparation of plasma for transfusion should be applied[13]. Thus, pathogen reduction should be applied if it has been the normal practice in the blood

[10] Hartman WR, Hess AS, Connor J. Prolonged viral RNA shedding after COVID-19 symptom resolution in older convalescent plasma donors. medRxiv. 2020:2020.05.07.2009062

[11] This takes into account evidence from previous corona infections and hyper-immune plasma donation where antibody levels drop after 3-6 months.

[12] For ISBT 128 users, ICCBBA has issued a range of product description codes for Convalescent Plasma – COVID-19 and further codes are being processed in response to user requests. An up-to-date list of codes is available on the ICCBBA website. For users of other coding standards, the standards organisation should be contacted.

[13] Quarantining of plasma with retesting of donors is required in some Member States. It will not be possible to apply this for convalescent plasma for COVID-19.

establishment and should not be introduced for this particular blood component if not normally applied for plasma for transfusion[14].

Any serious adverse reactions in the donor should be notified to the competent authority without delay, in line with national and EU blood legislation.

Testing of donated plasma

It is strongly recommended that SARS-CoV-2 total antibodies or neutralizing antibody titers be measured in the specimen obtained from a donor before donation or from donated plasma after donation or after processing (including pathogen reduction). The volume of the specimen should be sufficient for repeat testing. CE marked or in-house tests that have been approved at the national level or validated by nationally recognized virology or public health institutions or laboratories should be used.

There is currently no robust scientific evidence to apply a strict cut-off for the neutralising antibody titer for the release of convalescent plasma for transfusion. Titers vary depending on the assay performance and a precise correlation with clinical efficacy is not proven. Depending on the assay used and the clinical protocol being followed, each programme should establish its own policy. The FDA proposes a threshold of 1:160 but notes that 1:80 might also be acceptable.

Where neutralising antibody titration is not yet available, plasma can be collected and frozen until release for use once the test has been performed on an archived sample and the result is available. When antibodies are not detected in the collected plasma, it cannot be considered for COVID-19 therapeutic purposes and should be made available for other standard uses (transfusion or fractionation). If there are surplus donations, with adequate antibody levels, after the current outbreak has subsided locally, they could be retained for possible future waves of infection. In emergency cases, where plasma is released for transfusion without any antibody testing, archived samples should be tested at a later date once testing is available.

It is advised that additional archive samples of the donated plasma are saved for reference studies, e.g. 10 x 0.5ml frozen aliquots from plasma samples taken at the time of donation.

For repeat plasmapheresis donations, services should collect plasma from donors with higher rather than lower titres, as collection capacity permits.

Distribution of COVID-19 convalescent plasma

Convalescent plasma should be distributed by blood establishments on the request of a hospital in the following circumstances:

- the specific patient has laboratory confirmed COVID-19;
- the patient has been hospitalised;
- the patient, or their legal representative, has given informed consent to transfusion with COVID-19 convalescent plasma.

[14] The risks associated with a significant change to processing methods at this time do not appear to be justified by a benefit of introducing pathogen inactivation at this time.

The uncertainty about the efficacy of convalescent plasma in treating people with COVID-19 should be communicated to potential recipients or their legal representatives, whether they are part of a clinical trial or of monitored use, to avoid fostering unfounded expectations and to ensure that prospective recipients or their legal representatives make informed decisions regarding treatment.

Blood services should aim to issue the components with the highest antibody titres available.

It is strongly encouraged that patients receiving convalescent plasma are entered into a trial or are monitored through sharing of coded data on the EU public access platform described below. Convalescent plasma for use in an approved randomised or case-controlled clinical trial should be distributed according to the protocol of that trial and, where relevant, in compliance with national legislation.

To demonstrate safety and quality and facilitate improvements to the collection, testing, processing and storage protocols, hospitals should agree to provide defined outcome data to the supplying blood establishment. The outcome data should at least include the following parameters:

1. Gender, age range (21 - 30, 31 – 40 etc.), body mass index range, co-morbidities
2. Transfusion time point (in days from disease onset)
3. Number, volume and anti-body titre (if evaluated) of transfused unit(s)
4. Therapies administered to the patient in parallel (other than supportive care)
5. Clinical symptoms and laboratory parameters– according to the disease progression scale (Annex 1) at the following time points:
    - Prior to transfusion
    - > 5 days after transfusion[15]
    - At discharge (if the patient survives)
6. Any serious adverse reactions or events possibly linked to the transfusion
7. Length of hospitalisation (if no death).

The outcome data listed above should be reported to blood establishments and, by them, to the EU platform to allow a comprehensive picture to be constructed at EU level. Data from controlled clinical trials shall be first analysed according to pre-defined analysis plan in the clinical trial protocol and published as soon as possible. In these circumstances, the minimum outcome data shown above should also be reported to the EU platform to allow meta-analysis in a larger dataset thereafter.

Serious adverse reaction and event (SARE) notifications by hospitals to blood establishments should also be proactively reported to the competent authority without delay, as well as being included in the annual EU SARE reporting exercise to the European Commission, whether the plasma has been transfused in a controlled clinical trial or an observational study.

Data reporting and aggregation at the EU level – The EU CCP Platform

The European Commission COVID-19 Convalescent Plasma (EU CCP) platform has been developed and hosts a database[16], in compliance with Data Protection Regulations 2016/679 and 2018/17/25, to

[15] The EU platform requests a follow-up assessment at weekly intervals after each transfusion.

support the monitoring of convalescent plasma donation and use. The platform has been designed in collaboration with the European Blood Alliance (EBA) and its deployment is ongoing. The EBA will be responsible for co-ordinating the data entry by all blood establishments across the EU and for carrying out scientific analysis of the data.

Submission of donation data

Access to the platform for the submission of data is provided by DG DIGIT to EBA co-ordinators and to contact persons in the participating blood establishments in EU/EEA countries. Blood establishments submit data on donations, including defined the donor parameters listed above. The Commission, DG DIGIT, will produce standard aggregated donation data reports for the public part of the website.

Submission of clinical outcome data

Blood establishments will gather the outcome data listed above from the user hospitals and enter it to the EU CCP platform. The Commission, DG DIGIT, will produce standard outcome data reports on for the public part of the website.

Access to EU data on COVID-19 convalescent plasma

In the interests of transparency and open science, aggregated data that is not donor or patient identifiable will be publicly accessible and the database will be linked to the Open Science Cloud space for COVID-19 under development by the European Commission, DG RTD. Standard reports and specific queries, including data aggregated by Member State, will be available for national competent authorities and blood establishments. This will allow regular evaluation of safety and effectiveness by authorities and professionals and support updating and improvement of collection, testing, processing storage and distribution protocols, as evidence emerges to support changes to the criteria defined here.

[16] EU Survey is used for Blood Establishment registration. The donation, transfusion and clinical outcome data collection, storage and analysis is performed in the Big Data Test Infrastructure (BDTI) which is part of the Connecting Europe Facility programme.

ANNEX 1: WHO Ordinal Scale for COVID-19 Clinical Improvement[17]

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

[17] WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. February 18, 2020, Geneva, Switzerland