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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 will be updated as needed, in line with scientific developments.

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Background

Plasma collected from patients that have recovered from an infectious disease has been used over many decades for a variety of different infectious agents[i], although evidence of its effectiveness and safety is mostly limited to empirical reports. Referred to as convalescent plasma, it can be transfused to patients fighting an infection or can 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[i], an organised programme to collect convalescent plasma or serum from disease survivors could provide a 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.

Transfusion of convalescent plasma, as an immediately available experimental therapy with low risk, should be considered as an urgent priority and its outcome monitored. Data from the SARS outbreak[ii], and preliminary data from China for COVID-19[iii],[iv],[v] suggest that the treatment has promise, particularly while effective medicinal products or vaccines are still under development and testing, although robust scientific evidence and solid haemovigilance data are still lacking. The safety and effectiveness of convalescent plasma transfusion should be tested ideally in randomised case-controlled clinical trials and enrolment of patients in those trials should be favoured when they meet eligibility criteria.

However, in the current COVID-19 crisis, and given that these 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 proceed in parallel[vi].

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 blood-based treatment options. It aims to launch a co-ordinated 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 or randomised and case-controlled clinical trials, 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.

Blood establishments that have put in place systems for gathering outcome data to demonstrate safety and quality, as defined below, should be authorised for convalescent plasma **distribution**, 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 treating hospitals. Personal data sharing strategies must comply with national and EU data protection rules. The following criteria for donor eligibility should be applied:

1. A prior diagnosis of COVID-19 documented by a laboratory test or a clear history of COVID-19 symptoms when testing was not available.
2. At least 14 days should have passed since full recovery or at least 14 days after laboratory evidence for viral RNA clearance from the upper respiratory tract. Asymptomatic, COVID-19 laboratory confirmed, persons may also donate convalescent plasma at least 14 days after the end of their preventive isolation or quarantine period (which is 14 days after testing positive). Blood establishments might delay the timing of plasma collection when findings regarding the timing of optimal and maximal antibody production in those who have recovered from COVID-19 become available.
3. Donors without a history of blood transfusion and female donors who have never been pregnant or are tested and found negative for anti-HLA/HPA/HNA antibodies using a validated assay. Standard donor criteria for blood or plasma donation must be met.
4. Informed consent.

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 by plasmapheresis more than once. Plasma obtained by plasmapheresis should be split before freezing into 2-3 separate units (e.g. 3x200 ml). Final products should be specifically labelled as COVID-19 Convalescent Plasma/Blood[1] 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[2]. Thus, pathogen reduction should be applied if it has been the normal practice in the blood establishment and should not be introduced for this particular blood component if not normally applied for plasma for transfusion[3].

Any serious adverse reactions in the donor should be notified to the competent authority without delay.

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[1] 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.

[2] 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.

[3] 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.

Testing of donated plasma

It is strongly recommended that defined SARS-CoV-2 neutralizing antibody titers be measured in the donated plasma. It is suggested that neutralising antibody titers should optimally be greater than 1:320, but lower thresholds might also be effective. Where such testing 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 the measured neutralizing activity in the collected plasma is considered to be too low, the plasma should be made available for other use (ideally fractionation). In the absence of neutralizing antibody testing, a test for the presence of anti-SARS-CoV-2 antibody should ideally be performed prior to release. 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.

If an adequate correlation between neutralizing activity and Elisa antibody testing were to be demonstrated, this could replace the test for neutralising antibodies.

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;
- has been hospitalised due to acute illness or a risk of acute illness;
- has given informed consent.

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

Blood services should aim to issue the components with the highest antibody titres available. The transfused dose of plasma should be adjusted to its neutralizing antibody titer and the plasma volume of the recipient.

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 database 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 (30-39, 40-49 etc.), co-morbidities
2. Transfusion time point (in days from disease onset)
3. Number, volume and anti-body titre 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
    - At discharge (if the patient survives)
6. Any serious adverse reactions or events possibly linked to the transfusion[4]
7. Length of hospitalisation (if no death).

The outcome data listed above should be reported to blood establishments and, by them, to the EU database 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 European Database to allow meta-analyis 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 European Commission, DG DIGIT, is developing and will host a database[5], in compliance with Data Protection Regulations 2016/679 and 2018/17/25, to support the monitoring of convalescent plasma donation and use. The database is being designed in collaboration with the European Blood Alliance (EBA). Once the database is live, the EBA will be responsible for co-ordinating the data entry by all blood establishments across the EU.

<u>Submission of donation data</u>

Access to the database for the submission of data will be provided by DG DIGIT to EBA co-ordinators and to contact persons in the participating blood establishments in EU/EEA countries. Blood establishments will submit coded data on donations, including defined the donor parameters listed

[4] In particular, the risk that passive transfer of antibodies might enhance the hyperinflammation, characteristic of severe COVID-19, cannot be ruled out and should be monitored.

[5] EU Survey will be used for data collection and the data storage and analysis will be performed in the Big Data Test Infrastructure (BDTI) which is part of the Connecting Europe Facility programme.

above. The Commission, DG DIGIT, will produce standard data reports on donations for the Commission, the competent authorities and the EBA.

Submission of clinical outcome data

Blood establishments will gather the outcome data listed above from the user hospitals and enter it to the Commission database. The Commission, DG DIGIT, will produce standard data reports on use and outcome for the Commission, the competent authorities and the EBA.

Access to EU data on convalescent plasma

In the interests of transparency and open science, 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 provided to national competent authorities and to the EBA. 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.

ANNEX 1: WHO progression scale

OMS Progression scale	Descriptor	Score
Uninfected	Uninfected; non viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
Ambulatory	Symptomatic; Independent	2
Ambulatory	Symptomatic; Assistance needed	3
Hospitalized : mild disease	Hospitalized; No oxygen therapy	4
Hospitalized : mild disease	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	6
Hospitalized : severe disease	Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200	7
Hospitalized : severe disease	Mechanical ventilation, (pO2/FIO2<150 OR pO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min)	8
Hospitalized : severe disease	Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR ECMO	9
Death	Dead	10

[i] WHO Blood Regulators Network, September 2017 https://www.who.int/bloodproducts/brn/2017_BRN_PositionPaper_ConvalescentPlasma.pdf?ua=1;
[ii] Chen etal. Convalescent plasma as a potential therapy for COVID-19 Lancet Infect Dis Online Feb 27, 2020
[iii] https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1 Duan et al. The feasibility of convalescent plasma therapy in severe COVID19 patients: a pilot study Preprint March 23, 2020
[iv] Shen et al. Treatment of 5 Critically Ill Patients with COVID-19 With Convalescent Plasma. JAMA March 27, 2020
[v] Editorial Roback and Guarner, Convalescent Plasma to Treat COVID-19 Possibilities and Challenges JAMA, March 27, 2020
[vi] FDA Investigational COVID-19 Convalescent Plasma - Emergency INDs March 24, 2020