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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. **1 December 2020 Version 3.0**

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 (hyper)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 potentially valuable empirical intervention while data on effectiveness and safety of its use are being gathered through randomised controlled clinical trials. In its interim guidance on the blood supply during the Covid-19 pandemic, published in July 2020 [2], WHO reiterates that COVID-19 convalescent plasma, as an experimental therapy, is appropriate for evaluation in clinical studies or as a starting material for the manufacture of experimental hyper-immune immunoglobulins. European Union competent authorities for blood and blood components, and European Centre for Disease Prevention and Control agree that 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 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-CoV-2 outbreak [3], and preliminary data from China for COVID-19 [4-7]suggesting that the treatment might be useful, particularly while effective medicinal products or vaccines were under development and testing, although robust scientific evidence and solid haemovigilance data were still lacking. This recommendation was reinforced in an updated version of this guidance published on 22 June 2020 when further evidence was available. In particular, early data from 5000 transfusions in the USA, in the FDA 'expanded access' framework had confirmed that these transfusions in hospitalized patients with COVID-19 had a high level of safety[8]. A preliminary report in a group of 39 patients compared with case controls in Mount Sinai Hospital, New York, had also indicated clinical effectiveness in non-intubated patients [9]. In the first publication of a randomised controlled trial of transfusion in severely or critically ill patients in China, treatment had not significantly reduced the time to clinical improvement within 28 days, although the trial had been terminated early and may have been underpowered to detect a statistically significant difference [10].

Since then, further evidence of safety and efficacy has been published. The early safety data from the US expanded Access Programme was confirmed based on 20,000 CCP transfusions [11]. In September 2020, ECDC summarised a review of 31 relevant clinical research articles and 62 review articles on evidence for efficacy at a meeting of EU blood competent authorities. This included four randomised controlled trials [12-15], four controlled non-randomised studies [16-19]; five retrospective matched cohort studies [20-24] and multiple cases series. These studies were considered together with data published from the US Expanded Access Programme [25] and by the US FDA [26] when they granted an Emergency Use Authorisation for transfusion with Covid-19 convalescent plasma and led to the following conclusions:

- Results from various types of clinical trials and expanded emergency use of COVID-19 convalescent plasma in the US showed the expected frequency of adverse transfusion reactions typical of plasma transfusion in other situations.
- These studies also suggest that the transfusion of CCP containing a higher titre of neutralizing antibodies applied earlier in the clinical course is potentially effective in reducing the mortality of hospitalized non-intubated patients with moderate or severe illness. Convalescent plasma may also accelerate viral clearance, decrease progression into the critical phase of disease and shorten the hospital stay of such COVID -19 patients.
- More evidence from randomized controlled trials is required to fully demonstrate the efficacy of this therapy and to determine the indication, dosing and optimal CCP product characteristics.

This was consistent with the findings of Joyner et al. [27] in a pre-published meta-analysis of 12 studies involving the treatment of severe COVID-19 patients with CP. It is noted, however, that only 3 of these studies were randomised controlled trials. Additionally, the Placid study [15], a randomised controlled trial showing a lack of efficacy of convalescent plasma transfusion, had not been published and was not included in the Joyner review. The Placid trial involved large numbers of patients but generally with low (or unmeasured) neutralising antibody titre (median 1:40). A Cochrane review (including studies up to August 19, 2020) concluded that the current evidence of efficacy is low to very low due to study limitations [28].

In the light of these developments, it is recommended that the effectiveness of convalescent plasma transfusion should continue to be tested, ideally in randomised controlled trials; enrolment of patients in those trials should be favoured when they meet eligibility criteria. Several clinical studies, including randomised trials, are ongoing. Going forward, evidence suggests that studies should focus on early transfusion of convalescent plasma with high neutralising antibody titres. 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.

Objectives, scope and EU added value

This document proposes to continue drawing on 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 COVID-19 convalescent 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 could 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.

A prior diagnosis of COVID-19 documented by a positive RT-PCR or a positive test for SARS-CoV-2 antigen or a positive test for SARS-CoV-2 antibodies, whether the individual had symptoms or not[1]. NAT and serology tests should be CE marked tests or in-house tests that have been approved at the national level or validated by nationally recognized virology or public health institutions or laboratories. Individuals that have not been tested but have a clear history of COVID-19 symptoms[2] may also donate.

A deferral period of at least 14 days should be applied after symptom resolution[3].
Prospective donors that had no clinical signs of the disease should be accepted for donation at least 14 days after:

- laboratory evidence of viral RNA clearance from the upper respiratory tract
  or
- being tested positive for the presence of anti-SARS-CoV-2 antibodies.

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 [29].

Donors without a history of blood transfusion and female donors who have never been pregnant, or have been tested and found negative for anti-HLA antibodies using a validated assay, are eligible.

Informed consent should be 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. Antibody levels should be measured at every donation and donors should be deferred if there is evidence of potentially detrimental antibody depletion.

Plasma for transfusion obtained by plasmapheresis should be split before freezing into smaller aliquots of at least 200 ml per unit. Final products destined transfusion as convalescent plasma or for

[1] It is noted that many Covid-19 Convalescent Plasma programmes no longer collect from donors that were asymptomatic as, generally, they have low antibody levels.
[2] To prevent that citizens use the blood service as a way of obtaining a Covid-19 test, some services may require certification of diagnosis by a medical doctor.
[3] Symptom resolution should be understood to include donors still showing some minor symptoms that may last for weeks or months such as anosmia or coughing.

manufacture of a COVID-19 immunoglobulin product should be specifically labelled as COVID-19 Convalescent Plasma/Blood (or similar)[4]. The processing that is routinely applied in the country or blood establishment for the preparation of plasma for transfusion should be applied[5]. 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[6]. The convalescent plasma should be given the same shelf-life as plasma that has been processed in the same manner.

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

Evidence now suggests that those donations that have high neutralising activity are the most likely to be effective [23, 25, 26). Therefore, SARS-CoV-2 antibodies should be measured in a sample obtained from a donor prior to or during donation or from donated plasma after donation or after all processing steps when pathogen reduction is applied. 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.

A virus neutralisation test or a binding antibody IgG test can be used to directly or indirectly determine *in vitro* the titre of neutralising antibodies in donated plasma. The most frequently employed methods for antibody detection are enzyme-linked immunosorbent assays (ELISA) or chemiluminescence enzyme immunoassays (CLIA). Salazar et al. [30] showed that titres of anti-Spike protein IgG antibodies (anti-spike ectodomain (ECD) and anti-receptor binding domain (RBD)) correlate well with titres of virus neutralising antibodies *in vitro*. Thus, ELISA may be used as a surrogate for neutralising antibody activity where a good correlation has been demonstrated for the assay[7].

It is noted that to comply with EU Directive 2020/739 [32], and in accordance with WHO interim recommendations on laboratory biosafety for COVID-19 laboratory procedures, non-propagative diagnostic laboratory work involving SARS-CoV-2 should be conducted at a facility using procedures equivalent to at least containment level 2. Propagative work (virus culture, neutralisation assays) involving infectious SARS-CoV-2 should be conducted at a containment level 3 laboratory with air pressure negative to the atmosphere.

When neutralising antibody titre determination is not yet available, plasma can be stored and tested retrospectively, but prior to release. When antibodies are not detected in the collected plasma, it

[4] 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.

[5] 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.

[6] 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.

[7] For example, the US FDA recommends using Ortho VITROS SARS-CoV-2 IgG test as a surrogate ELISA test [31]. The signal-to-cut-off (S/C) value of 12 or greater in this test corresponds to the titre of neutralising antibodies > 1:160. Based on this titre, FDA requires labelling of convalescent plasma units as High Titer COVID-19 Convalescent Plasma or Low Titer COVID-19 Convalescent Plasma.

should not be considered for COVID-19 therapeutic purposes and should be made available for other standard uses (transfusion or fractionation).

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

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, unless the plasma is supplied in the context of a clinical trial on early transfusion of non-hospitalised patients;
- the patient, or their legal representative, has given informed consent to transfusion with COVID-19 convalescent plasma.

The uncertainty about the efficacy of convalescent plasma in treating patients 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, while respecting the treatment and clinical trial protocols in place locally. An evidence-base for a minimal titre of neutralising antibodies with significant clinical efficacy of convalescent is limited. The US data described above, together with initial research [5, 6], suggests that a titre of ≥1:160 might be an appropriate threshold to apply but a definitive threshold is yet to be established in clinical trials. Therefore, each CCP programme should specify its threshold titre of neutralizing antibodies to allow for a correlation of antibody titre and patient outcome. High neutralising titre CCP should be used in preference to low titre in the treatment of COVID-19 patients. A suggested dose of high titer convalescent plasma is one unit; for low titer plasma, two units of convalescent plasma might be transfused. If two units are to be transfused they should be from different donors.

It is highly recommended 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 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 patient data to the supplying blood establishment. The patient 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 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[8]
- 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).

Further parameters, such as pre-transfusion anti SARS-CoV-2 antibody titer of the patient, might be added to this list, depending on local clinical protocols. It is highly recommended that the outcome data listed above 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[9], in compliance with Data Protection Regulations 2016/679 and 2018/17/25, to 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 is responsible for co-ordinating the data entry by all blood establishments across the EU and the Support-e Horizon 2020 consortium 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, produce standard aggregated donation data reports for the public part of the website.

Submission of clinical outcome data

Participating blood establishments 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. The Support-e Horizon 2020 project, led by EBA, conducts detailed analysis for publication.

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

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

[9] 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.

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.

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ANNEX 1: WHO Ordinal Scale for COVID-19 Clinical Improvement [33]

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