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Convalescent plasma, an apheresis research project targeting and motivating the fully recovered COVID 19 patients: A rousing message of clinical benefit to both donors and recipients alike

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This paper aims to make suggestions for a small step forward in both preventative and therapeutic measures against the Coronavirus disease 2019 (COVID 19) pandemic. This targeted strategy consists of using fully recovered COVID 19 Heroes, that is, brave volunteers, as the source of antibodies in plasma collected by plasmapheresis, plasma exchange, or substitution therapy for use in those populations in need of antibody. This would include use in critically ill COVID 19 patients and, as a preventative measure, in those at potential risk of infection as no vaccine is yet available. This would be a small step forward, while we are waiting to produce an effective, validated vaccine and witnessing increasing testing, self-isolation, contact tracing, tracing which are the two most effective current strategies [1,2].

In line with this concept, some methodological aspects of the use of the UVC sterilization of FFP/ cryoprecipitate-depleted FFP or immunoglobulins containing neutralizing antibodies for clinical use against COVID-19 are highlighted. The plasmapheresis procedure is, of course, particularly targeted to male donors, who consist of about 75 % of the COVID-19 population and who are able to undergo multiple double, or even triple plasmapheresis procedures. Moreover, as some of these donors have already been in an induced-hypercoagulable state and prone to thrombosis and DVT, this strategy will be partially aimed at improving their health with the use of citrate based anticoagulants and removal of high molecular weight viscous components which contribute to the untoward clinical effects of DVT. Similarly, recipients getting at least two doses of high affinity antibodies directed against COVID 19. The recipients of such a derived FFP-product would benefit from the antibodies which could neutralize the viral antigens even at very low concentration if present in the early stage [3].

Needless to emphasize that, conceptually, the safety of donors in such special cases is paramount. An additional bonus to donors is that, in these authors' experiences, many laboratory haemostatic abnormalities are often seen in critically ill COVID-infected patients, this is considered to be a very important clinical issue, in view of the high incidence of thrombotic events observed in this population, some with kidney failure and a fatal outcome. Repeated targeted plasmapheresis or plasma exchange of selected COVID-19 positive individuals would undoubtedly lower their state of hypercoagulability and normalize their hypercoagulability. So, this practice would be a double-edged sword with benefits for both donors and recipients alike [4].

Both the plasmapheresis collection process and plasma exchange are very well accepted clinical procedures in transfusion practice in countries that are equipped with modern mobile apheresis technologies. Such mobile and fully automated tools, using digital technology, will allow this well-established practice to be available for use, by either a nurse or trained phlebotomy technologist who might be able to run 6 donors under the supervision of a trained skilled clinician even in home care sites. Therefore, transfusion of plasma or its derived products containing immunoglobulin from patients who have fully recovered from COVID-19 will be an additional intervention to be used for those who are not able to defend themselves against this pandemic virus, in the absence of the

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relevant vaccine. While early infection is identified by modern and sensitive.

RNA based PCR testing, extensive community testing for levels of antibody will be required to find patients who will volunteer to help others by donating plasma. Meanwhile, the current concept of mass testing by sensitive and reliable PCR methodology, mass testing, tracking, tracing, testing, and the recently proposed strategy of segregating and isolating the older populations, who are more at risk of getting fatal infections will be perused with rigour, to reduce the current rise in deaths. These strategies are of particular relevance for the hospital front line staffs and in the home care sections. There is nevertheless an increase in fatalities in younger populations as this virus does not recognize age or race and individual variability appears to matter as to how an individual responds to viral infection and the possibility of the second wave of infection cannot be totally rule out yet.

Conceptually, the plasmapheresis therapeutic approach is based on well-established passive immunotherapy, as achieved successfully after Ebola Virus outbreak. The neutralizing ability of sars cov-2 immunoglobulins, that thought to be present in COVID-19 convalescent plasma, would follow the same principal of the passive immunotherapy. Moreover, such a therapeutic intervention can be considered as a true reflection of the precision transfusion concept, consisting of the use of the right product for the right patient in the right time and the right condition, with no risk but added health benefits to donors and recipients alike. We would like to emphasize that these individuals will often be at an elevated risk for thrombosis and VTE, hence an appropriate risk assessment at the same time will be warranted and plasmapheresis donations, with citrated anticoagulant, would enormously help in lowering their existing and or induced-hypercoagulability by COVID-19 [4].

In this context, it should be noted that the safety and efficacy of convalescent COVID-19 plasma as a treatment for COVID-19 is yet to be validated. However, even as an experimental therapy, in line with the first principal of all newer bioproducts for transfusion, one needs to be consistent with ethical and legal safeguards (informed consent of donors and patients, institutional approval, special labelling as an investigational product and compliance with applicable regulatory requirements). Moreover, COVID-19 plasma should be used in the context of an organized research study designed to determine its safety and efficacy in comparison with standard of care or other therapeutic interventions. Even if used empirically it is vital to ensure monitoring of patient outcomes including clinical and laboratory indicators of safety and efficacy to optimized/ maximize the knowledge that might be gained [5].

Currently, the collection process and transfusion of plasma derived from patients who have fully recovered from COVID-19 is of wide spread interest both nationally and internationally as the development of the infection and its propagation are pandemic. Therefore, using neutralizing anti- SARS COV-2 immunoglobulins that are present in COVID-19 convalescent plasma as such or after isolating its more enriched immunoglobulin portion is logically an interesting targeted therapeutic approach, acting on the same foundation of the well-established concept of passive immunotherapy.

Transfusion services and many other establishments with the appropriate skills in handling therapeutic apheresis have the appropriate know how to effectively perform this procedure and in fact such a multiple horse trials on 6500 volunteers is planned and begun in the early May 2020 to overcome COVID-19.

Another validated strategic safety measure that could be implemented for the quality improvement of plasmapheresis FFP and its derived cryosupernatant, is based on pathogen reduction with UVC or others available technologies. This provides additional quality assurance even if low grade any others infectious viral agents might present, hence will be eliminated. This procedure has been validated and uses the principle of sterilization to kill both viruses and bacteria with a very good safety record. Alternatively, the application affinity column derived specific antibodies might prove useful as an essential part of a relevant clinical research development for purer and safer products.

In respect to total quality management of the whole process from donor to recipient, several key points of total quality management need to be addressed:

1] The collection and retention of blood specimens from both donors and recipients (pre- and post-treatment) to permit retrospective determination of the characteristics of an effective product and dosage regimen, as well as the characteristics of patients most likely to benefit from this intervention.
2] The collection of convalescent plasma only by apheresis in order to avoid unnecessary loss of red cells in the donor and to optimize the volume of plasma that can be generated for investigational use. Double plasmapheresis technologies and even triple procedures can be applied under continual supervision, if required and donor conditions permit.
3] The suitability criteria of COVID-19 convalescent plasma prepared from whole blood by component separation and considered for investigational use, if not clinically needed for general patient care. Transfusion of whole blood to provide convalescent plasma as a general rule should be avoided unless use of whole blood is clinically indicated.
Moreover, from both laboratory and clinical stand points, several other key items should be taken into consideration as critical preparative and therapeutic modalities, embodying: a.] The eligibility of convalescent COVID-19 individuals to donate whole blood or plasma with the following essential requirements; b.] Confirmation of previous infection with SARS-CoV-2 by a record of a validated diagnostic test at the time of illness; c.] An interval of at least 14 days after full recovery; d.] A standard selection criterion for whole blood or plasma donation according to local requirements and standard operational procedures; e.] To avoid the risk of Transfusion Related Acute Lung Injury (TRALI) preference should be given to the use of plasma from male donors or from female donors who have never been pregnant including having abortions. This measure is now well-established to dramatically lower the possibility of the presence in plasma of antibodies to HLA or granulocyte antigens that cause TRALI and appear to occur within 6 h after transfusion of the implicated plasma; f.] The assessment of hypercoagulability, which is of particular relevance to patients with COVID-19, should be fully assessed.

4] It is essential that pre-screening and pre-donation testing of convalescent COVID-19 donors' recovery from COVID-19 infection should be confirmed; a.] Physical examination of the donor to establish good health including the absence of fever and respiratory symptoms; b.] If plasma is collected prior to 28 days after full recovery from illness, then confirmation of the resolution of the infection should be obtained through demonstration of two non-reactive Nucleic Acid Tests for SARS-CoV-2 performed at an interval of at least 24 h on nasopharingeal swabs; c.] Viral in-activation of convalescent plasma is encouraged to address residual risks of known transfusion transmissible viruses in an experimental product; d.] The approximate date of COVID-19 infection, history of symptoms, treatments received and date of resolution of all symptoms should be documented and traceable; e.] The total and neutralizing titers of anti-SARS-CoV-2 antibodies determined as part of product characterization before use. Furthermore, donor blood/serum/plasma samples should be saved and frozen at −80 °C f or retrospective testing and further scientific investigations.
5] It is also essential that the main criteria for collection of COVID-19 plasma should be fully documented: a.] Performed in certified blood establishments (or under exceptional circumstances, hospitals and other health care facilities routinely engaged in performing whole blood collection with plasma separation and/or apheresis procedures) by appropriately trained staff; b.] Use only of legally

approved blood collection or plasmapheresis equipment under standard operating procedures; c.] Supervision of the collection process by trained staff; d.] Volume of plasma to be collected: at least 200–600 mL (without anticoagulant) based on the procedure and regulatory limits; e.] Plasma units intended for use, as convalescent plasma should be clearly labelled. The first plasma donation can be followed by further donations at a frequency compliant with local regulations and taking into account the health status of the donor (in many jurisdictions the interval between apheresis plasma donations of 600 mL or more should not be less than 7 days and that between whole blood donations should be at least eight weeks).

6] Post-donation treatment of plasma record keeping: a.] Where feasible, pathogen inactivation of plasma using a licensed technology is highly desirable to ensure the current strategies are strictly in place to effectively optimize the current practices that are in use in some European establishments. This is an essential regulatory requirement to control the residual risks of transfusion transmitted infectious diseases and to allay concern about possible super infections with SARS COV-2. This is a controversial point since pathogen in activation cannot be performed in all transfusion services, therefore limiting the widespread use of this treatment modality, despite being available in many modern establishments and existing even in some hospitals. b.] Freezing as soon as possible at −30 °C or preferably colder and stored frozen until administration; c.] Convalescent plasma collected from donors who do not fulfil post-COVID-19 suitability criteria for blood donation should be stored separately from other conventional FFP; d.] Plasma sample aliquots should be taken for archiving at −80 ° C and future potential scientific investigations.

7] Need for implementing additional recommendations for plasma transfusion: a.] To follow standard procedures and recommendations for thawing and transfusion of plasma; b.] It is crucial to ensure ABO compatibility between the donor and the recipient; c.] Transfusion of plasma from at least two donors may be therapeutically beneficial to achieve a more effective immune protection from delivery of diverse antibodies; d.] In the absence of published peer-reviewed reports of transfusion of convalescent COVID-19 plasma, patients could receive an initial dose of 200 mL, followed by one or two additional doses of 200 mL according to disease severity and tolerance of the infusions, e.] Further information on blood/serum/plasma samples of the recipient prior to and after transfusion should be taken for future potential scientific investigations. Details can be found in the following WHO document at http://www.who.int/bloodproducts/brn).

Another highly important issue that needs to be highlighted and emphasized is plasmapheresis in immune-compromised patients particularly in cases of haematological malignancy. Since morbidity and mortality associated with coronavirus are highest in the elderly and in individuals with underlying co-morbidities, it would be of great interest to identify the most susceptible disease categories for COVID-19 infection with the aim of proposing specific therapeutic interventions. In this context, with nearly 50,000 hematopoietic cell transplantations (HSCT) carried out annually, patients who are actively undergoing a HSCT, or those who survived HSCT with compromised immune systems make up a large population of susceptible patients in which COVID-19 infection may lead to severe pulmonary distress and could be fatal [6].

Moreover since COVID 19-related pneumonia is mediated by hyper activation of effector T cells and excessive production of inflammatory cytokines, such as IL-6, IL-1, interferon-gamma, and TNF. This inflammatory process may cause a pathological process that leads to plasma leakage, vascular permeability, and disseminated intravascular coagulation. This reaction, called “cytokine storm” is a life-threatening complication of COVID 19 infection. The immunocompromised status associated with haematological malignancies may enhance the risk of bacterial sepsis and COVID-19 and other viral infections [7].

Based on the above, it might be postulated that either the preventive or the therapeutic use of convalescent plasma may be beneficial in these patient subcategories, possibly mitigating the impact of COVID-19. However, well-designed clinical trials are needed to clarify this point. An Italian study has recently started (called “the Italian Haematology Alliance”) with the main goal of assessing the incidence and potential predictive parameters of mortality of COVID-19 in patients with haematological malignancies.

Finally, we believe that the suggested protocol of targeted plasmapheresis of volunteer recovered COVID-19 patients constitutes a feasible, well-established and effective therapeutic modality for the treatment of critically ill patients with severe respiratory distress syndrome or septic shock in COVID-19 infected patients. The phase of the disease in which this treatment modality may be most beneficial is still a matter of debate (early vs intermediate-late stages of the cytokine storm reaction phase associated with acute respiratory distress syndrome (ARDS) or other severe disease complications). Moreover, as highlighted above, these patients who often present with some laboratory abnormalities and a high incidence of thrombosis, some fatal, will benefit from intervention as their hypercoagulable states will improve and normalized. The added process of sterilization of the plasma would make it even safer in line with the use of the best available therapy. We also support the possibility of using on- line affinity columns for removing either the COVID 19 virus itself or its antibodies from the circulation of donors or patients. This process has been recently successfully achieved for haemophilia B patients, with a very high titter of antibodies to Factor IX in Malmo Sweden. This approach could be used for COVID patients with various matrixes to selectively remove the antigen or the antibodies, according to need and the column could be subsequently desorbed to obtain purer substances for sterilisation and intravenous or intramuscular injections. In fact, a capture ELISA, with a plate coated with recombinant ACE-2, or its complexes with S- Protein or its S1 subunit, as a specific receptor, could be designed for capturing possible allo- or autoantibodies present in COVID 19 patients, especially those with delayed severe complications. This would allow measurement of the kinetics of these antibodies during the pathological evolution. If present, these antibodies are expected to be alloantibodies, induced by the association of the viral protein. A similar design could be constructed on an affinity column matrix to capture antibodies or antigens as required either in the circulation or from FFP-derived from COVID-19 plasma. Nevertheless, in practice, what we need urgently is not easily matched with what we want [8].

Based on the concept of plasmapheresis of recovered volunteer COVID-19 patients we believe this is an attractive achievable project, which will benefit the targeted donors and the targeted recipients until a proper effective vaccine is developed and validated. Such activities should be used along with the current efforts in self-discipline and self-isolation already in place to reduce the impact and the ever-growing rate of infection in this crisis, which is paralyzing the economy and having major impacts on the health of the international community at large, beyond imaginable limits. There are, in life, many challenges to overcome but, the present crisis is beyond comprehension, and only by joining forces in a team effort we can turn these challenges into opportunities.

In conclusion, this project is only one small step forward in an overall, difficult task but it is achievable with due perseverance and hope. The single message to convey to all scientific communities from this commentary is to “isolate, isolate, isolate” and to “track, trace and treat” the population at risk or with potential risks of thrombosis and to collect the precious FFP to be used for the population in most need during this pandemic outbreak of coronavirus disease. This approach involving both the patients and donors health care could be considered as a double-edged sword with benefits to both patients and donors alike in this pandemic. Specific recommendations for a standardized preparation, and an optimal use of convalescent plasma at a global level are needed for COVID-19 patients. These proposals will be helpful in designing future clinical trials in this area of investigation.

The use of convalescent blood products with the goal of achieving passive immunity is not new and was proposed by WHO as one early option for treating patients with Ebola virus disease. This commentary on various applications of COVID-19 convalescent plasma and its derived bioproducts with the use of newer technological options that could theoretically be considered when there is a need to rely on the most practical therapeutic options are warranted subsequent to appropriate validation programmes. In countries without access to advanced blood-processing technologies, the choice may initially be restricted to convalescent plasmapheresis using modern apheresis tools that provide leucoreduced and cell free plasma in a close system that could be used to treat patients against COVID-19, if the realistic contents of antibody potency are established by testing. The use of at least two units from two different individuals and /or even preparation of minipool immunoglobulins containing antibodies from various individuals would be a preferred realistic option to be considered. In technologically advanced countries, additional options for pathogen inactivated and sterilised convalescent plasma or blood products such as immunoglobulins to COVID 19, including virally inactivated minipool plasma, as it is in current practice for both plasma and platelet concentrate or a fractionated immunoglobin-derived from either online or indirectly derived affinity column or others existing operationally practicable procedures with good or superior safety records could be used with success subsequent to appropriate validation programs to established the dosage and clinical trials for establishing the best practice.

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