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**Reflection on passive immunotherapy in those who need most:
some novel strategic arguments for obtaining safer therapeutic plasma or
autologous antibodies from recovered COVID -19 infected patients**

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COVID-19 pandemic is an emerging new human disease, where no vaccines, or monoclonal antibodies (mAbs), or drugs are currently available for therapy. Active vaccination requires the induction of an immune response against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease and this usually takes time to develop. Thus, the use of existing autologous Ab administration, obtainable from recovered COVID 19 patients, after 2 weeks recovery, is the best and the most practical strategy for providing immediate passive immunity to susceptible recipients in need. Recently, the use of convalescent blood- derived products was proposed by one of the Authors of this paper (JS) as an early option for treating patients with Ebola virus disease (Burnouf et al, 2014, WHO, 2020). Therefore, human

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convalescent plasma, obtainable by plasmapheresis of recovered COVID 19 attacks, who would be volunteering to donate plasma or immunoglobulin-containing fractions has been proposed and implemented with success in COVID 19 cases (Chen et al, 2020; Shen et al, 2020; WHO, 2020; Casadevall et al, 2020; Seghatchian et al, 2020). Specific requirements and standards for preparation, qualification, storage, and distribution of these blood preparations need to be fully explored. An administration of volumes ranging from 200 to 600 mL of immune plasma (8-10 mL/Kg) once per day and up to three-seven consecutive days is generally recommended to be safe. However, some technical issues still need to be solved such as the optimal threshold of serum titer of specific neutralizing antibodies (> 160 or > 320 by EIA method) in the preparation and the real utility of performing a pathogen (viral) inactivation treatment of such products. In fact, critically ill COVID 19 patients as well as those in early phases of the disease might be excellent candidates for passive immunotherapy, and further randomized clinical trials for addressing its clinical usefulness in various patient subcategories. The immunocompromised status associated with haematological malignancies may enhance the risk of COVID-19 infections. Based on this consideration, it might be postulated that either the preventive or the therapeutic use of convalescent plasma may be beneficial in chemotherapy-treated cancer patients, possibly mitigating the impact of COVID-19 (Dholaria B, et al, 2020). However, the incidence and potential predictive parameters of mortality of COVID 19 in patients with haematological malignancies is still matter of investigation (Seghatchan et al, 2020). Moreover, gene response, differing types of immunities, underlying conditions or life style behaviours in male and female, and races such as African (having 4 times more fatal outcomes than other populations) could be exposed to an increased risk for COVID 19-related complications. In this mini-report we propose three potential additional options as the source of such autologous Ab and provide some operational arguments, on evidence based to support implementation such strategic approaches urgently for those in need to save lives: a] the use of hyperimmune immunoglobulin concentrates, which derives from plasma of physiologically immunized donors. It is debatable that this method may be even more effective than plasmapheresis, since it uses smaller dose of about 200 ml which bring about higher number of donor variability as compared to plasmapheresis product providing 600 ml that can be used as triple satellite bags for 3 recipients. Moreover, the derived cryo-supernatant from well-established plasmapheresis donors is a better policy, as known plasmapheresis donors are virally safer populations and modern apheresis procedure provides a cleaner product in terms of consistency in leucodepletion and containing limited cellular contaminations and their fragments as compared to the variable routine conventional fresh frozen plasma (FFP) preparations. b] Abs may be obtained from cadaveric body fluid upon early consent or washed solution of severely damaged lung of patients with COVID 19, as new optional source. Interestingly, a washed solution on lung, even by using an oxygenated saline or even better plasmalyte, represents an excellent solution of choice

for clinical use as previously reported by our group (Blumberg N et al, 2018). The collected washed solution can then later sterilized in special blood packages obtainable from a biotech company, which can be used in some well-established means for their sterilization and pathogen reduction by the UVC. This is a well-known procedure in practice in some hospitals blood centers for sterilization of platelets concentrate. This protocol may allow a comparison between donor male vs female or others showing some difference in mortality rates as recently observed in Asian and African groups and those who recover versus who passed away. c] It is possible to isolate such a material from the a critically ill patients, via haemapheresis of volunteered patients which contain the appropriate Abs physiologically produced and circulating in patient blood with neutralizing potential or from bronchoalveolar lavage fluid as described above. In the former option some online adsorption affinity column can be incorporated in the system to remove directly the antibody in need that can be used in the recipient to remove the trace of circulating antigen and possibly its circulating complexes or desorbed as new source on immunoglobulin if required for further characterisation (Seghatchian J et al, 2020). Such a purer and cleaner sterilized antibody can be injected intramuscularly or intravenously in specific effective dose as required. Of course, such an affinity column procedure can be carried on off line in either types of source products, plasma- derived bioproducts or lung washed solutions.

It is conceivable that the pools of multiple sera from several patients will provide a multifunctional Abs against various infection diseases too. Furthermore, a combined validated physical sonication combined with UVC irradiation methodology could be applied for preparation of safer immunoglobulin products for therapeutic purposes.

There are several potential clinical applications related to the use of these novel and innovative proposed strategies. It is well known that COVID-19 patients may develop into acute respiratory distress syndrome and/or multiple organ failure (Monteleone G et al, 2020). One of the most important mechanisms underlying the deterioration of disease leading to the organ injury is cytokine storm. At present, some therapies such as interleukin-6 antibody blocker, stem cell therapy, and transfusion of convalescent plasma have been applied to counteract the cytokine storm with considerable success. Importantly, it has been demonstrated that this novel COVID 19 uses the same cell entry receptor, ACE2, as SARS-CoV2. Hence this provides a unique interventional substitution programme, currently under consideration by our group (Admiral et al, 2020).

To conclude, apart from the benefit of about operational proposals on collecting autologous human Abs from different sources for either prevention or treatment in COVID 19, hence it is timely that with no limit we put all the innovative inspiring proposals into action. In fact, a practical pathogen inactivation plays an important role,

especially in the light of newly discovered or unknown viruses, which cannot be safely excluded via prior testing. Hence building upon the information gained, on UVC and ultrasonic methods for an optimum pathogen inactivation of human plasma products, prior to transfusion as an additional safety measures, is a step forward by achieving a highest level of viral inactivation. These procedures if applied simultaneously leave blood products unaltered, making them especially fit for purpose in third world countries where virus contamination of blood preparations poses a major problem.

In summary, in countries without access to advanced blood-processing technologies, the choice may initially be restricted to convalescent whole blood or plasma. In technologically advanced countries, additional passive mode immunotherapy options may be taken into account. However, in western countries the use of convalescent plasma and related strategies may become a reality provided that our hospitals will recommend obtaining an informed consent from recovered COVID-infected patients in order to collect and store their FFP and their derived bioproducts. In UK the use of plasmapheresis in the preparation of FFP from some relatives that one of the family member experienced infection from COVID 19 is started in May 2020 and, so far, 150 units has been collected. The establishment of a comprehensive database including clinical and laboratory data from COVID patients/donors may be helpful in planning subsequent steps including convalescent plasma collection and much safer experimental and therapeutic interventions as the main goal of the precision transfusion. Our numerous plausible and evidence-based methodological interventions are one step forward in this direction. This will be helpful in designing future clinical trials, since an optimal use of convalescent plasma at a global level is highly demanding in COVID 19-infected patients.

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