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An update on COVID-19 infection control measures, plasma-based therapeutics, corticosteroid pharmacotherapy and vaccine research

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ABSTRACT

This communication provides a compilation on aspects of COVID-19 infection control measures, describes the potential role of therapeutic plasma exchange to reduce fatality rates, addresses precautions concerning dexamethasone pharmacotherapy and updates the current status on the availability of vaccines. As part of passive immunotherapy, it focuses on various blood derivatives. These include coronavirus neutralising antibodies extracted from different sources to be administered as a pure hyper concentrate intramuscularly or for upgrading and standardising the specific potency of high affinity antibodies. These processes are intended to compose standardised pooled bioproducts of corona convalescent plasma/cryosupernatant that are pathogen inactivated for additional safety by well-established UV technologies. For the best practice of optimising plasma exchange, hyper concentrate NAb should be added to the cryosupernatant, which contains some of the active principles of corona convalescent plasma. The cryosupernatant apart from the high molecular weight viscous part of cold insoluble proteins that are removed, is equivalent to CCP, but makes it safer for general application. Such a bioproduct is often used routinely for substitution therapy of thrombotic thrombocytopaenic purpura. Alternative resources of large-scale specific coronavirus antibodies warrant further exploration such as cadaveric donations. The early uses of therapeutic plasma exchange and low molecular weight heparin, for any clinical trial in development is warranted, in order to interdict the intense inflammatory/kinin driven cascade. Because coronavirus positive patients are highly prone to thrombosis, thromboprophylaxis is necessary, even some time after recovery guided by the laboratory data.

1. Objectives

The principal objectives of this communication are [1] to incorporate awareness of the exigencies to prevent the spread of COVID-19 [2]; to review effective infection control practices [3]; make recommendations to standardise therapeutics for the plasma derived bioproducts proposed for use in clinical trials [4]; highlight the serious complications of infection induced by hyperinflammatory and hypercoagulable states [5]; weigh-in on the controversy of corticosteroid pharmacotherapy [6]; discuss the current status of vaccine research [7]; advocate to save lives by the dissemination of sound scientific and medical information.

2. Background of the pandemic and introduction of passive immunotherapy

COVID-19 or the pandemic 2019 coronavirus also known by the name in the taxonomy SARS CoV-2 is thought to have originated in animal zoonotic vectors. The occurrence is possibly in bats to pangolins and then jumped human to human transmission. The first index cases of the contagion of pneumonias are believed to be connected to the Huanan Wholesale Seafood Market of the city of Wuhan, Hubei Province, China in December 2019. Because the virus is so exquisitely transmissible by the respiratory route and there are no licensed vaccines yet and coupled with deficient infection control practices, SARS cases have exploded worldwide. Though only a small percentage of infected patients develop the severest forms of the SARS/hypercoagulability profile, the resources of many ICUs have become stressed by the sheer volume of life-threatening cases. Our commentary focuses on the optimisation of infection control practices; the recommended introduction of standardised pathogen reduced convalescent plasma/cryosupernatant and hyperimmune globulin bioproducts in conjunction with therapeutic plasma exchange in an effort to attenuate the fatality rates; cautionary

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notes about overreliance upon corticosteroids as a therapeutic; and the status of the Oxford vaccine trial and other alternative vaccines in development

We are well cognizant of a nefarious strain of the Coronavirus SARS CoV2 that has been eclipsing the globe causing unprecedented health and economic chaos to the current generation. In a spirit of oneness to combat this marauding infection, we are challenged to develop and harness an arsenal of well-validated tools for the purposes of precision diagnoses, monitoring and treatment. Vigilance in these key areas is critical to protect our national health and economies against a formidable adversary. Currently, a collaboration of all international scientific and medical entities is summoned in an effort to develop effective preventative strategies to slow down the spread of this virus. Equally important are optimising therapeutics to reduce the morbidity and mortality associated with this infection run amok. Certain well-known interests have sought to downplay the seriousness of the coronavirus problem in order to advance their own political agendas. One notable unsubstantiated allegation is that up to 99 % of patient cases are harmless when in reality, the serious illness rate has fluctuated up to 14 %. Multiplicities of dangerous complications attendant to the virus, which cannot be ignored, include sepsis, refractory acute respiratory distress syndrome and multi-organ dysfunction and the severe vascular insults of thromboembolism and stroke. The propagation of the disease is of particular concern to a vulnerable patient population over the age of 65 years and among the ICU patients, wherein mortality rates may exceed 33 % for the elderly.

In a preliminary ICU study comparing the safety and efficacy of coronavirus convalescent plasma (CCP) derived by plasmapheresis to Ebola virus convalescent plasma, there are parallel developments of increased humoral immunity. Reported are low risk of complications by plasma therapy, and achievable reductions in mortality by this therapeutic in both [1–4]. Initial evidenced based data on CCP as a viable bioproduct indicates a large quantity of convalescent coronavirus specific antibodies. These are capable of neutralizing and reducing the load of coronavirus in the circulation and viral residuals in the pulmonary tissues and other susceptible organs expressing the angiotensin converting enzyme ACE-2 receptors. Nevertheless, further clinical studies with a higher number of patients and more homogeneous groups are imperative in order to validate possible improved survival and an attenuated inflammatory response as a result of plasma therapy.

3. Infection control

Consistent with the vision of this journal, our direction is to illuminate the current status of the public health crises encompassing the coronavirus pandemic. We are principally concerned with the state of the art of the interventions in evolution, at global levels to control the spread of infection and effectuate proper treatment. This has been highlighted by the EIC editorial of the June issue and some related articles [1–5]. Presently, about 4% of the population in the United Kingdom contain antibody in the circulation against Covid-19 infection and well below the often quoted 70 % figure to confer herd immunity. The population is exquisitely susceptible to contracting the virus by the respiratory route and as a result, there has been an explosion of deaths. There have been disproportionally high estimates that 30 % of the UK infected populations are asymptomatic and this is up to 40 % in the United States. A recent meta-analysis indicates a lower proportion of asymptomatic individuals at 15 % (95 % CI-12 % to 18 %) [10]. Overestimation of asymptomatic individuals could be predicated on not registering mild symptoms; patient bias being driven by a false denial of symptoms; and delayed symptoms not being tracked in those with the disease. Because of some occult infections, this leads to the public health conundrum of not being able to readily identify those that can easily transmit the disease by nasopharyngeal spread. There has been an argument to initiate massive testing by well validated assays of the viral antigen or antibody but of unclear benefit because of the question of the quality of the early tests, the impracticability of the onerous contact tracing and quarantining requirements, and the back-log of pending test results. For diagnostic purposes, the prescreening for the virus in hot infective areas, a saliva-based test has been proposed as practicable, yielding results within 20 min but is less accurate. Nevertheless, the goal is to statistically flatten the curve of the escalation in coronavirus infections utilising known effective infection control strategies. In order to safeguard the population, we have had some limited success with education through the media about hygienic methods of handwashing and sanitisers, using sanitary gloves, disinfection of hard surfaces, wearing filtering masks, physical distancing, the avoidance of congregation in mass gatherings and even partial lockdowns though with negative fiscal impact.

In the aftermath of the 4th of July, the UK government with due precautions is intending to reverse some severe stringent lock downs of the economy that heretofore have had major deleterious consequences. While the intent of safeguarding the population from infection and reopening the economy are not mutually exclusive, there are concerns about timing and the potential for recrudescence of infections. Examples of impediments to well instituted infection controls include the uncontrolled protests against law enforcement related to Black Lives Matter in the United States; compromised physical distancing in taverns; the poorly planned reopening of some amusement parks; overcrowding of the beaches; unsafe restaurant in-dining; and indoor political rallies absent proper respiratory protection. Moreover, evidence is now accumulating that there are two primary modes of infection transmission [1], the droplets expelled from mouth and nose; and [2] microparticles recirculating in poorly ventilated indoor areas. As a consequence, we can anticipate persistent spikes in infections as currently prevailing in the United States, Germany and some parts of China to name a few. Beyond human transmission, there has been a case of viral spread even to domesticated pets, and in the UK, we had the first case of a cat infected by coronavirus possibly via contact from the owner.

Certain groups are particularly prone to the ravages of infection such as the elderly, diabetics, those with pre-existing lung disease, the morbidly obese, uncontrolled hypertensive patients; and possibly individuals with immune dysfunction attendant to the administration of antibiotics that adversely impact intestinal and lung microbiomes. Women that have a predisposition to hypercoagulable states such as those that are using contraceptives or who are pregnant may be a greater risk. In theory, this is because of the concomitant hypercoagulable state induced in some patients by a heightened inflammatory state of the virus and the potential for thromboembolic complications. Wealth inequalities are unfortunately incriminating factors to contracting and dying from respiratory viral illness as in the African American and the Hispanic populations of the United States, the overcrowded Asian, Pakistani and Bangladeshi populations, and part of the industrial belt of Birmingham and Leicester in the UK.

We have experienced in excess of 15 weeks of self-isolation and lock down in major economies throughout the world and now the challenge of reopening. Contemporaneously, there are some significant gaps in leadership, often sending misinformation to the public that threatens the capacity to safely reopen. One poignant example is non-compliance in wearing face masks. There is very fine line between encouraging liberty for all juxtaposed to being responsible members of the society; working in concert to follow the medical guidelines and conscientiously foster public health safety.

4. Current scope of the coronavirus problem and treatment strategies

Given that the coronavirus has dangerous capacity to cause consequential morbidity and mortality in spite of contemporary therapeutic modalities, we need to aggressively pursue new treatment strategies within our armamentarium, one being therapeutic plasma exchange. As the virus can cause excess inflammatory mediators such as cytokines and

chemokines to circulate, in theory it would be advantageous to exchange patients with fresh frozen plasma or convalescent plasma containing a fixed dose of coronavirus neutralising antibody, NAb, if available from a donor.

The perpetuation of the coronavirus onslaught interestingly appears to be non-seasonal in nature and quite pernicious, an apparent continuous wave of infection worldwide. Of special concern to public health officials is the potential devastating impact of other viruses such as influenza in the fall superimposed on the coronavirus plague. This is especially an issue for those that are susceptible, not having received an influenza vaccination. The incidence of coronavirus disease activity in the population appears to fluctuate from partially controlled at lock down to exponential growth of virus dissemination upon opening. The latter problem is thought to be consequent to a lapse in executing effective infection control practices by some non-compliers, with consistency, in the public.

5. Therapeutic plasma exchange, TPE and coronavirus neutralising antibodies

Historically, "passive immunotherapy" has a positive track record as in the treatment of the Ebola virus; these are smaller observational studies but they encourage therapeutic use for coronavirus too [3,4]. In consideration of the very low risk of complications of plasma exchange therapy, it is a very attractive first treatment option for coronavirus. This is practicable if the usage is standardised, such as the use of [1] "a minipool of pathogen reduced CCP with an elevated dose of neutralising antibodies from at least two CCP donations" or as a second viable preparation alternative [2], namely a homogenous standardised cryosupernatant with a fixed potency of neutralising antibody, as previously proposed by one of us [2].

In order to apply the use of passive immunotherapy consistently, coronaplasma bioproducts for transfusion exchange should be standardised with respect to the level, potency and avidity of antibodies such as would be advantageous in the processing of minipool convalescent plasma [2]. Moreover, the antibody levels of CCP can be boosted by hyperimmune COVID antibodies obtainable by using a promising on line affinity column separation methodology or otherwise, as described earlier [2]; and such a pure hyperimmune coronavirus antibody can be delivered by intramuscular injections with fixed potency and could be prioritised to healthcare workers initially. Alternatively, the above purer hyperimmune products can be used for upgrading the antibody content of the potential pool of CCP or its cryosupernatant, that will be essential as the carrier of such bioproduct in therapeutic plasma exchange (TPE). Incorporating these hyperimmune products in plasma exchange is believed to have potential therapeutic value. To this end, it is currently indeterminate precisely which components of exchange plasmas might be integral to modulate the hyperinflammatory and hypercoagulable states triggered by the virus.

Exploring further, some large-scale alternative practicable sources of coronavirus neutralising antibodies are warranted for implementation. One possibility is consented cadaveric donations, either from the serum or a pulmonary lavage solution, but clearly in advance of decomposition. Such an approach, if proven to be viable, could alleviate the time and cost-pressure and the need for higher throughput that make developing therapeutic neutralising antibodies at the right dose a real challenge to overcome, given the limited availability of corona convalescent plasma.

Regarding the importance of continual quality and safety improvement strategies related to harvesting corona NAb, all bioproducts for reinfusion need to have pathogen reduction whether used as hyperimmune immunoglobulins or using targeted affinity column processing methods. In fact, this is a current requirement for all human derived bioproducts for which safety practices are already in place. Affinity column processing is a favoured option, to mainly enrich the useful circulatory corona autoantibodies. In concert with the manufacturers, sterilized bioproducts in ampule format could be produced immediately to satisfy demand. It is important to highlight that circulating coronavirus antigen has been identified by RNA assays in some adults who recovered from the infection. As a result of the possibility of a transmissible virus, the implementation of pathogen reduction methodology therefore must become an integral part of all reinfusion programs as highlighted before [1,2].

6. Novel clinical trial interventions to combat COVID-19

We propose early targeted therapeutic plasma exchange in combination with FFP or CCP/cryosupernatant to be administered in the course of respiratory viral illness. The planned specifics of this four-arm randomised/blinded clinical trial are currently in development and pending submission shortly to the Cytokine journal. As a consequence of a virally mediated hyperimmune inflammatory response and hypercoagulation that occur for some reason in certain susceptible hosts, we have a unique opportunity to identify key factors that presage the cytokine storm. The process of apheresis in the presence of escalated doses of low molecular weight heparin might have favorable impact in lowering both hypercoagulability and modulating cytokine and complement/kinin effects. There is a commonality of these serious hyperimmune medical complications, which surface not only in association with COVID-19 infections but extend notably in different types of respiratory viral transmissions, ie. influensa, MERS, SARS-CoV1, Ebola. Conceptually we could mitigate the inflammatory crises if early targeted treatment intervention is successful by TPE, the challenge being to identify those patients most vulnerable in advance of a rapidly progressive deterioration.

Whatever the outcome of this clinical trial, which targets a highly complex inflammatory process, the use of standardised pool CCP or its cryosupernatant and with its' NAb upgraded to fixed levels are worthy plasma processing interventions. The intent is to establish duration of stay of NAb in the circulation and this can be boosted upward if the levels fall below a minimum standard.

7. The hyperimmune inflammatory response

In COVID-19, an intriguing question is why there are a smaller percentage of individuals that are uniquely susceptible to developing an escalating systemic inflammatory reaction, which is associated with multi-organ damage and high morbidity and mortality. It is believed that a serine protease activates the virus's S spike protein, which in turn cleaves angiotensin converting enzyme (ACE-2 receptors on the host cell outer membrane) to facilitate viral binding and RNA endocytosis to the host cell. This then leads to the synthesis of hundreds of copies of the virion. Bronchial epithelial Type I and Type II cells, alveolar pneumocytes and capillary endothelial cells are specifically targeted for infection and subsequently release the virus recruiting a constellation of inflammatory T-cells, monocytes, neutrophils and macrophages. There is thought to be a predisposition to cytokine and/or chemokine release in selected patients triggering a dangerous hyperimmune reaction and associated severe cytopathic effects such as a rapidly progressive pulmonary edema and acute hypercoagulability [11].

One observation is that patients having the poorest medical outcomes after contracting the infection have a tendency to a higher viral load, an RNAemia as assessed by PCR but not always a consistent finding. Paradoxically, those that develop the highest titers of high affinity antibodies against the virion appear to have the poorest outcomes compared to patients with less severe disease. There is ongoing research into this inter-individual variability in response to coronavirus infection; to determine why these factors appear to be associated with an increased risk of developing a hyperimmune response and heightened allo/autoimmunity in some patients [2,5]. Post-acute infection, some patients have complained of unusual residuals of a longer-term chronic fatigue-like syndrome of uncertain duration. Hypothetically, this may

have an insidious autoimmune basis contemporaneously with infection. Causation could include autoantibodies being triggered against the widely distributed ACE-2 receptor in various organ tissues and to contiguous proteins complexed to ACE-2; the potential for a worrisome epitope spread.

8. Pharmacotherapy

Amongs the key objectives are the development of pharmaceuticals to prevent the extreme inflammatory and hypercoagulable states of coronavirus disease, intended to reduce the mortality rate. We are making progress evaluating some drugs thought to have potential effectiveness but discovery of a miracle anti-viral drug that resolves all the complications remains elusive and may be impracticable. We are probably better off targeting and treating the various manifestations of the disease with multiple drugs acting by different mechanisms, hopefully yielding a net overall positive medical effect. While there is a miscellany of drugs in the pipeline, we are limiting our perspectives herein to the proposed use of dexamethasone in the treatment of COVID-19. Additionally, we have some reflections about the role of steroids as a therapeutic for ARDS and being controversial over the course of several decades. The debate is fueled by the difficultly in interpreting interstudy results given the different formulations of steroids, dosages, timing of administration in the disease course and insufficient controlling for confounding variables. These include extra comorbidities such as notable in older groups of patients, who are often on some sort of antiviral and/or anti-inflammatory medications.

Despite the recent publicity in the United Kingdom about dexamethasone to treat COVID-19, physicians should be alerted that this drug is not a panacea for coronavirus or other serious respiratory viral illnesses. First and foremost, there is no uniformly accepted treatment for attendant severe acute respiratory syndrome to date. Dexamethasone is a strong anti-inflammatory corticosteroid, an older drug that was first approved by the United States Food and Drug Administration in 1958. It is one of the world's most potent immunosuppressants, approximately 30 times more so than cortisone on a mg basis and with a long biological half-life of 36−54 h. Because of the drug's potent immunosuppressive properties and prolonged activity, it needs to be utilised very cautiously because of the latent risk of infection. The UK health system has recently lauded its' use to be available on the NHS formulary for this purpose, the treatment of COVID-19. The large UK RECOVERY trial, their unpublished data, reports significant efficacy at reducing the risk of death in the short-term for COVID-19 patients, a subgroup supported by only oxygen or on ventilators. At 6 mgs daily dosage for 10 days duration, this randomised study has been interpreted preliminarily to show that the drug saved the lives of 1 in 8 patients on ventilators or 1 in 25 only on oxygen therapy [6]. Its' anti-inflammatory effects are believed to mediate an escalated cytokine proinflammatory response which causes underlying damage to the lung. Whether the overall study conclusion shall survive increased scrutiny remains to be ascertained given the variable timing of steroid administration in the disease course and when controlling for confounding factors such as co-morbidities and follow-up if any of delayed complications and deaths.

While dexamethasone is claimed to save lives in the short-term, there is a cautionary tale about the controversial medical aspects, long term side-effects and looming dangers. Steroids may, in fact, impede convalescence long term and have the potential to cause late deaths by various mechanisms: increasing a persistent viral plasma load and shedding; possibly harboring the virus in immunopriviledged sites; reducing the antibody production of B-cells; and impairing special T-cell and macrophage function essential for host defenses and recovery from the virus and/or nosocomial infection [7].

By comparison, it is instructive to reflect historically about the role of corticosteroids and the 2009 influensa A H1N1v outbreak. When studied in that pandemic, very early treatment by corticosteroids of ARDS occurred in a selected cohort of patients, the French registry that specifically excluded confounding comorbidities other than obesity. Statistical analyses showed no medical benefit and yielded poorer outcomes, excess deaths in association with the steroids [8]. This leads us to view extremely cautiously the current recommendation for dexamethasone to treat oxygen dependent COVID-19 patients. Moreover, an endorsement of the use of dexamethasone absent precise guidelines to initiate treatment is of concern. Ostensibly, patient's that would recover absent steroids may receive it anyway and now the ones we propose to protect are exposed to indeterminate risk.

9. Vaccine research

Numerous types of vaccines are currently in development, at least 140 internationally, in various phases including two large scale clinical trials that are promising at Oxford and the London Imperial College. Regarding the published results of phase 1/2 trials of the Oxford vaccine, 1077 volunteers were enrolled in the trial. While predominantly injections were given as a single dose, 10 participants received booster vaccine. The evidence to date provides some reassurance that the vaccine is safe and well tolerated and also indicates immune responses triggered at two levels: (1.) including elevated humoral immunity measured in part by total IgG against trimeric SARS-CoV-2 spike protein and rising neutralizing antibodies; (2.) heightened cellular immunity measured by an ex-vivo interferon-*y* enzyme-linked immunospot assay to enumerate antigen-specific T cells [9]. Whether the vaccine provides durable protection and for how long remains indeterminate. Nevertheless 9000 front line medical staff in the NHS are registered to receive the vaccine and a large order is already in place.

There are at least 23 different types of vaccines competing in clinical trials internationally including China, the USA, Russia and some joint venture studies ongoing in France and Germany. Apparently, there is no shortage of willing human subjects as highlighted in a recent UK survey; 73 % of adults want to volunteer and 90 % of the parents wish to have vaccination of their children. To establish if it is working effectively, some trials are targeting hot spot areas of significant disease activity such as in South Africa and Brazil. Regardless of the outcomes of the vaccine trials, modified pooled CCP remains a safe product to initiate further testing in our planned TPE studies.

Nevertheless, the fact is that vaccines take time to be fully implemented on a large scale globally. Even if any of the trials indicate that such a vaccine is potentially working, a key question is whether there is a durable protective response to promote herd immunity and for how long. It is for this reason that it is more than likely a requirement to implement several different types of effective candidate vaccines and our newer proposal of passive immunity through safer pooled CCP with an upgraded Nab protocol in parallel.

10. Concluding remarks

The COVID-19 pandemic has created unique challenges all over the world for infection control. In retrospect, given the easy respiratory transmission of the virus, we should have [1]: marshalled earlier efforts by the manufacturers to ramp-up production of N95 masks to effectively filter out the virus; and [2] promoted national educational campaigns on how to properly wear masks. As the virus shall likely linger with us for some years to come, it would clearly be productive to institute these two simple control measures going forward [3]; With respect to passive immunotherapy, there is a critical role for plasmapheresis and affinity chromatography technologies to manufacture an adequate supply of standardised CCP or its /cryosupernatant and hyperimmune globulins, an intent to improve disease prognosis [1,2,4]. Because the half-life of coronavirus Nab is less than four weeks, it is imperative to stockpile sufficient supply to meet clinical demand. The targeted administration of said bioproducts in concert with TPE early in the course of disease may abrogate the acute onset of SARS and the necessity for mechanical ventilation. With this goal in mind, we are enthusiastic about a

well-designed clinical trial, testing whether these bioproducts and the planned TPE protocol have a moderating effect on infection-induced inflammation.

Current vaccine trials appear promising in the hope to abort the COVID-19 pandemic but are not a panacea. The vaccine is likely to be ineffective for some and non-administered by many for various personal reasons. As a result, we need to encompass a range of therapeutic tools such as TPE, plasma derivatives and well-selected pharmacotherapies to supplant vaccines in order to treat the worst complications of this respiratory viral disease.

A continuous wave of infection is already in place in some parts of Europe and the USA and South America. In the absence of a reliable vaccine, preparation of hyperimmune coronavirus NAb must be pursued consistently and with standardisation from all sources.

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