

Convalescent Plasma for COVID-19: back to the future

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The global pandemic of the new coronavirus SARS-CoV-2 has not just medical, economic and social but also historical significance. In many parts of the world, the exponential epidemic curve of cases has overwhelmed hospital services. The primary pulmonary viral infection has required supportive care with oxygen and, if needed, mechanical ventilation, and clinical teams around the world have successfully cared for hundreds of thousands of severely ill patients.^{1,2} However, there is currently no specific anti-viral therapy that is proven to reduce mortality, although many putative anti-viral and anti-inflammatory regimes are being tested in large randomised clinical trials. The lack of a specific therapy has caused some sense of hopelessness in clinical staff, trepidation in the wider public and has not made plotting a route out of lockdown any easier.

However, the most promising therapy at the moment may be one of the oldest. It is one where transfusion services and hospital blood banks play a direct role in identifying donors, testing, manufacturing and issuing products. It is also one where patients who have had COVID-19 can donate plasma which can be used as a therapy for new patients who present with the disease.

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Convalescent plasma treatment, containing polyclonal antibody (Ab), has been used to treat severe viral pneumonia during previous pandemics. In fact, it has been used intermittently for over a century, including patients treated during the era of the Spanish Influenza pandemic in the early 20th century.³ Although, all the studies described at that time had significant methodological flaws, and none were randomised, they suggested a reduction in mortality.³

In the more recent past, convalescent plasma has been used to treat H1N1 influenza, and, more relevantly, SARS-CoV infections in 2003, with evidence of some considerable benefit cited in a systematic review, especially if convalescent plasma was given earlier in the course of the disease (within the first 14 days of symptoms).⁴ Convalescent plasma has already been used in observational studies of patients with severe COVID-19. However, a systematic review of the evidence has shown that the conclusions about the effectiveness and safety of convalescent plasma in people with COVID-19 that can be drawn from these studies is limited.⁵ There have been only 8 uncontrolled studies published, including a total of 32 participants. Some of the results reported in these studies are consistent with increased viral clearance and recovery from the disease.

In some way, it is remarkable that such a potentially useful treatment has not been rigorously tested to allow definition of evidence-based guidelines for its tactical use in epidemics and for strategic planning for collection of convalescent plasma to be incorporated into pandemic planning. Lack of evidence for a promising treatment is not unusual, but convalescent plasma has faced the challenge that it has always been very difficult to collect enough convalescent plasma during a pandemic to provide plasma to treat large number of patients. The other problem has been the lack of a co-ordinated national and international response to allow rapid and timely randomised controlled trials to take place.

The present COVID-19 epidemic has already been of such duration and magnitude to allow collection and use of plasma. However, it still takes considerable co-ordination to complete large-scale trials in a short time. A recent report of 5000 patients treated with convalescent plasma in the United States, almost entirely for compassionate use, suggested that convalescent plasma is safe with no obvious cases of antibody-dependent enhancement of disease. However, without data on control patients it is impossible to be confident whether convalescent plasma is either safe or effective in the treatment of COVID-19.⁶

More rigorous assessment of the role of convalescent plasma is underway. At the last count, 22 randomised trials around the world had been registered on trial registries.⁵ Two living systematic reviews of convalescent plasma will assess the benefits of treating people who have been diagnosed with COVID-19 and the benefits of preventative treatment for people at high risk of getting COVID-19.

In the UK, the Office of Life Sciences, NHS Blood and Transplant (NHSBT) and the Department of Health and Social Care (DHSC) have proposed and planned a new programme to collect high volumes of plasma. The work is funded as a new £20m project by DHSC. The strategy is to build up collection of plasma from convalescent donors to provide enough plasma not only for two large-scale randomised controlled trials to assess the efficacy and safety of convalescent plasma but also to provide enough plasma to treat hospitalised and/or intensive care patients with COVID-19 if the randomised controlled trials do show efficacy.

Within six weeks, NHS Blood and Transplant have set-up what is effectively a new production line with workstreams reaching out to potential donors who were admitted to hospital and/or testing

positive for COVID-19 and those who had symptoms consistent with the disease. NHSBT have established collection of over 5000 units a week by re-arranging work with existing donor centres, building three new collection centres in London, training over 200 newly-recruited staff by donor centre staff and the core nursing team, defining new manufacturing processes and new methods to evaluate the quantity and quality of anti-SARS-CoV-2 antibodies.⁷

These are certainly challenging targets and we have been faced high on-session deferral rates as we are plasmapheresing many first-time donors, who have recently recovered from serious infection. We are bringing deferral rates down and increasing the proportion of potentially high-titre units collected by continuously reviewing the possibilities for screening donors by call-centre or clinical staff and by targeting potential donors who are male and/or aged over 35 and/or who were hospitalised.

The design of the clinical studies has required assessment of the titre of anti-viral antibodies using series of recently developed assays including neutralising antibody of live SARS-CoV-2 invasion in tissue culture cell, neutralisation of pseudo-typed virus bearing the Spike protein from SARS-CoV-2 that contains the ligand for the host ACE2 receptor and immunological assays of antibodies against different formulation of Spike protein.⁸ Convalescent plasma for clinical trials will only use plasma that contains antibodies in the upper third of the range neutralising antibodies for invasion of Vero E6 tissue culture cells by a live virus measured in a series of 300 hospitalised COVID-19 patients (Havarla, manuscript in preparation). The median neutralising antibody titre is approximately 1:250 but range from approximately 1:80 to 1:4000 and giving each patient two units of plasma will give the clinical studies the best chance of showing efficacy while also in some sense optimising the number of people that could be treated should the trials be successful. It will be possible to correlate anti-coronavirus Spike protein antibodies, anti-Receptor Binding Domain antibodies and neutralising antibodies in a pseudo-typed viral assay in the donor plasmas with the eventual outcome of the respective patients in the randomised controlled trials (<https://www.remapcap.org/protocol-documents> and details of the protocols will be published in a future issue of *Transfusion Medicine*).

The first trial is for treatment for community acquired pneumonia in intensive care, REMAP-CAP. This international trial is randomising patients across the UK to several different treatments to assess whether they are beneficial to critically ill adults with COVID-19. One of these randomisations is comparing convalescent plasma to standard care. Patients can be independently and adaptively randomised to anti-inflammatory, anti-viral agents, anti-coagulation and antibiotics representing different arms of the study.

We are giving two doses of convalescent plasma to patients who have recently been admitted to intensive care and assessing whether this decreases the risk of remaining on a ventilator or dying due to COVID-19. We are also assessing whether there are any potential harms of this treatment. We plan to randomise up to 2000 participants to this trial. This is an adaptive trial and if there is evidence that convalescent plasma improves outcomes for critically ill patients the trial will be stopped and then all patients admitted to intensive care will be given convalescent plasma. The trial is currently open at 10 hospitals around the country and plans to open at more than 100 intensive care units around the country.

The second trial is a UK-wide trial of convalescent plasma in all hospitalised patients with COVID-19 as part of the RECOVERY trial and will start in May. Here, we are giving the same treatment, two doses of convalescent plasma, as in the REMAP-CAP trial. This will assess whether convalescent plasma decreases the risk of death or the need for mechanical ventilation for anyone who is hospitalised with COVID-19. It will include people with COVID-19 of any age, including neonates, who

are unwell enough to be admitted to hospital. We plan to randomise up to 5000 participants to this trial and open the trial at more than 200 hospitals around the UK.

It is inevitable that completing any trials of therapy in a pandemic is a race against time during the pandemic. These trials have proven no exception and while the convalescent arms of the REMAP-CAP and RECOVERY trials will be actively recruiting by the end of the May, the number of patients with COVID-19 admitted to hospitals and intensive care units has fallen substantially after several weeks of lockdown. Although many measures are being put in place to control the epidemic, it is almost inevitable that the multiplication of the virus will increase and it seems likely that there is will be a long tail of cases and quite probably a resurgence of the infection in the coming months allowing completion of the trials and we hope definition of possibly the first, but hopefully by no means the last, effective therapy for COVID-19.

In the year ahead, the data will be combined with the results of other clinical trials and also with the analysis of collection, use and outcome of convalescent plasma across the EU in collaboration with the European Blood Alliance (<https://europeanbloodalliance.eu/>) to provide recommendations for the collection and use of convalescent plasma in this and future epidemics.

The precise specificities of the anti-SARS-CoV-2 antibodies that can neutralise the virus are, at least in part, targeted at the Receptor Binding Domain (RBD) on the Spike protein.^{8,9} The clinical studies will be able to examine the relation between anti-SARS-CoV-2 antibodies directed at the RBD and other specificities and clinical outcome and so will not only provide evidence for the efficacy of passive immunotherapy with convalescent plasma, but also inform future development of hyperimmune globulin and human monoclonal antibodies to treat or prevent COVID-19.^{9,10}

If convalescent plasma improved outcomes in COVID-19, then fractionation of convalescent plasma that contained significant, but lower titres of anti-SARS-CoV-2 antibody may be suitable for production of hyper-immune globulin, permission was granted to proceed with fractionation in the UK.

The use of convalescent plasma may be the first of many therapies and preventive measures for COVID-19, although at the present time with the first wave of the pandemic just past us, this seems almost too much to hope for. Vaccines are yet to be tested in earnest, but some scores of different vaccines are being developed and some have completed preliminary safety studies. While the success of any one immunotherapy or vaccines or drug is not guaranteed, we may be stepping slowly but surely along a path to the beginning of the end of this pandemic and be better prepared for the next one.

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