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# COVID-19 convalescent plasma from Norwegian blood donors

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## PERSPECTIVES

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**The collection and use of convalescent plasma to treat COVID-19 has taught us important lessons about the organisation, testing and selection of blood donors and patients. This is knowledge that can be used in the next pandemic.**



Photo: Marcus Ericsson / NTB

Convalescent plasma is plasma taken from survivors of a severe infection. It can be obtained in the early stages of a pandemic, before other specific treatment is available, and can help treat patients whose immune systems are unable to mobilise a satisfactory antibody or vaccine response. Through the NORPLASMA project, Norwegian blood banks have provided COVID-19 convalescent plasma for experimental treatment.

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## Convalescent plasma

On 30 March 2020, the SARS-CoV-2 pandemic was declared an international public health crisis by the World Health Organization (WHO). As documented treatment was not available, various medications were used despite the lack of randomised controlled trials. The WHO issued guidelines on which treatment alternatives should be tested in clinical trials, and these included convalescent plasma [\(1\)](#).

*«Such treatment had already been tried during the Spanish flu 100 years ago»*

Such treatment had already been tried during the Spanish flu 100 years ago. It has subsequently been used to treat measles, swine flu and the previous coronavirus outbreaks SARS-CoV and MERS [\(2\)](#), but without large-scale randomised placebo-controlled trials. In March 2020, Casadevall et al. recommended use of convalescent plasma to treat COVID-19 [\(3\)](#). The rationale was based on previous clinical trials of patients with SARS-CoV, which had shown that neutralising antibodies could control the infection. Early published

research from China on the use of convalescent plasma to treat COVID-19 seemed promising, but sample sizes were small and the neutralising effect of the antibodies on the virus was not measured (4, 5).

In April 2020, leading hospitals and universities initiated clinical trials to clarify the efficacy and safety of treatment with convalescent plasma. The health authorities in several countries also allowed use outside the context of trials in exchange for collecting data before and after transfusion. In the United States, the Food and Drug Administration (FDA) allowed large-scale use through an Emergency Use Authorisation in August 2020 (6). The European Centre for Disease Prevention and Control (ECDC) and the European Blood Alliance (EBA) provided input for European guidelines (7), and the European Commission recommended experimental treatment of COVID-19 with convalescent plasma in clinical trials (8).

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## The NORPLASMA project

In April 2020, a national project for the collection and transfusion of convalescent plasma (NORPLASMA) was initiated in Norway in a collaboration between blood banks and the Norwegian Directorate of Health. The aim was to contribute to the scientific evaluation of convalescent plasma as a treatment through a randomised trial in a relevant patient population. The Norwegian Directorate of Health issued guidelines for the production, use and monitoring of treatment in Norway (9).

*«The aim was to contribute to the scientific evaluation of convalescent plasma as a treatment through a randomised trial in a relevant patient population»*

A steering group was established for the project as well as national expert groups for plasma collection (the transfusion group) and antibody testing and assessment of infection risk (the microbiology group) respectively. A third group was established for planning and conducting clinical trials.

The transfusion group drew up guidelines on how donors should be recruited and informed about the trial. The guidelines also advised how convalescent plasma should be collected, quality assured and distributed. Fifteen blood banks applied to the Norwegian Directorate of Health and were granted permission to collect and distribute convalescent plasma (10). As this was experimental treatment, every donor had to give consent to their health data on COVID-19, their plasma, and any necessary additional blood samples being used for research. Many of the blood banks also obtained consent for participation in general research biobanks for COVID-19 run by their own health trusts. The project for the collection and production of plasma was approved by the Regional Committees for Medical and Health Research Ethics (REK) on 14 May 2020 (REK no. 140845).

The microbiology group recommended adherence to current national guidelines on testing new blood donors for infection. PCR testing for SARS-CoV-2 in the donor prior to donation or of the blood product was not recommended. Supplementary information on microbiological diagnostics for the blood donors was provided for the microbiological laboratories. The group did not recommend pathogen inactivation or quarantine of the blood product. The risk of transmitting SARS-CoV-2 in connection with blood transfusion is considered minimal, and transmission of respiratory viruses (including coronavirus) via transfusion has not been documented (11).

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## Information, extraction and testing

Safeguarding the quality of uniform information for donors and blood banks was a lengthy process. Approved blood donors who had had COVID-19 were encouraged to donate plasma. The blood banks provided details of the project on their websites and the media helped to inform the public. Many donors reported recovery from COVID-19 when they were called on to donate blood, and some were recruited through Koronastudien.no. Other convalescents who met donor requirements were accepted at some blood banks. Ensuring that blood bank staff were rapidly informed of constantly changing rules was a challenge. Several blood banks lacked procedures for plasmapheresis, and there was uncertainty about the requirements for shipping blood samples to other laboratories for antibody testing.

### *«Several blood banks lacked procedures for extracting plasma»*

According to the first recommendation from the European Centre for Disease Prevention and Control, there should be a delay of at least 14 days between a positive SARS-CoV-2 PCR test in a respiratory sample and convalescent plasma collection. After the discovery of virus particles more than two weeks after the first positive PCR test in some individuals in early May 2020, the Norwegian Directorate of Health prolonged this to 28 days. Most potential plasma donors therefore had to wait 28 days before the first antibody test.

Plasma was harvested in three ways: by plasmapheresis, where up to 650 mL of plasma is collected while the blood cells are returned to the donor; in a whole blood donation, where red blood cells and platelets are used for the production of ordinary blood components (giving 200–250 mL of plasma); or by thrombapheresis, where the main product is platelets and 400–500 mL of plasma is collected as part of the procedure, while red blood cells are returned to the donor. Following plasmapheresis, the donor was invited to three more procedures at least one week apart. Donors with sufficient antibody levels were encouraged to undergo a new series of donations after a few weeks.

In Norway, the only whole plasma product in current use is a chemical pathogen-inactivated, mixed plasma from approximately 1000 donors. In cases of COVID-19, convalescent plasma is transfused from individual donors, which increases the risk of transfusion-related acute lung injury (TRALI). The

recommendation was therefore to use donors who had not been transfused or women who had never been pregnant, or to test donors for antibodies against human leukocyte antigens (HLA). Plasma from donors with HLA antibodies was not used to treat patients.

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## Antibody assays

The first commercial ELISA-based tests for antibodies to SARS-CoV-2 were available at project launch, and more and better assays became available during the project period. Microbiology departments validated and established these methods, and the expert microbiology group contributed to the exchange of experience between the laboratories. The Department of Immunology (Oslo University Hospital) developed antigens and established a method that could be performed at the hospital. The assay was based on flow cytometry and was eventually adapted for large-scale automated antibody assays. This platform has been used in a number of projects [\(12–14\)](#).

*«One of the main aims of the microbiology group was to develop methods for quantifying neutralising antibodies to SARS-CoV-2, a method that requires virus culture in a specialist laboratory»*

One of the main aims of the microbiology group was to develop methods for quantifying neutralising antibodies to SARS-CoV-2, a technology that requires virus culture in a specialist laboratory. Having such assays available nationwide proved to be unrealistic. Consequently, the blood donor testing was largely based on the tests developed at Oslo University Hospital [\(13\)](#), where a minimum of 60 % angiotensin-converting enzyme 2 (ACE2) inhibitory capacity was considered satisfactory. Plasma must be harvested when antibody levels are high, and approximately 1500 units of 200–300 mL plasma were harvested in 2020. Bags with ACE2 inhibitory capacity > 60 % were released for patient treatment. For patients who received treatment before the antibody test was established, the units were not standardised in this way.

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## Plasma for Norwegian patients

The first case of a patient receiving plasma in Norway was described in the Journal of the Norwegian Medical Association [\(15\)](#), and individual patients were subsequently treated as from 2020. Norwegian doctors were reluctant to use a treatment with unclear effects, in contrast to many international peers who were treating hundreds of thousands of patients. Such extensive use may have represented a barrier to recruitment in randomised trials, thereby delaying the desired knowledge base for evaluating this form of treatment [\(16\)](#). When the results of the largest clinical trial, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial, were presented in January 2021, an

analysis of > 10 000 patients showed that treatment with convalescent plasma had no effect on disease duration or mortality when given to hospital patients with moderate to severe disease [\(17\)](#).

*«Norwegian doctors were reluctant to use a treatment with unclear effects, in contrast to many international peers»*

Analysis of subgroups from this large dataset nevertheless opened up the possibility of effects in some patient groups [\(18\)](#). Following reports that convalescent plasma at an early stage could reduce the risk of severe symptoms in the elderly [\(19\)](#) and benefit patients with a poor immune response [\(20\)](#), the Norwegian Association for Infection Medicine recommended in November 2020 that treatment with convalescent plasma could be considered in immunocompromised patients [\(21\)](#).

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## Planning clinical trials

The Norwegian Directorate of Health wanted plasma to be offered to relevant patients on a nationwide basis with collection of data from treated patients for subsequent analysis, regardless of any consent to participate in research studies. We therefore conducted an observational study (Norplasma MONITOR, REK no. 148622), which will be presented in the near future.

It was not possible to conduct a randomised trial to examine the efficacy of COVID-19 convalescent plasma because the hospitals were already enrolling patients in the Nor-Solidarity trial, and capacity and patient numbers were therefore insufficient for a parallel plasma trial. Instead, the clinical trial group planned a randomised controlled treatment trial with 500 nursing home patients. The trial was approved by the Regional Committees for Medical and Health Research Ethics on 30 June 2020 (Norplasma PLEIE, REK no. 152704).

Specialist transfusion teams from health trusts were to perform transfusions and provide follow-up in nursing homes that lacked such expertise, but the trial was logistically complicated and never received funding. Several nursing homes had major infection outbreaks before vaccines were available, and early intervention with convalescent plasma could have had a positive effect.

*«Rapid funding of Norwegian-led studies would clarify whether the experimental treatment is beneficial in a pandemic situation»*

Obtaining results from good international randomised controlled trials takes time. Rapid funding of Norwegian-led studies would clarify whether the experimental treatment is beneficial in a pandemic situation. Based on the experiences in this project, we believe that funding for randomised controlled treatment trials on the effect of convalescent plasma in selected patient groups should be part of a pandemic response, regardless of normal funding application deadlines. Plans for clinical trials must be in place so that applications can be submitted without delay as soon as extraordinary funds are

announced. In the next pandemic, clinical trials should target two patient groups: those with weakened immune systems who are unable to mobilise a satisfactory antibody response in time (20), and those with other known risk factors.

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