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COVID-19

Is convalescent plasma still useful as a covid treatment?

Enthusiasm for one of the earliest promising treatments for covid-19 has waned. Katharine Lang finds that convalescent plasma for covid may still have a place, particularly in immunocompromised people

Katharine Lang *freelance journalist*

What is convalescent plasma?

It's a form of passive immunisation. Blood plasma containing antibodies from one person is given to someone else with the same infection. It's been used since the late 19th century to treat diphtheria, scarlet fever, and pertussis and, more recently, haemorrhagic fevers such as that caused by the Ebola virus.[1]

Someone who has recovered from or been vaccinated against covid can donate covid convalescent plasma (CCP). This will contain antibodies to the strain of SARS-CoV-2 virus they were infected with, as well as antibodies created in response to any vaccine. Plasma can also be drawn from existing blood donations.

Is it an effective treatment for covid-19?

Yes—but only if given very early, before severe symptoms appear.

The World Health Organization had advised against CCP in 2021[2 3] after early randomised control trials showed little efficacy.[4] But most of those trials focused on hospital inpatients with severe covid, particularly those requiring intensive care.

Arturo Casadevall, chair of molecular microbiology and immunology at the Bloomberg School of Public Health, Johns Hopkins University in Baltimore, USA, says that the early trials were run in conditions where the treatment "couldn't work, so people concluded that it wouldn't work"—namely, that the treatment was administered too late to have an effect. "Antibodies only work when the virus is active, not in the later stages [of disease]," he says.

Subsequent studies have shown how crucial timing is for CCP to work. We now know that by the time patients are admitted to intensive care with severe symptoms it's too late for CCP to have much benefit. A systematic review, published as a preprint in June 2023,[5] concluded that CCP was no longer effective one week after symptom onset (the time frame for mounting an endogenous immune response) or in patients in intensive care.

A 2019 meta-analysis of outpatient CCP treatment found a 3.7% absolute risk reduction and a 30.1% relative risk reduction for all cause hospital admission.[6] High titre transfusion, given within five days of symptom onset, increased this to a 7.6% absolute risk reduction and a 51.4% relative risk reduction. Daniele Focosi, specialist in haematology and PhD in virology at the North-Western Tuscany Blood Bank, Pisa University Hospital in Italy, says that high titre transfusions contain a high concentration of neutralising antibodies, giving the recipient a high dose of antibodies without overloading the person with fluid. When the treatment was given more than five days after symptom onset, or with antibody titres below median concentrations, no effect was seen.

The Capsid trial in Germany has shown a significant benefit in patients admitted to hospital who were given CCP containing a higher cumulative amount of neutralising antibodies, with the first transfusion given sooner after symptom onset.[7] Capsid found that 43.4% of patients in the CCP group and 32.7% in the control group achieved the primary outcome (survival and no longer fulfilling criteria for severe covid-19 on day 21). They also showed faster clinical improvement and were discharged on average 30 days earlier (21 days *v* 51 days) than the control group who received no CCP.

A separate trial in older adults found that high titre CCP administered soon after infection reduced the progression of covid-19, as 16% of those given CCP and 31% of control patients developed severe respiratory disease.[8]

Who will benefit most?

Primarily, it will help immunocompromised and immunosuppressed people for whom covid-19 remains a risk, says Casadevall. "We don't need convalescent plasma for 96% of the population," he explains. "It is immunocompromised people, particularly those who are B cell depleted, who need it. When they get covid, it can become chronic. Antivirals—remdesivir and Paxlovid—often don't clear it."

He adds, "For immunocompetent people, what kills people with covid-19 is inflammation, so you need to treat with convalescent plasma in the early stages to clear the virus before inflammation goes out of control."

Casadevall emphasises the importance of convalescent plasma for this latter group. "Now that covid is endemic, we aren't going to get rid of it," he says. "Our challenge now is immunosuppressed people. We need a therapy for those who cannot make antibodies. Immunosuppressed people are not dying of inflammation, because their immune systems do not work." He adds that the timing of when you give the treatment actually matters less in these patients because they can't clear the virus in the first place.

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With the virus changing all the time with new variants, the need for early diagnosis and treatment is crucial. "Many monoclonal antibody therapies are no longer effective against the newer variants of SARS-CoV-2," says Lise Estcourt, director of NHS Blood and Transplant's Clinical Trials Unit in the UK. "The virus has changed, but monoclonal antibody therapies cannot change [quickly enough] with it."

Convalescent plasma, on the other hand, comes from people who have made antibodies themselves—adapted to whatever virus forms they were in contact with (or vaccinated with). "CCP can adapt over time as plasma donors are exposed to new infection or updated vaccinations," says Estcourt.

Evidence for the benefit of CCP in immunocompromised people is growing. A 2023 systematic review of studies[9] found that transfusion of convalescent plasma was associated with a mortality benefit in immunocompromised patients with covid-19.

Pierre Tiberghien, professor of medicine, immunology at Université de Franche-Comté in France and president of the European Blood Alliance, tells *The BMJ* that despite a lack of trials assessing specifically immunosuppressed patients with covid-19, some are under way. These include the Remap-Cap trial, which is assessing the benefits of CCP in addition to standard care for immunocompromised patients in the UK.[10]

What does the future hold?

Even before results are available from further trials, the benefit of convalescent plasma for people who can't mount an immune response against infection is undoubted. Tiberghien says, "The future use of CCP for covid-19 will most probably stay focused on immunosuppressed patients—namely, patients unable to generate an efficient immune response after vaccination or prior infections."

The good news is that there's no shortage of CCP. Casadevall says, "Most people have a lot of antibody in their blood, because they've had several vaccinations and probably had covid. It's no longer a limited resource . . . the world is now full of convalescent plasma."

Focosi adds that the treatment is cost effective and, thanks to hybrid immunity due to circulating strains of SARS-CoV-2, plasma is likely to include antibodies that could protect against newer variants that the donor has never encountered.[11 -13]

CCP may also have other benefits. New evidence is emerging that early treatment with CCP may also help to prevent post-covid conditions, or long covid. A recently published randomised trial found that its early administration significantly reduced the odds of long covid.[14]

One problem, however, is that CCP doesn't have much support because it's not a profitable form of treatment—even though some, such as Tiberghien, say that it's much more cost effective overall than existing drug treatments. He explains, "While several months are necessary to produce one or more new monoclonal antibodies more suited to the evolution of circulating viral strains, convalescent plasma—notably from vaccinated donors—has demonstrated increased resilience to immune resistant SARS-CoV-2 variants; increased scalability, as it may rely on existing collection infrastructure; [and] increased adaptability and overall affordability."

Experts fear that the lack of interest from drug companies may mean that the funding to develop CCP as a therapeutic line will always be limited. However, says Casadevall, "One of the good legacies of the pandemic is that we learnt how to use convalescent plasma. We know when it does and doesn't work. If we encounter another viral calamity, such as bird flu, we'll know how to use it."

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