Should convalescent plasma be used for COVID-19?

This write-up summarises a rapid evidence review of convalescent plasma in patients with COVID-19. The information may be revised as new evidence emerges.

Background

Convalescent plasma is blood plasma from a person who has recovered from an infection. It contains antibodies against the infection such as COVID-19. Recovered patients with high titres of neutralising antibody can donate plasma for administration to those at-risk to prevent infection (prophylaxis) or to those with confirmed disease to reduce symptoms and mortality. This is known as passive antibody therapy or passive immunotherapy.

Related to convalescent plasma is immunoglobulin for intravenous use (IVIG), which contains concentrated globulin from pooled human plasma with the benefit that it can be given in a smaller volume and is a more uniform product compared with plasma. Hyperimmune immunoglobulin (H-IVIG) is IVIG chosen for its high titre of specific antibodies.

Published articles have raised convalescent plasma as a potential treatment option for COVID-19 citing its use and perceived efficacy in SARS, Ebola virus, H1N1, and MERS outbreaks. International news coverage has reported that convalescent plasma has been applied in China against COVID-19.

The Food and Drug Administration (FDA) in the USA has listed COVID-19 convalescent plasma as an emergency Investigational New Drug (eIND) for patients who are critically ill with COVID-19. This allows COVID-19 convalescent plasma to be used as treatment for an individual patient by a licensed physician upon FDA authorisation. Eligible patients must have laboratory confirmed COVID-19 with severe or immediately life-threatening disease. The FDA also provides guidance on the criteria for plasma collection and the eligibility of both donors and recipients.

Clinical evidence

There is no published evidence for convalescent plasma, IVIG, or H-IVIG in the treatment of patients with COVID-19. Existing literature covers the use of these products in viral severe acute respiratory syndrome (SARS) and severe influenza with conflicting results:

- A systematic review of convalescent plasma in SARS and severe influenza showed a reduction in mortality especially when treatment was administered early (odds ratio [OR] of 0.25, 95% confidence interval [CI]: 0.14 to 0.45; $I^2$ 0%). In addition, there was limited evidence of a reduction in the use of critical care resources and hospitalisation length. The studies were of low quality and predominantly uncontrolled.
- A recent randomised controlled trial (RCT) compared H-IVIG and placebo in 313 hospitalised participants with influenza. The primary endpoint was an outcome with six categories describing clinical status at day seven (ranging from death to resumption of normal activities post discharge) and the adjusted OR was 1.25 (95% CI: 0.79 to 1.97; p=0.33). The investigators concluded that H-IVIG plus standard care (mostly oseltamivir) was not superior to placebo.
- Anti-influenza plasma plus standard care was compared with standard care alone in an RCT of 98 patients hospitalised with severe influenza A or B. No significant effect of plasma treatment on time to normalisation of respiratory status was observed (OR 1.17 95% CI: 0.96 to 3.06; p=0.069) but the treatment was well tolerated. A follow up phase III RCT was started but terminated early and no significant benefit was observed.
- Convalescent plasma was fractionated to H-IVIG and compared with IVIG in an RCT in patients with severe influenza A in the ICU requiring ventilation. The investigators found that respiratory viral load was significantly lower at days 5 (p=0.04) and 7 (p=0.02) in the H-IVIG group. Subgroup analysis revealed that H-IVIG was the only factor to reduce mortality (OR 0.14; 95% CI: 0.02 to 0.92; p=0.04).
Four trials have been registered and are in planning or active recruitment phases with data anticipated to mature in the near future.

**Table 1: Ongoing or planned studies for convalescent plasma in patients with COVID-19**

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Date of primary completion</th>
</tr>
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<tr>
<td>NCT04292340</td>
<td>observational</td>
<td>Anti-SARS-CoV-2 inactivated convalescent plasma</td>
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<tr>
<td>NCT04264858</td>
<td>OL clinical trial</td>
<td>Immunoglobulin of cured patients</td>
<td>γ-globulin</td>
<td>April 2020</td>
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<td>NCT04261426</td>
<td>OL, phi/phiII, RCT</td>
<td>IVIG</td>
<td>standard care</td>
<td>April 2020</td>
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<tr>
<td>NCT04321421</td>
<td>OL, longitudinal assessment</td>
<td>Hyperimmune plasma</td>
<td>-</td>
<td>May 2020</td>
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</tbody>
</table>

**Abbreviations:** OL, open label; phi, phase II; phiIII, phase III; RCT, randomised controlled trial; SARS, severe acute respiratory syndrome.

### Recommendations from professional bodies

The World Health Organization (WHO) makes no official mention of convalescent plasma or related products specifically in relation to COVID-19 and it does not appear in the interim clinical guidance. However, Dr Mike Ryan (head of WHO health emergencies program) notes “hyperimmune globulin… has been proven “effective and life-saving” against other infectious diseases. It is a very important area to pursue [although] it has to be carefully timed and it’s not always successful.”

The China National Health Commission (NHC) has issued a seventh edition of guidance for COVID-19 diagnosis and treatment in which it refers to the use of recovered patients’ plasma therapy as suitable for severe and critically severe patients with rapid disease progression.

COVID-19 operational recommendations from the Peking Union Medical College Hospital list early intravenous infusion of human immunoglobulin for critically ill patients based on their clinical condition.

In addition to the eIND classification, the US FDA, National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) are developing master protocols to coordinate the collection and use of COVID-19 convalescent plasma.

### Conclusion

There is currently no published evidence on the use of convalescent plasma for treating COVID-19 infection. Studies are underway with results expected later this year. Evidence to date for convalescent plasma (including H-IVIG) is for the treatment of other viral infections with mixed results. Positive survival benefit is based on small, low-quality studies and case reports, while two RCTs in severe influenza do not show any significant benefit.

### References

18. Taisheng Li (2020) Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0), Emerging Microbes & Infections, 9:1, 582-585