RAPID RESPONSE

COVID-19 and Passive Antibody Therapy
(Convalescent Plasma)

Produced by the Institut national d’excellence en santé et en services sociaux (INESSS)

March 31, 2020
This document, as well as the findings and position statements stated herein, were drafted in response to a request from the Ministry of Health and Social Services regarding Quebec’s COVID-19 health emergency. The objective was to carry out a summary review of data in published documentation and in grey literature to inform public decision-makers and health care professionals. Given the expedited nature of this review, the subsequent findings are not based on an in-depth literature search or an assessment of studies involving a systematic method. Due to this public health emergency, the INESSS is staying abreast of all new data that could result in a change in its position.

Position of INESSS

Despite the encouraging preclinical data on passive antibody therapy (convalescent plasma) to treat COVID-19, the currently available data do not support its widespread use in infected patients. Additional data are expected from clinical trials that are currently underway.

- The uncertainty about the safety and efficacy of these treatments do not support widespread use of convalescent plasma in patients diagnosed with COVID-19, regardless of the stage of the disease, or as prophylaxis.
- Every effort should be made to ensure that research protocols integrate patients with a confirmed diagnosis into receiving this treatment.

Passive antibody therapy, which involves the direct administration of antibodies from recovered patients and is directed against a pathogen agent, is a possible treatment option in the current fight against COVID-19, pending the development of a vaccine or other recognized treatment [Casadevall and Pirofski, 2020]. This technique, which dates back to the 19th century, can be used prophylactically to provide protection against an infectious agent, or to treat acute infections. The objective is to provide immediate temporary immunity for individuals at risk. Passive antibody therapy has been widely used to help control poliomyelitis [Park, 1932], measles [Gallagher, 1935; Park, 1926], mumps [Rambar, 1946], and influenza [Luke et al., 2010] epidemics. The antibodies given in passive therapy may be derived from a transfusion of plasma collected from patients recovered from the disease or from an immunoglobulin concentrate from a plasma pool from various recovered patients [Young et al., 2014].

Based on experience with other coronavirus strains — such as SARS-CoV-1, influenza A, and MERS-CoV — plasma from recovered patients contains antibodies that can neutralize the specific virus [Ko et al., 2018; Mair-Jenkins et al., 2015; Zhang et al., 2005]. According to Public Health England, passive antibody therapy using convalescent plasma is a valid treatment option for MERS-CoV infections [Public Health England, 2017]. The recent outbreak of the Ebola virus disease in West Africa led to a focus on using convalescent plasma for the treatment of infectious diseases given the lack of any available vaccine, drugs, or other effective treatments [Mulangu et al., 2019; Gunn et al., 2018; Sahr et al., 2017; Delamou et al., 2016; van Griensven et al., 2016]. And in 2014, the World Health Organization (WHO) recommended the use of plasma collected from patients recovered from the Ebola virus as an empirical treatment during the outbreak in West Africa [WHO, 2014].
Brief Overview of the Request

Some clinicians in Quebec and in other parts of the world have brought up the possibility of using passive antibody immunization with convalescent plasma to treat COVID-19–infected patients, thereby prompting questions about the therapy’s potential promise.

Methodology

Assessment questions: Is the promising nature of passive antibody therapy via the administration of convalescent plasma sufficient to add it to the list of COVID-19 treatment options? And if so, what patient subpopulation would be most likely to benefit from this treatment?

Selection criteria: All studies were considered that involved the treatment of patients with a viral infection (respiratory or non-respiratory) who received passive antibody immunization (convalescent plasma).

Review methods:

Date of search: March 21, 2020

Keywords used: SARS\textsuperscript{a}, MERS\textsuperscript{b}, Ebola, convalescent plasma, viral respiratory infection, coronavirus

Databases consulted: PubMed

Other data sources: References from identified documents, grey literature (websites of scholarly societies, governments, etc.)

Languages: English, French

\textsuperscript{a} Severe acute respiratory syndrome.
\textsuperscript{b} Middle East respiratory syndrome.
Background and Current State of Knowledge

To date, the use of passive antibody therapy with convalescent plasma in patients infected with the COVID-19 virus has not been mentioned as a treatment option in most identified clinical practice guides and other guidelines (WHO, ECDC, the BMJ–British Medical Journal, SIMIT, HCSP–High Council of Public Health in France, SEFH, CDC in the US, and the Government of Canada). Only China identifies passive antibody therapy as a treatment option in patients with severe and rapidly progressing disease, basing that on the CNHC–Complementary & Natural Healthcare Council recommendations.

China

In addition to the preliminary outcomes of a case series outlined in the following section, seven clinical studies are currently underway. Three of these studies involve all levels of disease severity for COVID-19, whereas the others focus on patients with severe disease. Study outcome measures include disease severity, duration of hospitalization, and mortality.

United States

The FDA recently launched a call for projects to determine the efficacy of convalescent plasma in the treatment of COVID-19 through clinical trials. The purpose of this simplified administrative measure is also to facilitate access to convalescent plasma treatment for severely ill patients. The American Red Cross is supporting the FDA in this initiative to collect and process plasma from patients who have recovered. Approval has already been granted for two clinical studies currently underway at the Mayo Clinic and Johns Hopkins Hospital. These studies involve patients hospitalized for COVID-19–related complications and patients exposed to COVID-19, respectively. And New York City recently announced that it is using this treatment option for patients with severe infections. Several American partners are also working to develop a protocol to collect and use SARS-CoV-2 convalescent plasma.

Europe

An interventional clinical trial with a cohort of 49 patients is being carried out in Italy. The purpose of the trial is to determine the efficacy and safety of convalescent plasma for the treatment of patients with COVID-19 presenting with moderate-to-severe respiratory distress. Data will be compiled on mortality, time to extubation, length of hospital intensive care stay, time to CPAP weaning, as well as viral load.


NCT04292340, ChiCTR2000030929, ChiCTR2000030702, ChiCTR2000030627, ChiCTR2000030179, ChiCTR2000030039, ChiCTR2000030010, ChiCTR2000029850, ChiCTR2000029757


NCT04325672

NCT04323800


NCT04321421

Continuous positive airway pressure.
Scientific Knowledge Overview — COVID-19

Preliminary results of a Chinese case series of five critically ill patients (on a ventilator) were recently published [Shen et al., 2020]. The data were collected from January 20, 2020 to March 25, 2020 and outcomes were compared before and after convalescent plasma transfusion. Plasma, obtained from five patients who recovered from SARS-CoV-2, was administered between 10 and 22 days after admission. Of the five patients, three were discharged from the hospital (length of stay: 53, 51, and 55 days) and two patients were in stable condition at 37 days post-transfusion. Although these preliminary results are encouraging, they are derived from a non-randomized and uncontrolled study. As well, four of the five patients had no comorbidities prior to being infected with the virus, and all patients received various drug treatments (steroids and antivirals) concurrently with the convalescent plasma transfusion. Consequently, the actual effects attributed to the transfusion of convalescent plasma need to be confirmed through additional clinical trials.

Scientific Knowledge Overview — Other Respiratory Viruses

A series of three case studies in the 2015 Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in Korea reported recovery in three patients in respiratory distress who were treated with convalescent plasma [Ko et al., 2018]. However, it is difficult to attribute recovery with the use of convalescent plasma, as, according to the study, antibody levels detected in the plasma used and patient serological responses were low for two of the three cases.

A systematic review and meta-analysis published in 2015 [Mair-Jenkins et al., 2015] evaluated the effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections (SARIs) of viral etiology:

- According to the meta-analysis, there was a significant reduction in risk of mortality (odds ratio = 0.25)\(^1\) in patients who received convalescent plasma or serum. The meta-analysis compiled data from eight comparative studies: of SARS-CoV infection [Soo et al., 2004; Zhou et al., 2003], influenza A (H1N1)pdm09 infection\(^m\) [Hung et al., 2011; Chan et al., 2010], avian influenza A (H5N1) infection [Yu et al., 2008], and of Spanish influenza A (H1N1) [Gould, 1919; Kahn, 1919; O'Malley, 1919]. However, it is important to point out the following:
  - Because of the limited available evidence, the authors considered the meta-analysis to be exploratory.
  - According to the authors, the eight comparative studies included in the meta-analysis involved a moderate-to-high risk of bias.
  - There are limited data on viral antibody levels in the patients treated with convalescent plasma.

- The systematic review reported the following:
  - An observational study and a case series reported that convalescent plasma treatment reduced the length of hospitalization [Cheng et al., 2005; Soo et al., 2004], whereas a comparative case study reported no difference [Chan et al., 2010].
  - A retrospective observational study and two case studies noted non-significant reductions in the time spent in intensive care [Chan et al., 2010].

\(^{1}\) 95% CI, 0.14 to 0.45; \(P < 0.001\); \(I^2 = 0\%\)

\(^{m}\) 2009 pandemic influenza A (H1N1).
Two studies, considered by the authors to have a high risk of bias, reported a rapid decrease in viral load in the respiratory system of patients treated with convalescent plasma [Yeh et al., 2005; Kong, 2003].

Figure 1: Forest Plot of Pooled Odds Ratios of Mortality Following Treatment With Convalescent Plasma or Convalescent Serum (Eight Studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al</td>
<td>0.09 (.00–2.01)</td>
<td>3.55</td>
</tr>
<tr>
<td>Soo et al</td>
<td>0.08 (.00–1.50)</td>
<td>4.01</td>
</tr>
<tr>
<td>Chan et al</td>
<td>0.24 (.01–8.62)</td>
<td>2.74</td>
</tr>
<tr>
<td>Gould</td>
<td>0.18 (.04–.78)</td>
<td>16.63</td>
</tr>
<tr>
<td>O’Malley et al</td>
<td>0.21 (.06–.72)</td>
<td>22.73</td>
</tr>
<tr>
<td>Hung et al</td>
<td>0.21 (.06–.68)</td>
<td>24.99</td>
</tr>
<tr>
<td>Zhou et al</td>
<td>3.53 (.11–111.67)</td>
<td>2.96</td>
</tr>
<tr>
<td>Kahn</td>
<td>0.46 (.13–1.62)</td>
<td>22.40</td>
</tr>
<tr>
<td></td>
<td>0.25 (.14–.45)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.
Source: Mair-Jenkins, 2015

Scientific Knowledge Overview — Ebola Virus and Measles

In 2016, a non-randomized, comparative study [van Griensven et al., 2016] conducted in patients infected with the Ebola virus who received two transfusions of 200 mL to 250 mL of compatible plasma from recovered patients showed a 3% reduction in the risk of mortality compared to the control group of patients who had been treated at the same centre during the previous five months. The transfusions were given up to two days after diagnosis and the level of neutralizing antibodies in the plasma was unknown at the time of administration. No adverse effect was observed with the use of convalescent plasma.

A meta-analysis [Young et al., 2014] showed the superiority of passive immunity obtained with the administration of immunoglobulins for preventing measles compared to no treatment (RR 0.17). Although less effective than the administration of immunoglobulins, intramuscular injection of convalescent serum was shown to be a beneficial treatment option in preventing measles in individuals who have had contact with the virus (RR 0.2 and RR 0.49). Passive immunization with serum from recovered patients was given within seven days after exposure to the virus. The data are insufficient to determine a minimum effective antibody dose.

n 95% CI: 0.08 - 0.36
o 95% CI: 0.15 - 0.29 compared to the control group
p 95% CI: 0.44 - 0.54 compared to the immunoglobulin group
Adverse Events
Few adverse events or complications associated with the use of passive immunization with convalescent plasma are reported in the literature. However, fluid overload, transfusion-related acute lung injury, and anaphylactic shock may be related to its use [MacLennan and Williamson, 2006]. Some isolated cases of these events have been reported [Chun et al., 2016; Mora-Rillo et al., 2015]. As well, organizations that collect and prepare plasma have a number of measures in place to mitigate the risk of infection. However, the risk of transmission of harmful infectious agents is low but still possible.

Strength of the Evidence
There is limited literature on passive immunization with convalescent plasma and they involve a number of bias risks. The literature mainly involves the treatment of acute infections. Very few studies have a control group, most studies are case studies or case series, and most participants were in declining health or critically ill. In addition, very few methodological or statistical measures to control bias have been applied in the studies.

INESSS Findings
- Encouraging preliminary data on the safety and efficacy of convalescent plasma in treating COVID-19 (SARS-CoV-2) have been published recently. Other clinical studies are currently underway.
- A systematic review and meta-analysis presents positive mortality rate outcomes following treatment with convalescent plasma in patients infected with SARS-CoV, influenza A (H1N1)pdm09, avian influenza A (H5N1), and Spanish influenza A (H1N1).
- In most of the studies and reviews identified, the authors find that rapid initiation (at onset of symptoms) of convalescent plasma therapy is best to maximize the potential benefits.
- Despite the widely recognized importance in the literature of rapidly initiating treatment, most experiences in a real-world care setting considered this treatment as a last-resort option for severely ill patients.
- No result on the preventive effect of giving convalescent plasma subsequent to contact with coronavirus was identified. However, a clinical benefit was observed with the measles virus.
- The antibody titre present in the recovered plasma can vary a great deal between patients and is a determining factor in treatment success. As well, the antibody level required to produce passive immunity in an at-risk patient is not known.
- To date, only a limited number of patients with COVID-19 have received this investigational treatment through clinical trials and compassionate access programs.
- Despite the limited number of publications, convalescent plasma’s safety profile does not seem to be an issue. However, there are still risks of transmission of infectious agents, fluid overload, transfusion-related acute lung injury, and anaphylactic shock.
References


