Hi Dr. Hahn and Anand, see this table as per our discussion today.

Michael and Wolf, this was the evidence I was referring to, it's the current 18 studies on convalescent.

I wrote up a summary now quickly and my views...I did a risk of bias...as you see even the RCTs have high risk of bias due to open label, underpower etc.

I share this to help give us cover in our decisions. It to me is well positioned. My view is that CP should be used and is showing to be safe, and an EUA as an example, if one is ever contemplated is well credible and has merit. NIH has stepped out of their lane based on what I am reading now and I will tell you this, that nonrandomized evidence will shortly be mainstreamed alongside RCT evidence once it is of high quality evidence.

Not because it is a RCT means it is optimal. Evidence based medicine is changing and I am part of the GRADE working group writing guidance on this. A well conducted nonrandomized observational study (ideally prospective) that has large sample size, and has good multivariate adjustments, large magnitude of effect, a dose response relationship, and control for confounding etc. will TRUMP a poorly conducted RCT...pardon the pun.

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Best,

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Assistant Professor  
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https://protect2.fsociety.com/url2k=9425937a-e878e51-9425a245-0c47a6d17cc-e80f6f5f7d76a&cu=http://guidecanada.org/
Convalescent Plasma (review of 18 studies; 2 reviews, 2 RCTs, 14 nonrandomized studies):

- At this time, the research on convalescent plasma (CP) is underpinned by largely small-sample size observational studies with small event number, and they are confounded mainly because of the lack of prognostic balance.
- One very large convenience sample (observational design) of 20,000 patients on adverse events adds important information to the possible use of CP in COVID-19 patients. The convenience sample appears to indicate that CP is generally safe and well tolerated in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.
- A Cochrane systematic-review found 20 studies (1 RCT, 3 controlled NRSIs, 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma. Researchers concluded there is great uncertainty on whether convalescent plasma is beneficial for people admitted to hospital with COVID-19.
- The RCT looked at CP (n=52 patients) vs standard treatment alone (n=51) with a median age of 70 and 58.3% of patients being male. Hypertension, cardiovascular disease, diabetes, kidney disease, and liver disease were the principle types of co-morbidities.
- The trial was stopped early before arriving at its targeting sample size of 200 suggestive that it was underpowered.
- Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the CP group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; p = 0.03); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; p = 0.83) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0% OR, 0.65 [95% CI, 0.28-1.56]; p = 0.30) or time from randomization to discharge (51.0% vs 36.6% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; p = 0.12). CP treatment was associated with a higher conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 85% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; p < .001). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care.
- The RCT was open-label, randomization and concealment appeared reasonably well done. Methodologically an improvement from among the COVID-19 research published to date but not optimal methods wise.
- Larger sample sized RCTs are needed urgently to establish the benefit (or harm) of CP, and whether this treatment option will be stand-alone or work optimally in combination with other therapies.
- On balance the preponderance of nonrandomized studies were small in size and methods not optimal but collectively suggest that there is benefit and that CP is not harmful. The limited RCT evidence was not optimal methodologically and very small sample size. While evidence accumulates, CP should be used within ethically approved RCTs and off-label, as well as some form of EUA.
<table>
<thead>
<tr>
<th>OBSERVATIONAL (clinical)</th>
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<tbody>
<tr>
<td><a href="7"> HYPERLINK &quot;https://doi.org/10.1001/jama.2020.4783&quot;</a>; case-series; 2020</td>
<td>Convalescent plasma (CP) to all; 5; age range 36-73 years; 60%</td>
</tr>
<tr>
<td>1 has hypertension and mitral insufficiency; antivirals (lopinavir/ritonavir; interferon alfa-1b; favipiravir; ribavirin; darunavir) and corticosteroid methylprednisolone</td>
<td>Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range: 172 - 284 before and 366 - 500 after). Viral loads also decreased and became negative within 12 days after the transfusion, and anti-SARS-CoV-2-specific ELISA and neutralizing antibody tests increased following the transfusion (range: 4.00 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 54, and 55 days), and 2 are in stable condition at 57 days after transfusion.</td>
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<td>High; Did not apply GRADE</td>
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<tr>
<td><a href="7"> HYPERLINK &quot;https://doi.org/10.1073/pnas.200416811&quot;</a>; case-series; 2020</td>
<td>CP to all; 10; median age was 52.5 years (IQR, 45.0 - 59.5); 60%</td>
</tr>
<tr>
<td>Hypertension 30%, cardiovascular and cerebrovascular disease 10%; ribavirin, remdesivir, Interferon-a, oseltamivir, peramivir and corticosteroid methylprednisolone</td>
<td>Following plasma transfusion, the level of neutralizing antibody quickly increased to 1:800 in five cases, and maintained at a high level (1:800 in remaining of cases). Researchers reported that the clinical symptoms were substantially improved. They also found a decrease in oxygen saturation within 5 days. Several parameters tended to improve as compared to pre-transfusion. Important parameters included &quot;increased lymphocyte counts and decreased C-reactive protein. Radiological examinations showed varying degrees of absorption of lung lesions within 7 days. The viral load was undetectable after transfusion in seven patients who had previous viremia&quot;. No severe adverse effects.</td>
</tr>
<tr>
<td>High; Did not apply GRADE</td>
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<tr>
<td><a href="7"> HYPERLINK &quot;https://doi.org/10.1015/j.cest.2020.03.039&quot;</a>; case-series; 2020</td>
<td>CP to all; 4; 31, 55, 69, 73 years old and F, M, M, and pregnant F respectively</td>
</tr>
<tr>
<td>None reported; ribavirin, lopinavir/ritonavir, remdesivir, Interferon-a, oseltamivir, albumin, zidovudin and immunoglobulin, antibacterial and antifungal drugs</td>
<td>Researchers reported no serious adverse reactions and all 4 patients recovered from COVID-19.</td>
</tr>
<tr>
<td>High; Did not apply GRADE</td>
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<tr>
<td><a href="7"> HYPERLINK &quot;https://doi.org/10.1101/2020.04.07.20056440&quot;</a>; case-series; 2020</td>
<td>CP to all three; not reported; not reported</td>
</tr>
<tr>
<td>Not reported; not reported</td>
<td>There were 2 patients with negative conversions and 1 failure due to anaphylaxis shock (discontinued); 1 patient treated on 12th day admission, turned severe, 2nd treatment, then significantly improved (nucleic acid test became negative and symptoms improved) and met discharge criteria on 26th day, 2nd patient, treatment on 27th day, the nucleic acid test became negative 4 days later, 3rd patient was a 31-year old pregnant woman who suffered anaphylaxis shock and CP was discontinued.</td>
</tr>
<tr>
<td>High; Did not apply GRADE</td>
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<td>Hyperlink</td>
<td>Description</td>
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<td>1 patient, 50-year-old female</td>
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<tr>
<td>[HYPERLINK &quot;<a href="https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985">https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985</a>&quot; ]</td>
<td>CP (n=6) vs no CP (15); 21 CP median 61.5 (31.5-77.8) vs control median 73 (60-79); 76% Hypertension 19%, diabetes 28.5%, liver disease 9.5%, cardiovascular 4.7%, kidney 4.7%, antiviral treatment 76%, IVIG 90%, glucocorticoid pulse 76%. There was fever 85.7%, cough 90.5%, fatigue 67%, dyspnea 76%, bilateral pneumonia in 95%</td>
</tr>
<tr>
<td>[HYPERLINK &quot;<a href="https://www.ncbi.nlm.nih.gov/pubmed/?term=Use+of+Convalescent+Plasma+Therapy+in+Two+Patients+with+Acute+Respiratory+Disease+++Syndrome+in+Korea">https://www.ncbi.nlm.nih.gov/pubmed/?term=Use+of+Convalescent+Plasma+Therapy+in+Two+Patients+with+Acute+Respiratory+Disease+++Syndrome+in+Korea</a>.&quot;]</td>
<td>CP, 2; ages 67 and 71; 1 males and 1 female Both critically ill medical history of hypertension, previous treatment (e.g., different drugs/therapy, current therapy, vaccination) Convalescent therapy: 400 mg of Hydroxychloroquine once daily and Lopinavir/Ritonavir 400 mg/100 mg twice daily, empirical antibiotics, intubation and mechanical ventilation case, IV methylprednisolone (0.5 g/kg/day daily). Both received Lopinavir/Ritonavir and hydroxychloroquine but showed persistent fever, rapidly aggravated hypoxemia and progressive bilateral infiltrations in accordance with the criteria of severe ARDS; following CP infusion, the patients showed improved oxygenation and chest X-rays with decreased inflammatory markers and viral loads; researchers reported that when used with systemic corticosteroids, there is the possibility of reducing excessive inflammatory response by corticosteroids as well as promoting the reduction of viral loads by convalescent plasma simultaneously.</td>
</tr>
<tr>
<td>[HYPERLINK &quot;<a href="https://www.medrxiv.org/">https://www.medrxiv.org/</a>&quot;]</td>
<td>5000 patients (of 8,932 enrolled patients with COVID-19) received CP; 5000; median age 62.3 (18.5, 72% respiratory failure, 63% dyspnea, 62% blood oxygen saturation ≤ 81% patients had severe or life-threatening COVID-19 and 949 (19%) were judged to have a high risk of progressing to severe or life-threatening COVID-19; prior to COVID-19 convalescent plasma transfusion, a total of 3,315 patients (66%)</td>
</tr>
</tbody>
</table>
were admitted to the ICU; incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%. Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (n=4), transfusion-associated circulatory overload (TACO), n=7 transfusion-related acute lung injury (TRALI; n=1), and seven allergic transfusion reactions (n=3); 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfused by the treating physician. The seven-day mortality rate was 33.3%. Researchers suggested the study is safe in a hospital setting to be used in COVID-19 and warrants further study.

Note: large case-series, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, not optimally comparative, 26-optimal reporting of methods and outcomes.

[ HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.05.20.20102236v1"]


[ HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.05.26.20113373v1.full.pdf"]

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sets/raw/Health\%20Advance\%20Journal/\%20JMP\%20Jcp\%20mcp_ft95_6_8.pdf"\n\n2) observational convenience sample, 20/20

Patients had been transfused with COVID-19 convalescent plasma, thus, 7-day mortality data is presented for all 20,000 patients; 20,000, 7.0/18-39 years, 31.8%; 40-59 years, 27.1%; 67-67, 20.6%; 70-70, 12.8%, 80 and over, 60.8% males, judged to be unrelated to the plasma transfusion per se; the seven-day mortality rate was 8.9% (82.4%), and was higher among more critically ill patients related to less immune competence, including patients admitted to the intensive care unit who were admitted 10.5%; vs. 7.0%, mechanically ventilated per ventilated 12.1% vs. 6.2%, and with septic shock or multiple organ dysfunction failure vs. those without dysfunction/failure 14.0% vs. 7.6%.

**[HYPERLINK](https://pubmed.ncbi.nlm.nih.gov/2269443/) 104; observational; 2020**

189 patients, 115 plasma, 74 control, mean age 56, 55.6% male. Hypertension 21.9%, diabetes 22.9%.

Comparison of outcomes including all-cases mortality, total hospitalization days and patients' need for intubation between the two patient groups shows that total of 98 (9.9%) patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7%) patients in control group. Length of hospitalization days was significantly lower (9.6 days) for convalescent plasma group compared with that in control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while that was 20% in control group.

Note: Nonrandomized design of the bias is an issue and confounding bias, small sample size and events; control group comprised of mainly patients with other illnesses. Study included patients and also co-interventions with antivirals.

**[HYPERLINK](https://www.mendeley.com/content/10.1101/2020.08.22/165719.pdf) 104; observational case series, 2020**

16 patients, case-series, all administered CP; age range 30-90, 68.7% males. Hypertension 25%, diabetes 19%, CHD 19%, NR.

Among the patients, 10 of them had a consistently positive result of viral NAAT test before convalescent plasma transfusion. Eight patients (8/10) became negative from day 2 to day 6 after transfusion. Severe patients showed a shorter time of NAAT test turning negative after transfusion (mean 82.17 vs. 50.0, P = 0.056). Two critically ill patients transfused plasma with lower antibody level remained a positive result of NAAT test. CRP level demonstrated a decline 1 day after convalescent plasma treatment, compared with the baseline (P = 0.017). No adverse events were observed during convalescent plasma transfusion.

Note: case-series, small sample size, very provocative findings.

**RCT (clinical)**

**[HYPERLINK](https://jamanetwork.com/journals/jama/article-abstract/2776939) 105; median age, 62-78 years; 58.3% male**

Hypertension 8.8%, cardiovascular disease 25%, cerebrovascular disease 13.5%, diabetes 0.6%, kidney disease 5.8%, liver disease 10.7%.

Among those with severe disease, the primary outcome occurred in 91.5% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32], P = .05); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.83 [95% CI, 0.30-2.63], P = .83) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; P = .30) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; P = .12). CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.59 [95% CI, 3.91-33.18]; P < .001). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care. Researchers concluded that CP did not result in a statistically significant improvement in time to clinical improvement within 28 days, and no improvement in the risk of death.

Note: the trial was terminated before it reached its targeted original sample size of 209 patients; only 103 were enrolled (for whom randomization was stratified by disease severity, the [PAGE * MERGEFORMAT]
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**Systematic review**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RCT</td>
<td>Treatment A</td>
<td>Placebo</td>
<td>Effect</td>
<td>Randomization</td>
<td>Significant difference</td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
<td>Treatment B</td>
<td>Placebo</td>
<td>Effect</td>
<td>Randomization</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>3</td>
<td>RCT</td>
<td>Treatment C</td>
<td>Placebo</td>
<td>Effect</td>
<td>Randomization</td>
<td>Significant difference</td>
</tr>
</tbody>
</table>

**Quality of evidence**

- Level 1 evidence: Randomized controlled trials
- Level 2 evidence: Non-randomized controlled trials
- Level 3 evidence: Observational studies
- Level 4 evidence: Case reports
- Level 5 evidence: Expert opinion

**Notes**

- The results were consistent across all studies.
- Further research is needed to confirm these findings.

**Conflicts of interest**

- None declared.

**Summary**

The results of the systematic review indicate a significant benefit of Treatment A over Placebo, with Treatment B showing no significant difference, and Treatment C also showing a significant benefit but only in a non-randomized controlled trial. Further research is needed to confirm these findings.

**References**


**Acknowledgments**

The authors would like to thank the participants and the institutions involved in the studies for their contribution to this systematic review.
plasma. The duration of follow-up varied. Some, but not all, studies included death as a serious adverse event.

**Grade 3 or 4 adverse events (13 studies, 201 participants)**

The studies did not report the grade of adverse events. Thirteen studies (201 participants) reported on adverse events at any grade 3 or 4 severity. The majority of these adverse events were allergic or respiratory events, very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence).

**Serious adverse events (14 studies, 5212 participants)**

Fourteen studies (5212 participants) reported on serious adverse events. The majority of participants were from one non-controlled RCT (5000 participants), which reported only on serious adverse events limited to the first four hours after convalescent plasma transfusion. This study included death as a serious adverse event; they reported 11 deaths, four of which they classified as potentially probable or definitely related to transfusion. Other serious adverse events reported in all studies were predominantly allergic or respiratory in nature, including anaphylaxis, transfusion-associated dyspnoea, and transfusion-related acute lung injury (TRALI); very uncertain whether or not convalescent plasma affects the number of serious adverse events.

Researchers concluded there is great uncertainty on whether convalescent plasma benefits for people admitted to hospital with COVID-19.

| [HYPERLINK "url:3620https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v1.full.pdf"] | 12 studies including three RCTs, five matched control studies, and four case series studies containing 804 COVID-19 patient outcomes; 804; mean or median age of patients enrolled in these studies ranged from 48 to 70 years, with a greater proportion of men than women in most studies (proportion of women: 25% to 56%). | NR; NR | AMSTAR II critical appraisal of the review: high-quality |

| [HYPERLINK "https://doi.org/10.1101/2020.03.21.20040691"] | All comparator studies demonstrated relatively low mortality rates for COVID-19 patients transfused with convalescent plasma (0% to 1.5%). Among RCTs, patients transfused with convalescent plasma exhibited a reduced mortality rate (13%) compared to non-transfused COVID-19 patients (26%; OR: 0.49, P = 0.03). Among matched control studies, patients transfused with convalescent plasma exhibited a reduced mortality rate (12%) compared to non-transfused COVID-19 patients (25%; OR: 0.41, P = 0.001). When patient outcomes from controlled studies were aggregated, patients transfused with convalescent plasma exhibited a reduced mortality rate (15%) compared to non-transfused COVID-19 patients (25%; OR: 0.43, P < 0.001). Meta-regression analysis indicated that mean or median cohort age, proportion of cohort receiving mechanical ventilation, and duration of study follow up did not affect the aggregate OR computed for all controlled studies (all coefficients P > 0.22). The fixed effect OR (OR: 0.44, P < 0.001) |

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