Convalescent Plasma for COVID-19

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Updated 12/31/22
CP – Conceptual Model

Adapted from Casavedall & Pirofski 2020
Notable Historic Uses of Antibody TX Against Infectious Diseases

Montelongo-Jauregui et al. PIOS Path 2020
## Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

**Figure 2. Absolute risk differences in mortality among patients treated with convalescent blood products and controls.**

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Mortality Rate, n,n (%)</th>
<th>Risk Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>Sto&lt;sup&gt;1&lt;/sup&gt; (17)</td>
<td>25/56 (45)</td>
<td>20/179 (33)</td>
</tr>
<tr>
<td>O'Malley and Hartman (18)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>3/46 (7)</td>
<td>28/111 (25)</td>
</tr>
<tr>
<td>Ross and Huyd (19, 20)</td>
<td>6/28 (21)</td>
<td>9/21 (43)</td>
</tr>
<tr>
<td>Kahn (21)</td>
<td>12/25 (48)</td>
<td>12/18 (67)</td>
</tr>
<tr>
<td>Gould (22)</td>
<td>2/30 (7)</td>
<td>82/230 (28)</td>
</tr>
<tr>
<td>McGuire and Redden (23, 24)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>6/151 (4)</td>
<td>120/400 (30)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>54/336 (16)</td>
<td>452/1219 (37)</td>
</tr>
</tbody>
</table>

### Influence of Time of Injection of Antitoxin on Mortality

<table>
<thead>
<tr>
<th>Time of Injection after Onset</th>
<th>Patients</th>
<th>Died</th>
<th>Mortality, Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>355</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td>2nd day</td>
<td>1,018</td>
<td>17</td>
<td>1.67</td>
</tr>
<tr>
<td>3rd day</td>
<td>1,509</td>
<td>57</td>
<td>3.77</td>
</tr>
<tr>
<td>4th day</td>
<td>720</td>
<td>82</td>
<td>11.39</td>
</tr>
<tr>
<td>Later</td>
<td>469</td>
<td>119</td>
<td>25.37</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4,071</strong></td>
<td><strong>276</strong></td>
<td><strong>6.77</strong></td>
</tr>
</tbody>
</table>
History Shows For Antibody Therapy—
Early Use, High Titer Essential!
Twitter Saves Lives?
WSJ February 27, 2020

OPINION | COMMENTARY

How a Boy’s Blood Stopped an Outbreak

A school physician’s approach to measles in 1934 has lessons for the coronavirus.

By Arturo Casadevall
Feb. 27, 2020 6:48 pm ET

It isn’t every day that a school physician’s work gets published in a medical journal. But it happened in 1934, and the story contains a lesson for the coronavirus epidemic.
Early Signals of Efficacy 2020-2021

- Experiments of Nature?
- Dose Response Relationship Between Abs vs Outcomes?
- Matched Control Data?
- Real World Data?
Experiment of Nature Patients

- Proof of concept
- Smoldering cases
- Replacement therapy
- Ethical to wait for trials?
- Epistemology in a Pandemic?
Patients With Deficient Antibody Responses: Dramatic Temporal Associations Frequently Noted

Panel: Anecdotal statements supporting the efficacy of convalescent plasma

- In the present case, the rapid clinical improvement followed by viral clearance after administration of hyperimmune plasma argue that passively transferred antibodies played a key role in COVID-19 recovery. 23
- One day later [after convalescent plasma transfusion], the patient was afebrile for the first time in 3 weeks and had improved energy. 23
- On day 122 (of illness), due to worsening symptoms, the patient was given convalescent plasma. He defervesced within 24 hours and was discharged nine days later. 31
- …she was transferred to the intensive care unit for intubation. In the meantime… the patient received convalescent therapy instead and did not undergo intubation following the immediate improvement after plasma therapy infusion. 52
- Based on the lack of clinical improvement…we transfused 1 unit of convalescent plasma…Importantly, the patient did not receive any other treatment potentially having an effect on the course of COVID-19. …After transfusion of the convalescent plasma, the patient showed a dramatic clinical improvement, became asymptomatic, and was discharged home only 2 days later. 58
- The patient was discharged after 2 weeks [convalescent plasma transfusion] with a dramatic response to therapy. Both newborns had no COVID-19 symptoms and negative PCR results. 49
- 36 hours after [convalescent plasma] transfusion, the patient was discharged from the hospital reporting that he felt improved. 59
- COVID-19 antibody testing showed complete lack of COVID-19 antibodies. …She received 2 units of convalescent plasma…with rapid improvement in oxygen requirements. She was weaned off high-flow nasal cannula within 48 h and within a few days was discharged home in stable condition. 52
- Intravenous convalescent plasma…was administered…her health condition quickly improved, allowing [withdrawal of oxygen supplementation]. 52
- Within a day of receiving her first transfusion of convalescent plasma, she reported improvement in shortness of breath and cough, had fever resolution, and decreasing oxygen requirements. 44
- She received COVID convalescent plasma…She showed remarkable improvement [the next day]…with reduction of respiratory rate… and oxygen requirements. 24
- …the patient received a transfusion of convalescent plasma…one day later her [arterial oxygen saturation] increased to 98%…clinical symptoms and pathological criteria improved rapidly within 3 days. 59
- Within hours after receiving the convalescent plasma…[The patient’s] fever started going down. Days later, his breathing and kidney function improved. 45
- [The patient] received a transfusion of convalescent plasma…He is recovering at home after spending two and a half weeks in a coma fighting for his life… 44
- …received 217 ml of convalescent plasma…24 hours later, his heart rate had improved to 60-70 bpm with less frequent premature atrial contractions and premature ventricular contractions and he was breathing comfortably on room air…36 hours after transfusion the patient was discharged from the hospital…35
- Stagnancy in the patient’s evolution, as represented by the lack of response to any of the treatments dispensed… we administered on day 23 COVID-19 convalescent plasma… after 24 hours of infusion, fever ceased without subsequent reappearance and with progressive improvement of asthenia. 44

Senefeld et al Transfusion 2021
US Expanded Access Program - 2020

- **3/30** FDA contacts Joyner/Mayo about EAP
- **4/1** Mayo IRB approves EAP & is central IRB
- **4/1** *Enrollment Cap set at 5000, ↑ many times*
- **4/3** Website roll-out Including:
  - Site, MD, and patient enrollment
  - Workflow
  - Navigator and FAQ functions
  - Case report tools
  - Full-service communication center
- **4/6** 1*st* patient transfused
- **8/24** Emergency Use Authorization (EUA) issued
- **8/31** *Enrollment Stops – 100,000 patients treated all over the US, ~2500 mostly community hospitals, high patient diversity*
January 2021

• Dose Response Relationship
• Early use
• Confirms pre WW2 insights about antibody therapy
• Pre-print available in August of 2020
• 5 months
  - Access
  - Safety
  - Efficacy
Antibody Dose Response Seen in EAP Ortho Vitros Qualitative Assay

Joyner et al NEJM 2021
Houston Matched Control Data Oct 2020

Value of Preprints!

Early transfusion of a large cohort of COVID-19 patients with high titer anti-SARS-CoV-2 spike protein IgG convalescent plasma confirms a signal of significantly decreased mortality.

Eric Salazar\textsuperscript{ab}, Paul A. Christensen\textsuperscript{a}, Edward A. Graviss\textsuperscript{b}, Duc T. Nguyen\textsuperscript{a}, Brian Castillo\textsuperscript{a}, Jian Chen\textsuperscript{a}, Bevin Valdez Lopez\textsuperscript{a}, Todd N. Eagar\textsuperscript{ab}, Xin Yi\textsuperscript{c}, Picheng Zhao\textsuperscript{c}, John Rogers\textsuperscript{a}, Ahmed Shehabeilid\textsuperscript{d}, David Joseph\textsuperscript{a}, Faisal Masud\textsuperscript{a}, Christopher Leveque\textsuperscript{d}, Randall J. Olsen\textsuperscript{ab}, David W. Bernard\textsuperscript{ab}, Jimmy Golihar\textsuperscript{a}, and James M. Musser\textsuperscript{ab,cd}
CP Used at Scale in the US
Sept 2020 – Feb 2021 CP Collections & Distributions

Convalescent Plasma: Industry Collections, Distributions & Inventory

> 40k Units/Wk Collected
Early use of high titer plasma was happening!

Mozaffari et al 2021
RWD - Hospital Corp America: JCI 2021
The Population Data Shows An Inverse Relationship Between Plasma Use & Mortality

Casadevall et al. eLife 2021
2021: What Happens When You Aggregate Early K-M Curves?
By Fall/Winter of 2020-21 We Knew:

1. CP was safe
2. High titer likely worked if given early
3. Clinicians using high titer in the real world
4. Especially promising in the immunocompromised
   
   • No concerns about variants “yet”...
2021 RECOVERY & The Valley of Death

- Large UK platform trial
- Late use
- No benefit of plasma
- Preprint over-interpreted
- Signals of efficacy in key use cases
- Methodological issues

Why did they continue to test late use when all other sources of data indicated early use a key?
Recovery: Signals of Efficacy In Key Use Cases

1. Early tx  p=0.07
2. No O2  p=0.06
3. No Steroids  p=0.10
4. No Abs  p=0.21

All consistent with the early use & less severe disease use case.
We (& Others) Persisted
Twitter Saves Lives Again

CP & Heme Malignancies

• CCC19 generates a cancer focused registry
• Mike Thompson Tweets
• Oct of 2020 - MJJ asks a question
• Collaboration born
• Matched Control study shows CP saves live

(The M Thompson back story is wild)
CP Improves Survival in Heme Malignancy Patients

- Heme Malignancy
- Patients who don’t make endogenous antibodies
- Prolonged disease course
- Rapid improvement seen post CCP administration in many
- Low mortality reported in these high-risk patients

Figure 1: Primary Outcome in the A) Overall Population and B) Propensity-Score
Matched Population

Thompson et al. 2021, *JAMA Onc*
Early Use of CCP in the Outpatient Setting Reduces More Than 50% of COVID-19 Related Hospitalizations

Figure 2. Cumulative Incidence of Coronavirus Disease 2019–Related Hospitalization.

On the left, the results of the unadjusted analysis are shown. Shading indicates the 95% confidence interval. On the right, estimates according to the adjusted targeted minimum loss–based estimation model are shown. The insets show the same data on an expanded y axis.

Sullivan et al, NEJM 2022
Meta-analysis - Outpatient Trials: <5 Days & High Titer

Levine... & Sullivan et al Preprint 2022
CP “Rescues” B-Cell Depleted Patients With mAb Escape Variants

Pommeret et al Annals of Onc 2021
2021- “VaxPlasma” Becomes Available

• Plasma harvested from vaccinated donors post breakthrough infection
• Extremely high titer
• Polyclonal/broad spectrum
• Adapts to variants
• Potentially widely available
• Low cost
Breakthrough (Hybrid) VaxPlasma & Commercial Assays (Roche)

- Triple vaxed donor
- Omicron breakthrough May 2022
- Assay maxes out at 250
- Serial dilutions ~ 25,000
- 100x compared to summer 2020
- Seems to cover/keep up with variants

The results (U/mL) were as follows:
Neat = >250
On board X10 = >2500
X10 = 10*250 = >2500
X100 = 231*100 = 23,100
X500 = 56.8*500 = 28,400
X1000 = 29.4*1000 = 29,400

The following comment with the result will be as follows:
“A x10 dilution was performed and the result was >2500 U/mL. The laboratory is unable to perform additional dilutions to achieve an absolute concentration. No minimum antibody level or threshold has been established to indicate long-term protective immunity against re-infection.”
VaxPlasma: High Post Infusion Ab Levels

- Received 1 unit VaxPlasma
- Received 2 units “standard” high titer CCP

Leon et al Trans Aph Sci 2021
VaxPlasma in a B-cell Depleted Patient COVID+ 270 Days!

Pre-VaxPlasma

3 days post VaxPlasma

Espinosa et al MCP 2021
**Tx of Last Resort:** VaxPlasma in Immune Suppressed COVID Patients - Mayo Experience

- 31 Pts, 2/3 heme malignancy
- 16 anti CD20, 5 BK inhibitors, 3 CAR T
- 7/12 ICU survived
- 19/19 non-ICU survived/“cured”
- 5 PCR+ >150d survived/“cured”
- Many had rapid improvement/“cure”
- Currently 1-2 per wk
- 2 Units VaxPlasma (or more)

~ 50 pts per week in France

Outpatient non-last resort use started on 11/30/22

**Graph:**
- Triangles = ICU
- Red = Death
- Circles = Floor/OP
- Blue = Survive

**Legend:**
- Treatment of Last Resort

**Axes:**
- WHO Disease Severity Score
- Time to vax-plasma transfusion (days)
CCP & Hospitalized Immunocompromised Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>CCP Group</th>
<th>Usual care group</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Müller-Tidow et al, 2022</td>
<td>2/68 (18%)</td>
<td>5/65 (23%)</td>
<td>0.71 (0.31-1.67)</td>
</tr>
<tr>
<td>REMAP-CAP, 2021</td>
<td>3/166 (1%)</td>
<td>3/60 (62%)</td>
<td>0.66 (0.32-1.37)</td>
</tr>
<tr>
<td>Lacombe et al, 2022</td>
<td>4/22 (18%)</td>
<td>11/27 (41%)</td>
<td>0.32 (0.09-1.22)</td>
</tr>
<tr>
<td>Bar et al, 2021</td>
<td>1/15 (7%)</td>
<td>5/17 (29%)</td>
<td>0.17 (0.02-1.66)</td>
</tr>
<tr>
<td>RCT Total</td>
<td>48/171 (28%)</td>
<td>68/169 (40%)</td>
<td>0.58 (0.35-0.95)</td>
</tr>
<tr>
<td>Cristelli et al, 2021</td>
<td>13/58 (22%)</td>
<td>9/22 (41%)</td>
<td>0.91 (0.43-1.92)</td>
</tr>
<tr>
<td>Lanza et al, 2022</td>
<td>19/79 (24%)</td>
<td>46/169 (29%)</td>
<td>0.78 (0.42-1.45)</td>
</tr>
<tr>
<td>Thompson et al, 2021</td>
<td>19/143 (13%)</td>
<td>20/823 (25%)</td>
<td>0.47 (0.28-0.77)</td>
</tr>
<tr>
<td>Hueso et al, 2022</td>
<td>13/61 (21%)</td>
<td>29/76 (38%)</td>
<td>0.44 (0.20-0.95)</td>
</tr>
<tr>
<td>Bernat et al, 2021</td>
<td>33/23 (13%)</td>
<td>9/22 (41%)</td>
<td>0.22 (0.05-0.95)</td>
</tr>
<tr>
<td>MCT Total</td>
<td>67/364 (18%)</td>
<td>297/1102 (27%)</td>
<td>0.57 (0.42-0.78)</td>
</tr>
<tr>
<td>Overall</td>
<td>15/535 (21%)</td>
<td>365/1271 (29%)</td>
<td>0.57 (0.44-0.74)</td>
</tr>
</tbody>
</table>

Mortality benefit associated with COVID-19 convalescent plasma

Odds Ratio: 0.57 (0.44-0.74)
- CCP group (n = 535)
- Control group (n = 1,271)
- 9 trials

Senefeld, Casadevall & Joyner unpublished
VaxPlasma – Give 2 Units
VaxPlasma Covers Newest Variants

Sullivan et al submitted
Why Do We Need VaxPlasma In Late 2022?

- New COVID-19 variants have “escaped” previously effective monoclonal antibodies.
- VaxPlasma has very high anti-COVID antibody activity that can neutralize the new variants. [https://pubmed.ncbi.nlm.nih.gov/36309490/](https://pubmed.ncbi.nlm.nih.gov/36309490/)
- Unless VaxPlasma is available, IC patients will be out of options and vulnerable when the emerging COVID-19 variants become dominant.
Antibody Therapy for COVID-19 After Three Years: *Take Home Messages*

- Convalescent Plasma (CP) is safe.
- High titer CP is effective if used early and in patients who don’t make endogenous antibodies.
- mAbs are safe and effective in preventing hospitalization and in patients who don’t make endogenous antibodies – *however, mAbs are subject to escape by novel variants.*
- Very high titer VaxPlasma from donors who have been both vaccinated and infected *adapts to and retains efficacy against variants.*
- High titer CP including VaxPlasma is available worldwide at relatively low cost.
Outpatient Antivirals, mAbs & CP Comparison

No longer in use due to escape

<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>Days to Intervention</th>
<th>Odds Ratio (95% CI)</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molnupiravir</td>
<td>yes (&lt; 5 days)</td>
<td>0.5853 (0.3986 to 0.8595)</td>
<td>9.7%</td>
</tr>
<tr>
<td>Nirmatrelvir/ritonivir</td>
<td>yes (&lt; 5 days)</td>
<td>0.1152 (0.0550 to 0.2412)</td>
<td>6.3%</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>yes (&lt; 7 days)</td>
<td>0.1290 (0.0292 to 0.5695)</td>
<td>5.3%</td>
</tr>
<tr>
<td>Bamlanivimab</td>
<td>yes (&lt; 3 days)</td>
<td>0.2686 (0.0865 to 0.8158)</td>
<td>5.7%</td>
</tr>
<tr>
<td>Sotrovimab</td>
<td>yes (&lt; 5 days)</td>
<td>0.1912 (0.0789 to 0.4633)</td>
<td>5.6%</td>
</tr>
<tr>
<td>Bamlanivimab/etesevimab</td>
<td>yes (&lt; 7 days)</td>
<td>0.2899 (0.1459 to 0.5760)</td>
<td>6.9%</td>
</tr>
<tr>
<td>Casirivimab/imdevimab</td>
<td>yes (&lt; 7 days)</td>
<td>0.2697 (0.1587 to 0.4583)</td>
<td>4.6%</td>
</tr>
<tr>
<td>CCP Argentine</td>
<td>yes (&lt; 3 days)</td>
<td>0.4289 (0.1998 to 0.9120)</td>
<td>31%</td>
</tr>
<tr>
<td>CCP CSSC004</td>
<td>yes (&lt; 5 days)</td>
<td>0.1850 (0.0697 to 0.4912)</td>
<td>9.6%</td>
</tr>
<tr>
<td>CCP CSSC004</td>
<td>yes (&lt; 9 days)</td>
<td>0.4411 (0.2455 to 0.7928)</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

Courtesy D Sullivan