Convalescent Plasma: Therapeutic Clarity, Efficacy & Lessons Learned During the SARS-CoV-2 Pandemic.

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https://www.uscovidplasma.org/
Convalescent Plasma (CP): Conceptual Model & Principles

Principles of Antibody Therapy

- Specificity
- Early Timing
- High Dose

Give enough of the right stuff early

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

Smallpox Vaccinia 1940s-present

Montelongo-Jauregui et al PIOS Path 2020
CP Pandemic Timeline – Highlights 2020-2022

2/20 use in China

2/20 Casadevall WSJ
3/20 FDA eINDs
3/20 FDA/Mayo EAP

8/20 FDA EUA
NY Sinai
Houston Methodist
+Immunosuppressed

Recovery is “negative” but late use

Libster NEJM & ++ Matched control studies
Thompson et al
Huseo et al
Bcell Depleted

US Clinicians = high titer early

Hybrid VaxPlasma
++ Titer covers VOCs

More “negative” late use trials with signals of efficacy
++ RCTS - Sullivan, Bar, O’Donnell, Korper, TBI etc.

Rigid Application of EBM vs nuanced epistemology?

Guidelines start to catch up with +data
Outpatient RCTs To Prevent Hospitalization
Antivirals, mAbs & CP Comparison

No longer in use due to escape
CP & Antibody Therapy for COVID-19 After Two Years: 
Take Home Messages

• Convalescent Plasma (CP) safety profile similar to FFP
• No evidence of ADE
• High titer CP is effective if used early and especially 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
### CP & The Immune Suppressed: RCT and Cohort Data $0.65 \ (0.54-0.79)$

#### Table: Study Results

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CP Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bar</td>
<td>1</td>
<td>15</td>
<td>5</td>
<td>2.2% 0.23 [0.03, 1.73]</td>
</tr>
<tr>
<td>Estcourt-REMAP-CAP</td>
<td>31</td>
<td>66</td>
<td>37</td>
<td>18.2% 0.76 [0.55, 1.05]</td>
</tr>
<tr>
<td>Lacombe</td>
<td>4</td>
<td>22</td>
<td>11</td>
<td>4.6% 0.45 [0.16, 1.21]</td>
</tr>
<tr>
<td>Muller-Tidow</td>
<td>12</td>
<td>68</td>
<td>15</td>
<td>7.2% 0.76 [0.39, 1.51]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>171</strong></td>
<td><strong>169</strong></td>
<td><strong>32.2%</strong></td>
<td><strong>0.68 [0.51, 0.91]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>48</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi$^2$ = 2.39, df = 3 (P = 0.50); I$^2$ = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.61 (P = 0.009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 1.1.2 cohort

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CP Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biernat</td>
<td>3</td>
<td>23</td>
<td>9</td>
<td>4.3% 0.32 [0.10, 1.03]</td>
</tr>
<tr>
<td>Cristelli</td>
<td>13</td>
<td>58</td>
<td>28</td>
<td>8.8% 0.93 [0.52, 1.65]</td>
</tr>
<tr>
<td>Hueso</td>
<td>13</td>
<td>61</td>
<td>29</td>
<td>12.1% 0.56 [0.32, 0.98]</td>
</tr>
<tr>
<td>Lanza</td>
<td>19</td>
<td>79</td>
<td>46</td>
<td>14.3% 0.83 [0.52, 1.32]</td>
</tr>
<tr>
<td>Thompson</td>
<td>19</td>
<td>143</td>
<td>204</td>
<td>28.3% 0.54 [0.35, 0.83]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>364</strong></td>
<td><strong>1196</strong></td>
<td><strong>67.8%</strong></td>
<td><strong>0.64 [0.50, 0.82]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>67</td>
<td>316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi$^2$ = 5.06, df = 4 (P = 0.28); I$^2$ = 21%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.59 (P = 0.0003)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### Total (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>CP Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events</strong></td>
<td>115</td>
<td>384</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi$^2$ = 7.69, df = 8 (P = 0.48); I$^2$ = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.42 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi$^2$ = 0.10, df = 1 (P = 0.75), I$^2$ = 0%</td>
<td></td>
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</tr>
</tbody>
</table>

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Senefeld et al preprint
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.”
Hybrid (BA1 Breakthrough) VaxPlasma Neutralizes BA4/5

Sullivan et al in revision
Thinking About Year 3 & Next Time

• VaxPlasma for smoldering cases in the immune suppressed – **DO NOW**

• Readiness for Next Time
  - CP will always be the 1st Ab available
  - Bioplausible & **totality of data perspective needed**
  - Blood banking preparedness
  - Community engagement & motivated donors
  - Adaptable assay system for model organisms that can be scaled quickly for a specific pathogen
  - Worldwide access!

• High Titer *(locally sourced ?)* - **Early Use, Early Use, Early Use plus High Risk**

• Expanded access plus pre-designed adaptive trials

• Templates for trials, compliance & funding

• Integrated approach to data/evidence - EBM and related methodology can be **hammers** and pandemics are not always **nails**....
Backup
# High Titer CP Used Early “Works”

Mortality rates among randomized clinical trials of optimal use convalescent plasma therapy for COVID-19

<table>
<thead>
<tr>
<th>Study</th>
<th>Survivor</th>
<th>Non-Survivor</th>
<th>Mortality</th>
<th>Survivor</th>
<th>Non-Survivor</th>
<th>Mortality</th>
<th>Mechanical ventilation (%)</th>
<th>Titer</th>
<th>Time to transfusion (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avendaño-Solà et al.</td>
<td>172</td>
<td>7</td>
<td>4%</td>
<td>157</td>
<td>14</td>
<td>8%</td>
<td>0%</td>
<td>High titer</td>
<td>1 (admission)</td>
</tr>
<tr>
<td>Bar et al.</td>
<td>38</td>
<td>2</td>
<td>5%</td>
<td>29</td>
<td>10</td>
<td>26%</td>
<td>0%</td>
<td>High titer</td>
<td>1 (admission)</td>
</tr>
<tr>
<td>Bennett-Guerrero et al.</td>
<td>43</td>
<td>16</td>
<td>27%</td>
<td>10</td>
<td>5</td>
<td>33%</td>
<td>19%</td>
<td>High titer</td>
<td>4 (admission)</td>
</tr>
<tr>
<td>Devos et al.</td>
<td>258</td>
<td>20</td>
<td>7%</td>
<td>138</td>
<td>7</td>
<td>4%</td>
<td>0%</td>
<td>High titer</td>
<td>7 (symptoms)</td>
</tr>
<tr>
<td>Gharbharan et al.</td>
<td>37</td>
<td>6</td>
<td>14%</td>
<td>32</td>
<td>11</td>
<td>26%</td>
<td>12%</td>
<td>High titer</td>
<td>2 (admission)</td>
</tr>
<tr>
<td>Korper et al.</td>
<td>42</td>
<td>11</td>
<td>21%</td>
<td>35</td>
<td>17</td>
<td>33%</td>
<td>30%</td>
<td>High titer</td>
<td>2 (admission)</td>
</tr>
<tr>
<td>Libster et al.</td>
<td>78</td>
<td>2</td>
<td>3%</td>
<td>76</td>
<td>4</td>
<td>5%</td>
<td>0%</td>
<td>High titer</td>
<td>3 (symptoms)</td>
</tr>
<tr>
<td>Menichetti F et al.</td>
<td>217</td>
<td>14</td>
<td>6%</td>
<td>221</td>
<td>19</td>
<td>8%</td>
<td>0%</td>
<td>High titer</td>
<td>7 (symptoms)</td>
</tr>
<tr>
<td>O'Donnell et al.</td>
<td>131</td>
<td>19</td>
<td>13%</td>
<td>55</td>
<td>18</td>
<td>25%</td>
<td>11%</td>
<td>High titer</td>
<td>9 (symptoms)</td>
</tr>
<tr>
<td>Ortigoza et al. (No corticosteroids subgroup)</td>
<td>85</td>
<td>9</td>
<td>10%</td>
<td>69</td>
<td>18</td>
<td>21%</td>
<td>0%</td>
<td>High titer</td>
<td>1 (admission)</td>
</tr>
<tr>
<td>Simonovich et al.</td>
<td>203</td>
<td>25</td>
<td>11%</td>
<td>93</td>
<td>12</td>
<td>11%</td>
<td>0%</td>
<td>High titer</td>
<td>8 (symptoms)</td>
</tr>
<tr>
<td>Sullivan et al.</td>
<td>592</td>
<td>0</td>
<td>0%</td>
<td>586</td>
<td>3</td>
<td>1%</td>
<td>0%</td>
<td>High titer</td>
<td>6 (symptoms)</td>
</tr>
<tr>
<td>The CONCOR-1 Study Group (high titer subgroup)</td>
<td>268</td>
<td>75</td>
<td>22%</td>
<td>133</td>
<td>40</td>
<td>23%</td>
<td>0%</td>
<td>High titer</td>
<td>5 (diagnosis)</td>
</tr>
<tr>
<td>The RECOVERY Collaborative Group (No corticosteroids subgroup)</td>
<td>317</td>
<td>74</td>
<td>19%</td>
<td>313</td>
<td>100</td>
<td>24%</td>
<td>5%</td>
<td>High Titer</td>
<td>2 (admission)</td>
</tr>
<tr>
<td>The REMAP-CAP Investigators (Moderate state subgroup)</td>
<td>54</td>
<td>8</td>
<td>13%</td>
<td>17</td>
<td>7</td>
<td>29%</td>
<td>0%</td>
<td>High titer</td>
<td>2 (admission)</td>
</tr>
<tr>
<td>The SIREN-C3PO Investigators</td>
<td>252</td>
<td>5</td>
<td>2%</td>
<td>253</td>
<td>1</td>
<td>0%</td>
<td>0%</td>
<td>High titer</td>
<td>4 (symptoms)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>2787</strong></td>
<td><strong>293</strong></td>
<td><strong>9.5%</strong></td>
<td><strong>2217</strong></td>
<td><strong>286</strong></td>
<td><strong>11.4%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\chi^2 = 5.44, P = 0.019$; 16.7% relative mortality reduction associated with convalescent plasma therapy
CP Pandemic Timeline – Highlights 2020-2022

- **2/20 use in China**
- **2/20 Casadevall WSJ**
- **3/20 FDE eINDs**
- **3/20 FDA/Mayo EAP**

**Highlights 2020-2022**

- **Recovery is “negative” but late use**
- **Libster NEJM & ++ Matched control studies**
- **Hybrid VaxPlasma ++ Titer covers VOCs**
- **More “negative” late use trials with signals of efficacy**
  - ++ RCTS - Sullivan, Bar, O'Donnell, Korper, TBI etc.

- **US Clinicians = high titer early**

**Rigid Application of EBM vs nuanced epistemology?**

- **12/19 1/20**
- **4/20**
- **8/20**
- **12/20 1/21**
- **4/21**
- **8/21**
- **12/21 1/22**
- **4/22**
- **8/22**

- **Joyner et al NEJM**
- **Casadevall et al eLife**
- **Thompson et al JAMA Onc**
- **Sullivan et al NEJM**

**Graphs and Data**

- Propensity score-matched comparison
- Recipients of convalescent plasma vs nonrecipients
- Overall survival probability
- Stratified log-rank test $P = 0.004$
- Time, d
- Percent of admissions receiving convalescent plasma
- Days Time Transfusion
- Figure: Cumulative Incidence of Convulsion Among 2019, Related Hospitalization.