Convalescent Plasma For COVID-19 Disease

https://www.uscovidplasma.org/

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Disclaimer

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What is convalescent plasma?

• Relies on principles of passive immunity
• 1\textsuperscript{st} “best shot” on biological goal
• Transfer of antibodies from a recovering patient or animal
  – Post exposure to prevent disease
  – To treat disease
• Long history
THE USE OF CONVALESCENT HUMAN SERUM IN INFLUENZA PNEUMONIA—A PRELIMINARY REPORT.*

FIG. 1. Temperature Chart of Officer.

McGuire & Redden AJPH 1918
2. Meta Analysis 1918

**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>Stoll (17)</td>
<td>25/56 (45)</td>
<td>201/379 (53)</td>
</tr>
<tr>
<td>O’Malley and Hartman (18)*</td>
<td>3/46 (7)</td>
<td>28/111 (25)</td>
</tr>
<tr>
<td>Ross and Hund (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>82/290 (28)</td>
</tr>
<tr>
<td>McGuire and Redden (23, 24)*</td>
<td>6/151 (4)</td>
<td>120/400 (30)</td>
</tr>
<tr>
<td>Overall</td>
<td>54/336 (16)</td>
<td>452/1219 (37)</td>
</tr>
</tbody>
</table>

3. Argentine Hemorrhagic Fever

Double blind trial with immune plasma: Between 1974 and 1978, a double blind placebo-controlled study was performed among patients with a clinical diagnosis of AHF hospitalized in Pergamino with less than 8 days from onset of symptoms. The patients were randomly allocated to receive intravenously either 500 ml of immune plasma or normal plasma. Ultimately, 188 cases with a laboratory confirmation of infection with Junin virus entered in the trial. The case-fatality rate among cases treated with normal plasma was 16.5% while the rate in those patients treated with immune plasma was 1.1% (Maiztegui et al., 1979).

Enria et al Antiviral Res 2008
4. SARS early 2000s

Y. Cheng · R. Wong · Y. O. Y. Soo · W. S. Wong ·
C. K. Lee · M. H. L. Ng · P. Chan · K. C. Wong ·
C. B. Leung · G. Cheng

Use of convalescent plasma therapy in SARS patients in Hong Kong

Abstract In order to evaluate the efficacy of convalescent plasma therapy in the treatment of patients with severe acute respiratory syndrome (SARS), 80 SARS patients were given convalescent plasma at Prince of Wales Hospital, Hong Kong, between 20 March and 26 May 2003. Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death or hospitalization beyond 22 days. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; \( P < 0.001 \)) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; \( P = 0.001 \)).
Summary: Has it worked in the past?

• Yes
• Prophylaxis – many examples
• Early use seems better
• Rescue therapy?
• Concentrated products follow plasma
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.

Arturo is a friend of mine......
Use of Convalescent Measles Serum to Control Measles in a Preparatory School

J. ROSEWELL GALLAGHER, M.D.


SUMMARY

1. In a threatened outbreak of measles in a group of preparatory school boys, 66 of whom had not had measles, convalescent measles serum was used prophylactically. Only 3 cases of measles, all decidedly attenuated, subsequently developed in this group. On the basis of past experience, at least 25 per cent of this group might have been expected to develop measles.

2. The use of convalescent measles serum is suggested as the most practical method of controlling an outbreak of measles among adolescents in a preparatory school or in a similar situation. A dose of 10 c.c. is considered adequate for members of this age group.

Am J PH 1935
Mid-March

- Network self-assembles around the idea of CP
- Many members know each other as a result of their shared concerns about excessive reductionism in biomedical research
- Hopkins generates prophylactic protocol
- Mayo adapts for early treatment
Late March: Lots of Interest Nationally

- FDA announces eINDs for compassionate use
- Houston Methodist & NY Mt Sinai use it
- Blood bankers get mobilized
- Demand for eINDs overwhelms FDA
- Expanded Access Program (EAP) developed
EAP Timeline

• 3/30 FDA contacts Joyner/Mayo about EAP
• 4/1 Mayo IRB approves EAP & is central IRB with e
• 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
• 4/7 1st patient transfused
• 8/24 Emergency Use Authorization (EUA) issued
• 8/28 **Enrollment Stops**
Enrollment Ends Late August

Enrollment Summary

2,764
Total Sites Registered

14,513
Total Physicians Registered

105,880
Total Patients Consented

78,774
Total Patients Transfused

Transfused subjects included for outcomes

Enrolled patients from April 13 to August 31.
~2800 Hospitals Throughout the US

Patient Enrollment and Counties with Active Recruitment
Enrollment by State and Sites per County

Number of Registered Hospitals Per City
- 20
- 40
- 60

Number of Enrolled Patients
- 200
- 400
- 600
- 800
- 1000
- 1200+
Teamwork & Repurposing Skill Sets Made it Happen

1. Casadevall – idea
2. Joyner – could be done at scale
3. FDA – need for EAP
4. Wright – Mayo IRB & novel ideas about streamlining trials
5. Fairweather & Bruno – web based forms
6. Carter – Rapid data analysis
7. Lab – novel assays developed and done at scale under great time pressure
8. Fellows, Jr Clinicians & Analytics Staff – repurpose and generate novel solutions to problems on a daily basis
9. Administrative & Compliance Staff – strong and flexible support throughout
10. Institutional Leadership – very supportive
11. BARDA funding
12. Philanthropy - assay development & covers gaps like food and coffee for individuals working nights and weekends
EAP - Our Charge

1. **Provide broad access to COVID-19 Convalescent Plasma**

   **Inclusion Criteria**
   1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
   2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
   3. Admitted to an acute care facility for the treatment of COVID-19 complications
   4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
   5. Informed consent provided by the patient or healthcare proxy

2. **Perform Robust Safety Analysis**

   **Objectives:**
   - Primary Objective: Provide access to COVID-19 convalescent plasma
   - Secondary Objectives: Safety

   **Endpoints:**
   - Primary Endpoint: Availability of convalescent plasma
   - Secondary Endpoints: Serious adverse events

3. **Explore Efficacy**
Access: Plasma Supply Key

Thousands of Orthodox Jewish New Yorkers donate plasma to fight coronavirus

By Amanda Woods

April 23, 2020 | 1:04 pm

A member of the Orthodox Jewish community gets evaluated as a potential plasma donor.

Shmuel Shoham via Twitter
Access: Every Referral Region But 1

Enrolled Hospitals by Hospital Referral Regions
HRR's specify a market within which people generally go to the same hospitals
Safety: Very Low Rates of TACO & TRALI

Early safety indicators of COVID-19 convalescent plasma in 5000 patients

Michael J. Joyner,1 R. Scott Wright,2,3 DeLisa Fairweather,4 Jonathon W. Senefeld,1 Katelyn A. Bruno,4 Stephen A. Klassen,1 Rickey E. Carter,5 Allan M. Klompas,1 Chad C. Wiggins,1 John R.A. Shepherd,1 Robert F. Rea,2 Emily R. Whelan,4 Andrew J. Clayburn,1 Matthew R. Spiegel,5 Patrick W. Johnson,5 Elizabeth R. Lesser,5 Sarah E. Baker,1 Kathryn F. Larson,1 Juan G. Ripoll,1 Kylie J. Andersen,1 David O. Hodge,5 Katie L. Kunze,6 Matthew R. Buras,6 Matthew N.P. Vogt,1 Vitaly Herasevich,1 Joshua J. Dennis,1 Riley J. Regimbal,1 Philippe R. Bauer,7 Janis E. Blair,8 Camille M. Van Buskirk,9 Jeffrey L. Winters,9 James R. Stubbs,9 Nigel S. Paneth,10,11 Nicole C. Verdun,12 Peter Marks,12 and Arturo Casadevall13

Table. Convalescent Plasma Transfusion Reactions

<table>
<thead>
<tr>
<th>Four Hour Reports</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion-Associated Circulatory Overload (TACO)</td>
<td>0.14% (0.07%, 0.29%)</td>
</tr>
<tr>
<td>Transfusion-Related Acute Lung Injury (TRALI)</td>
<td>0.22% (0.12%, 0.39%)</td>
</tr>
<tr>
<td>Severe allergic transfusion reaction</td>
<td>0.06% (0.02%, 0.18%)</td>
</tr>
</tbody>
</table>
Explore Efficacy
Disclaimers – Not an RCT

• A guesstimate dose
• An uncharacterized product
• Diverse group of hospitalized patients
• Many with disease stages least likely to show a positive effect
• Any hospital
• Teams with no training
• *Many elements of plane built while flying it*
Nevertheless:

*Potential Signals of Efficacy*

1. Embedded in Enrollment & Safety Data
   - Volume Administered
   - Time to Treatment
2. Exploratory analysis using antibody titers
3. Volume, Time, and Abs are variable & have elements of randomization
4. Other supportive data
Volume Administered Varied

7 Day Mortality

<table>
<thead>
<tr>
<th>Volume (Grouped)</th>
<th>7 Day Crude Mortality</th>
<th>0.0016</th>
<th>30 Day Crude Mortality</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>One unit</td>
<td>30,196</td>
<td>3,138</td>
<td>10.4% (10.1%, 10.7%)</td>
<td>23,560</td>
</tr>
<tr>
<td>Two units</td>
<td>9,019</td>
<td>820</td>
<td>9.1% (8.5%, 9.7%)</td>
<td>6,677</td>
</tr>
</tbody>
</table>

Volume of Plasma on First Day of Transfusion
Time to Tx

*rho = 0.96*

Weekly Crude Mortality Rate (7 Day) vs. Days from Diagnosis to Transfusion
Antibodies, Time & Mortality

A. Ortho IgG Groups

7-Day Adjusted Mortality

B. Ortho IgG Groups and Days to Transfusion

<= 3 days

4+ days

C. Ortho IgG Groups

30-Day Adjusted Mortality

D. Ortho IgG Groups and Days to Transfusion

<= 3 days

4+ days
Interim Summary

- Give early
- Give enough
- Give higher titers
- *Data can help frame RCTs*
- *Needs additional validation*
Other Supportive Data: *Animal Models*

Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development

At the end of 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) was detected in Wuhan, China, that spread rapidly around the world, with severe consequences for human health and the global economy. Here, we assessed the replicative ability and pathogenesis of SARS-CoV-2 isolates in Syrian hamsters. SARS-CoV-2 isolates replicated efficiently in the lungs of hamsters, causing severe pathological lung lesions following intranasal infection. In addition, microcomputed tomographic imaging revealed severe lung injury that shared characteristics with SARS-CoV-2–infected human lung, including severe, bilateral, peripherally distributed, multilobular ground glass opacity, and regions of lung consolidation. SARS-CoV-2–infected hamsters mounted neutralizing antibody responses and were protected against subsequent rechallenge with SARS-CoV-2. Moreover, passive transfer of convalescent serum to naïve hamsters efficiently suppressed the replication of the virus in the lungs even when the serum was administered 2 d postinfection of the serum-treated hamsters. Collectively, these findings demonstrate that this Syrian hamster model will be useful for understanding SARS-CoV-2 pathogenesis and testing vaccines and antiviral drugs.

Imai et al. PNAS 2020
Other Supportive Data: **Pooled Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Convalescent Plasma</th>
<th>Control</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Survivor</td>
<td>Non-Survivor</td>
<td>Mortality</td>
</tr>
<tr>
<td>Clinical Trials - Randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Avendano-Sola et al.</td>
<td>ESP</td>
<td>38</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Gharbharan et al.</td>
<td>NLD</td>
<td>37</td>
<td>6</td>
<td>14%</td>
</tr>
<tr>
<td>Li et al.</td>
<td>CHN</td>
<td>43</td>
<td>8</td>
<td>16%</td>
</tr>
<tr>
<td>Fixed Effect Model</td>
<td></td>
<td>118</td>
<td>14</td>
<td>11%</td>
</tr>
<tr>
<td>Clinical Trials - Randomized by availability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasheed et al.</td>
<td>IRQ</td>
<td>20</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>Abolghasemi et al.</td>
<td>IRN</td>
<td>98</td>
<td>17</td>
<td>15%</td>
</tr>
<tr>
<td>Fixed Effect Model</td>
<td></td>
<td>118</td>
<td>18</td>
<td>13%</td>
</tr>
<tr>
<td>Clinical Trials Fixed Effect Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched-Control Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duan et al.</td>
<td>CHN</td>
<td>10</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Perotti et al.</td>
<td>ITA</td>
<td>43</td>
<td>3</td>
<td>7%</td>
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<tr>
<td>Hegerova et al.</td>
<td>Washington, USA</td>
<td>18</td>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>Zeng et al.</td>
<td>CHN</td>
<td>1</td>
<td>5</td>
<td>83%</td>
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<tr>
<td>Donato et al.</td>
<td>New York, USA</td>
<td>36</td>
<td>11</td>
<td>23%</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>New York, USA</td>
<td>35</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>Salazar et al.</td>
<td>Texas, USA</td>
<td>131</td>
<td>5</td>
<td>4%</td>
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<tr>
<td>Xia et al.</td>
<td>CHN</td>
<td>135</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Fixed Effect Model</td>
<td></td>
<td>409</td>
<td>34</td>
<td>8%</td>
</tr>
<tr>
<td>Overall Fixed Effect Model</td>
<td></td>
<td>645</td>
<td>66</td>
<td>9%</td>
</tr>
</tbody>
</table>

OR, odds ratio
Preliminary Electronic Health Record

“Data Mining”

Convalescent Plasma

Survival probability

Time (days)

p = 0.0048

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>1040</td>
<td>124</td>
</tr>
<tr>
<td>490</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>32</td>
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</tr>
<tr>
<td>72</td>
<td>23</td>
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</tr>
<tr>
<td>51</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
Summary – Not an RCT

• Dosing left to discretion of treating physicians – 1 to 2 units and could be repeated
• No pre-clinical data
• CP did not have any pre-administration measure of nAB or other immune activity

Arturo Casadevall notes:
“Remarkably, in the EAP, signals of efficacy break through despite many potential confounders.”
The Epistemic Climb To Establishing Efficacy

- Convalescent Plasma Is Safe and Effective
- Randomized control trials
- The EAP Analysis with > 35,000 patients
  - Joyner et al 2020
- Case Series with Matched Controls
  - Sinai, Houston, Italian, Iran, Iraq Experiences
- Human Convalescent plasma is therapeutic in animal model
  - Sun et al. Cell 2020
- Case Series Observations
  - Duan et al. PNAS 2020
- Antibody Mechanism of Action well Understood
  - Numerous reports that antibody can neutralize SARS-CoV-2
- Historical Precedent & Immunology theory
  - Casadevall & Pirofski JCI 2020

2nd FDA action? 1st FDA Action 3/24/20
Discussion
EFFECTS OF VERY EARLY SERUM TREATMENT IN PNEUMOCOCCUS TYPE I PNEUMONIA

RUSSELL L. CECIL, M.D.
NEW YORK

It is a fundamental principle in all serum therapy that to obtain the best results the serum must be given early in the disease. This statement holds true regardless of whether one is using antitoxic or antibacterial serum.
Antibodies & Timing: Conceptual Model Confirmed

Early convalescent plasma therapy neutralizes SARS-CoV-2 and enhances the developing immune response by ADCC, complement activation, and possibly immune modulation.

Later convalescent plasma therapy neutralizes SARS-CoV-2 and possibly modulates immune function.

Casavedall, Joyner & Pirofsky JCI in press