Convalescent Plasma

A Review of Pertinent Information for SARS-CoV-2

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Data as of August 31th, 2020
Mechanism of Action

• Adaptive (humoral) immunity:
  • Host development of pathogen-specific antibodies allowing for immune-mediated neutralization and clearance of pathogen
  • Accomplished via: Active infection vs. vaccination
    • Note: Seroconversion in SARS-CoV-2 = 8-21 days after symptom onset

• Convalescent plasma therapy:
  • Harvest of antibodies (in plasma) of recovered patient for administration to acutely ill patient
  • Adaptive immune transfer resulting in passive immunity
  • Thought to confer immunity for weeks to months
• Serologic profile analysis of 41 patients:
  • Stratified analysis by disease severity.
  • IgG Seroconversion:
    • Median = 11 days (range 8-16 days)
    • Peaked on day 30
    • Steeper slope of IgG response in critically ill population
  • IgM Seroconversion:
    • Median = 14 day (range 8-28 days)
    • Peaked in 18 days then declined
  • Confirms:
    • Previously demonstrated seroconversion profile of IgG
    • Potential low utility of IgM profile in tracking disease/immunity

1892: Diphtheria
1920s: Scarlet Fever
1970s: Pertussis Tetanus
1934: Measles outbreak
Up to 1970s: Pertussis, Tetanus
2009: Influenza A H1N1
2004: SARS-CoV-1
2012: MERS-CoV
2015: Ebola

**SARS-CoV-1**

**Population/Intervention:** 80 patients with SARS-CoV-1 (2003 Hong Kong) given 1-3 units (160-640 mL IV of convalescent plasma)

**Primary Outcome:** Discharge by day 22 post-infusion

**Results:** 33/80 (41.3%) patients met primary outcome
- Median time from symptom onset to receipt of convalescent plasma: 14 days (range 7-30)
- Factors associated with good outcomes:
  - Receipt of convalescent plasma within 14 days of symptom onset.
    - 56% good outcome vs. 15.6% poor outcome patients had admin ≤14 days (p<0.001)
  - PCR positivity with seronegativity at the time of treatment.
    - 61% good outcome vs. 21% poor outcome patients had PCR positive/serology negative (p<0.001)
### MERS-CoV

**Population/Intervention:** 3 patients in respiratory failure secondary to infection with MERS-CoV given 1-2 IV infusions of convalescent plasma

**Primary Outcome:** Recipient seroconversion following convalescent plasma administration

**Results:**
- All recovered
- Only 1/3 (33%) patients experienced successful seroconversion following therapy
  - Patient who seroconverted was the only patient that received plasma with a neutralizing antibody ratio of ≥1:80

## Available Evidence

### Duan K, et al.

**Population/Intervention:** 10 adult patients with severe COVID-19 without end organ dysfunction

**Intervention:** 200 mL of convalescent plasma with neutralizing antibody titers of >1:640

*(Note: all 10 received antiviral therapy and 6/10 received methylprednisolone)*

**Results:**
- Improvement in all symptoms within 1-3 days
- Varying degrees of absorption of pulmonary lesions
- Tendency towards declined inflammatory markers
- No deaths

### Shen, et al.

**Population/Intervention:** 5 adult, critically ill patients with severe COVID-19

**Intervention:** 400 mL of convalescent plasma (2 x 200 mL infusions) – Donor requirements = IgG >1:1000 / neutralizing antibodies >1:40.

*(Note: all 10 received antiviral therapy and methylprednisolone)*

**Results:**
- Normalization of body temperature within 3 days
- Decreased SOFA / increased PaO2:FiO2 w/in 12 days.
- Viral loads decreased then became negative in all
- Increases in recipient neutralizing antibody titers
- No deaths


Available Evidence


<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>69 y/o Female</td>
<td>55 y/o Male</td>
<td>73 y/o Female</td>
<td>31 y/o Female</td>
</tr>
<tr>
<td>Total administered</td>
<td>900 mL (3 infusions)</td>
<td>200 mL (1 infusion)</td>
<td>2400 mL (8 infusions)</td>
<td>300 mL (1 infusion)</td>
</tr>
<tr>
<td>Convalescent Plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>900 mL (3 infusions)</td>
<td>200 mL (1 infusion)</td>
<td>2400 mL (8 infusions)</td>
<td>300 mL (1 infusion)</td>
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</tbody>
</table>

- No discussion of antibody titers of donors
- All experienced positive clinical and virologic outcomes
- All 3 studies should be interpreted cautiously given lack of control groups.

Clinical efficacy of convalescent plasma for treatment of COVID-19 infections – results of a multicenter clinical study

- Prospective, multicenter observational study of CPT vs. standard care
- Dosing 500 mL x 1 followed by a second dose at physician discretion if not clinical improvement within 24 hours
  - Had to be administered within 3 days of admission
- Inclusion: Age >18, confirmed COVID-19, presence of symptoms, SpO2 <93% on room air, and ≤7 days since illness onset
- Exclusion: Intubated patients, severe liver or kidney disease, septic shock, physician discretion, and patients with improving clinical condition who meet discharge criteria

Available Evidence

### Available Evidence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plasma (n = 115)</th>
<th>Control (n = 74)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>14.8%</td>
<td>24.3%</td>
<td>0.09</td>
</tr>
<tr>
<td>Length of Stay (Mean +/- SD)</td>
<td>9.54 +/- 5.07</td>
<td>12.88 +/- 7.19</td>
<td>0.002</td>
</tr>
<tr>
<td>Length of Stay ≤ 5 days</td>
<td>28.1%</td>
<td>8.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>No intubation</td>
<td>93%</td>
<td>79.7%</td>
<td>0.006</td>
</tr>
</tbody>
</table>

- Limitations:
  - Lack of randomization
  - Concomitant use of antivirals was permitted

Available Evidence

Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19

- Design: Open-label, multicenter, randomized clinical trial
- Setting: 7 hospitals in Wuhan, China
- Time Course: Feb 14 – April 1, 2020
- Enrollment: 103 adult inpatients with severe/life-threatening COVID-19 not enrolled in other clinical trials
  - 52 Convalescent plasma
  - 51 Control group (standard care)
- Exclusion criteria:
  - Pregnancy
  - Immunoglobulin allergy
  - IgA deficiency
  - High risk of thrombosis
  - Life expectancy <24 hours
  - Disseminated intravascular coagulopathy
  - Severe septic shock
  - PaO2/FiO2 <100
  - Severe CHF
  - SARS-CoV-2 IgG antibody ≥1:640
  - “other contraindications” as determined by the patient’s physician

Available Evidence

Donors:
- 18-55 years of age
- Lab confirmed COVID-19
- Recovery (i.e. asymptomatic for 14 days)
- Measured IgG antibody titers ≥ 1:640

Dosing: 4-13 mL/kg of recipient body weight

Primary Outcome: Time to clinical improvement within a 28 day period

Secondary Outcomes:
- 28 day mortality
- Discharge by day 28
- Conversion of PCR at 24, 48, and 72 hours.

Outcomes:
- **Clinical improvement**: No differences (HR 1.4 [95% CI 0.79-2.49])
  - Better effect in severe vs. life-threatening disease
  - By both percentage with improvement by day 28 and time to improvement (4.94 days faster [95% CI -9.33 to -0.54 days])
- **28 day mortality**: No difference (OR 0.65 [95% CI 0.29-1.46])
- **Discharge by day 28**: No difference (HR 1.61 [95% CI 0.88-2.93])
- **Rates of negative PCR conversion**: Higher in CPT group at all points
  - 24 hours: 44.7% vs. 15%, p = 0.003
  - 48 hours: 68.1% vs. 32.5%, p = 0.001
  - 72 hours: 87.2% vs. 37.5%, p <0.001

Available Evidence

**Cochrane Review of Convalescent Plasma Therapy in COVID-19:**

- **20 Studies**
- **5443 Patients**
- **Overall Risk of Bias: High**

**Efficacy – Mortality:**
Included 4 studies
Very uncertain whether CPT has an impact on all cause mortality

**Efficacy – Symptomatic Improvement:**
Included 2 studies
Very uncertain whether CPT has an impact on improvement in clinical symptoms

**Efficacy – Time to Death:**
Included 2 studies
Very uncertain whether CPT prolongs time to death

**Safety – Serious Adverse Events:**
Included 14 studies
Very uncertain whether or not CPT is associated with serious adverse effects.

*Piechotta V, et al. Cochrane Database of Systematic Reviews 2020;7.* [http://doi.org/10.02/14651858.CD013600.pub2.](http://doi.org/10.02/14651858.CD013600.pub2.)*
Effect of Convalescent Plasma on Mortality Among Hospitalized Patients with COVID-19: Initial Three-Month Experience

• 3 month summary of data from National Expanded Access Program (EAP)
• Study design: Open-label (not randomized or blinded)
• Evaluated impacts of time from diagnosis to transfusion and antibody levels and on mortality (both 7-day and 30-day)
  • Time to diagnosis: ≤3 days vs. >3 days
  • SARS-CoV-2 specific IgG antibody levels: High = Signal to cutoff ratio (S/Co) >18.45, medium = S/Co 4.62-18.45, low = S/Co <4.62
• Inclusion: >18 y/o, hospitalized with (+) SARS-CoV-2 PCR, severe/life-threatening illness (or risk of progression to)
  • For antibody analysis: Only patients who received one unit of plasma with known antibody titers
• Exclusion: Enrolled but not transfused or missing data

Available Evidence

Available Evidence

- Total patients enrolled in EAP: 47,047
- Total patients transfused: 36,226
- Patients with adequate data for follow-up: 35,322
  - April 4th – May 1st, 2020: 6,990 patients
  - May 1st – June 4th, 2020: 14,846 patients
  - June 4th – July 4th, 2020: 13,486 patients
- Patients with known transfusion antibody titers who received one unit of plasma: 3,082
  - April 4th – May 1st, 2020: 775 patients
  - May 1st – June 4th, 2020: 1,949 patients
  - June 4th – July 4th, 2020: 358 patients

Available Evidence

• Early Administration:
  • Mortality:
    • Lower mortality rates observed if plasma transfused ≤3 days from diagnosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Admin ≤3 days</th>
<th>Admin &gt;3 days</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-Day Morality</td>
<td>8.7% (95% CI 8.3-9.2%)</td>
<td>11.9% (95% CI 11.4-12.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30-Day Mortality</td>
<td>21.6% (95% CI 12-22.3%)</td>
<td>26.7% (95% CI 26.1-27.3%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

• Held true for each period in the study

Available Evidence

• SARS-CoV-2 Specific IgG Antibody levels
  • Mortality:
    • Mortality benefit observed with administration of higher antibody plasma

<table>
<thead>
<tr>
<th></th>
<th>High (S/Co* &gt;18.45)</th>
<th>Medium (S/Co* 4.62-18.45)</th>
<th>Low (S/Co* &lt;4.62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-Day Morality</td>
<td>8.9% (95% CI 6.8-11.7%)</td>
<td>11.6% (95% CI 10.3-13.1%)</td>
<td>13.7% (95% CI 11.1-16.8%)</td>
</tr>
<tr>
<td>30-Day Mortality</td>
<td>22.3% (95% CI 18.9-26.1%)</td>
<td>27.4% (95% CI 25.5-29.4%)</td>
<td>29.6% (95% CI 26-33.5%)</td>
</tr>
</tbody>
</table>

*S/Co = Signal to cutoff ratio (tested on Ortho-Clinical Diagnostics VITROS Anti-SARS-CoV-2 IgG Chemiluminescent immunoassay (CLIA))

• Held true when accounting for time to transfusion
  • Specifically between extremes
## Available Evidence

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Large (n = 35,322)</td>
<td>No control group</td>
</tr>
<tr>
<td>Multicenter (n = 2,807)</td>
<td>No randomization</td>
</tr>
<tr>
<td>Built in blinding regarding antibody levels in plasma transfusions</td>
<td>Did not allow for assessment of the presence of pre-transfusion antibodies</td>
</tr>
<tr>
<td>Continues to add to evidence regarding early transfusion and higher antibody levels</td>
<td>Differences in baseline characteristics of group</td>
</tr>
<tr>
<td></td>
<td>Use of signal to cutoff ratio as antibody assessment</td>
</tr>
</tbody>
</table>

Available Evidence

• What we know:
  • Convalescent plasma has been historically used as a therapeutic in several other viral infections including other coronaviruses.
  • Data pertaining to the efficacy of convalescent plasma in COVID-19 is currently mixed and derived from small case series, a few small studies, and some open-label, uncontrolled, observational data.
  • Signals exist that plasma may be most beneficial if administered as high antibody level transfusions early in the course of disease.

• What we don’t know:
  • If convalescent plasma is definitively effective when compared to placebo or other standards of care
  • How a recipient’s baseline antibody titers may impact the efficacy of convalescent plasma
  • Optimal timing of transfusion with regards to symptom onset
  • Optimal dosing with regards to donor antibody titers and number of units to transfuse
# Obtaining Approval for Convalescent Plasma

## Enrollment in Clinical Trial
- Prophylaxis
- Mild/Moderate
- Severe

## Emergency Use Approval
- Convalescent plasma therapy for COVID-19 was granted emergency use approval by the US FDA on 8/23/2020 for use in hospitalized patients with COVID-19
- National expanded access program discontinuing enrollment after 8/28/2020

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Patient Selection

• EUA Directed Patient Selection: “For use in hospitalized patients”
  • Notes:
    • Expanded access program specifically evaluated severe/life-threatening disease (or risk of progression to severe/life threatening disease)
    • Optimally administered within 3 days of diagnosis
  • Special populations:
    • Not evaluated in: pediatrics, pregnancy, nursing mothers
    • Geriatrics: Not specifically evaluated, but included in EAP safety analysis

• EUA Requirements (with administration a health care provider must):
  • 1) Provide Fact Sheet for Patients/Caregivers
  • 2) Notify the patient of emergency approval of biologic (not formally FDA approved)
  • 3) Notify the patient they have the right to refuse administration
  • 4) Explain the known risk and benefits and the extent of with risk/benefit is unknown
  • 5) Provide information on the availability of alternative treatments and their risk/benefit

https://www.fda.gov/media/141478/download
1. Adverse effects
   • Hospitals of health care providers must maintain records and conduct an investigation of adverse reactions observed after transfusion
   • Serious adverse events related to administration of convalescent plasma should be reported to the FDA
     • EUA specifies that fatalities related to transfusion must be reported, as required under 21 CFR 606.170.

2. Record keeping
   • Blood establishments must keep records of collection, process, and distribution
   • Hospitals must maintain records regarding the receipt, storage, and administration of convalescent plasma
Donors

- Donations/processing through American Red Cross or other participating blood bank
  - The FDA EUA requires determination of antibody levels from donors prior to release of product
    - Approved for testing using the Ortho VITROS SARS-CoV-2 IgG test with a signal to cutoff ratio ≥12
    - S/Co <12 can be used, but must be labeled as “COVID-19 Convalescent Plasma of Low Titer”
    - If alternative testing methodology to be used blood center must contact the Center for Biologic Evaluation and Research (CBER)
- Requirements:
  - Proven disease (i.e. positive nasopharyngeal PCR or serologic test for SARS-CoV-2)
  - Recovery:
    - 1) Complete resolution of symptoms at least 14 days prior to donation
  - Eligible to donate blood products and HLA antibody negative
  - 300-1000 mL of plasma collected per donation / may donate every 28 days.
- Refer potential donors to: ccpp19.org or FDA or American Red Cross websites

SIDP
Society of Infectious Diseases Pharmacists

Dosing

Considerations:
- Plasma infusion volume
- Antibody titers
- Optimal regimen unknown
- Current COVID-19 studies/cases series = wide variety of volumes/titers
- Duration of activity = weeks-months

Treatment:
1-2 units (~200-500 mL) of high antibody plasma

Infusion Rate:
500 mL/hr

**Safety**

### Various Infection Risks

- Antibody-dependent infection enhancement
- Transmission/transfusion of SARS-CoV-2
- Transmission of SARS-CoV-2 to healthcare personnel
- Transmission of other infectious pathogens (e.g.* HIV, HCV, HBV)

*Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus

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**Adverse Reactions**

- Similar to other human plasma administration:
  - Infusion reactions:
    - Life Threatening:
      - Transfusion-related acute lung injury (TRALI)
      - Transfusion-associated circulatory overload (TACO)
      - Allergic/anaphylactic transfusion reactions
    - Non-life threatening:
      - Febrile non-hemolytic transfusion reactions
      - Urticarial transfusion reactions
  - Consider:
    - Pretreatment with acetaminophen/diphenhydramine
    - Slowing infusion

Available study protocols recommend stop infusion if:
- Any signs of anaphylaxis
- Respiratory compromise
- Hypotension
- Tachycardia/bradycardia
- Provider clinical judgement


Adverse Reactions

National Expanded Access Program: April 3rd – May 11th, 2020:

- 14,288 patients enrolled with 8932 transfused
  - Safety data from first 5000 patients:
    - Serious adverse events with 4 hours:
      - 36 Events:
        - 15 Deaths
        - 21 non-deaths:
          - 7 – Transfusion associated circulatory overload (0.14%)
          - 11 – Transfusion associated lung injury (0.22%)
          - 3 – Severe allergic transfusion reactions (0.06%)
      - Mortality at 7 days: 602 (14.9%)
        - ICU: 456 (16.7% of total ICU admitted patients)
        - Non-ICU: 146 (11.2% of total non-ICU admitted patients)

Drug-Drug Interactions

• Theoretical reduction in INR for patients on warfarin
  • Convalescent plasma = Fresh frozen plasma from patient previously infected with SARS-CoV-2.
  • INR reduction related to:
    • Baseline INR
    • Volume of FFP administered

• Recommendation: Carefully monitor INR in patients receiving convalescent plasma in conjunction with warfarin

Labeling and Expiration

- Labeling should be uniform

- Expiration date: Similar to other plasma products.
  - Frozen within 8 hours after collection and stored at -18°C or colder
  - Expires 1 year from the date of collection
  - Once thawed, can be refrigerated for up to 5 days prior to transfusion


Resources

- FDA Release:
  - Methods for enrollment
  - Donor requirements
  - Labeling requirements

- Ccpp19.org:
  - Donor requirements/registration
  - Study protocols
  - Guidance on non-trial use

- American Red Cross:
  - Information for Potential Donors

- Uscovidplasma.org
  - US expanded access program website

- Key Reviews:


**Summary**

- **Mechanism**: Transfusion/transfer of passive immunity
- **Data**: Limited evidence from other coronaviruses, small studies/case series, and experience from the National Expanded Access Program
- **Donors**: Confirmed infection with recovery prior to donation
- **Recipients**: Clinical trials or emergency use authorization
- **Dosing**: 1-2 units (200-500 mL) of (ideally) “high antibody” plasma
- **Safety/Adverse Reactions**: Infection risk and typical blood product concerns
- **Drug-drug Interactions**: Theoretical lowering of INR for patients on warfarin
Convalescent Plasma

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