Convalescent Plasma

A Review of Pertinent Information for SARS-CoV-2

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Data as of July 31st, 2020
• 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

Seroconversion in COVID-19

- 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
History

1892: Diphtheria
1918: Spanish Flu
1920s: Scarlet Fever
1934: Measles outbreak
Up to 1970s: Pertussis Tetanus
2009: Influenza A H1N1
2012: MERS-CoV
2015: Ebola


### SARS-CoV-1

<table>
<thead>
<tr>
<th><strong>Population/Intervention</strong></th>
<th>80 patients with SARS-CoV-1 (2003 Hong Kong) given 1-3 units (160-640 mL IV of convalescent plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Discharge by day 22 post-infusion</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>33/80 (41.3%) patients met primary outcome</td>
</tr>
<tr>
<td></td>
<td>• Median time from symptom onset to receipt of convalescent plasma: 14 days (range 7-30)</td>
</tr>
<tr>
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<td>• Factors associated with good outcomes:</td>
</tr>
<tr>
<td></td>
<td>• Receipt of convalescent plasma within 14 days of symptom onset.</td>
</tr>
<tr>
<td></td>
<td>• 56% good outcome vs. 15.6% poor outcome patients had admin ≤14 days (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>• PCR positivity with seronegativity at the time of treatment.</td>
</tr>
<tr>
<td></td>
<td>• 61% good outcome vs. 21% poor outcome patients had PCR positive/serology negative (p&lt;0.001)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Population/Intervention</strong>: 10 adult patients with severe COVID-19 without end organ dysfunction</td>
<td><strong>Population/Intervention</strong>: 5 adult, critically ill patients with severe COVID-19</td>
</tr>
<tr>
<td><strong>Intervention</strong>: 200 mL of convalescent plasma with neutralizing antibody titers of &gt;1:640</td>
<td><strong>Intervention</strong>: 400 mL of convalescent plasma (2 x 200 mL infusions) – Donor requirements = IgG &gt;1:1000 / neutralizing antibodies &gt;1:40.</td>
</tr>
<tr>
<td><em>(Note: all 10 received antiviral therapy and 6/10 received methylprednisolone)</em></td>
<td><em>(Note: all 10 received antiviral therapy and methylprednisolone)</em></td>
</tr>
<tr>
<td><strong>Results</strong>:</td>
<td><strong>Results</strong>:</td>
</tr>
<tr>
<td>• Improvement in all symptoms within 1-3 days</td>
<td>• Normalization of body temperature within 3 days</td>
</tr>
<tr>
<td>• Varying degrees of absorption of pulmonary lesions</td>
<td>• Decreased SOFA / increased PaO2:FiO2 w/in 12 days.</td>
</tr>
<tr>
<td>• Tendency towards declined inflammatory markers</td>
<td>• Viral loads decreased then became negative in all</td>
</tr>
<tr>
<td>• No deaths</td>
<td>• Increases in recipient neutralizing antibody titers</td>
</tr>
</tbody>
</table>

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 Convalescent Plasma 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>
</tr>
</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

• 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

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.

Cochrane Review of Convalescent Plasma Therapy in COVID-19:
20 Studies
5443 Patients
Overall Risk of Bias: High

Donors

• Donations/processing through American Red Cross or other participating blood bank
• 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
    • *Note: A negative PCR is no longer required for donor qualification*
  • Eligible to donate blood products and HLA antibody negative
  • Optimally, neutralizing antibody titers >1:80
  • 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

7/31/2020 Update

## Patient Enrollment

**Obtaining Approval for Convalescent Plasma**

<table>
<thead>
<tr>
<th>Enrollment in Clinical Trial</th>
<th>Expanded Access Program</th>
<th>Single Patient Emergency IND</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prophylaxis</td>
<td>- Facility enrollment</td>
<td>- Similar enrollment to</td>
</tr>
<tr>
<td>- Mild/Moderate</td>
<td>- Lab confirmed COVID-19</td>
<td>expanded access</td>
</tr>
<tr>
<td>- Severe</td>
<td>- Patients with severe</td>
<td>- Fill out FDA form 3926</td>
</tr>
<tr>
<td></td>
<td>or life-threatening</td>
<td>(turn-around: 4-8 hours)</td>
</tr>
<tr>
<td></td>
<td>disease NOT eligible</td>
<td>- Call 1-866-300-4374</td>
</tr>
<tr>
<td></td>
<td>for clinical trials</td>
<td>(turn-around: &lt;4 hours)</td>
</tr>
</tbody>
</table>


Dosing

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

Currently available study protocols:

**Prophylaxis:**
- 1 unit (~200-250 mL)

**Treatment:**
- 1-2 units (~200-500 mL)

Infusion Rate: 500 mL/hr

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
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:
  • Must include the following statement: “Caution: New Drug – Limited by Federal (or United States) law to investigational use.”
  • Labels should be uniform
    • FDA recommends use of International Society of Blood Transfusion (ISBT) format outlined in the United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components.

• 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
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

• **Donors**: Confirmed infection with recovery prior to donation

• **Recipients**: Clinical trials, expanded access, single patient eIND

• **Dosing**: Optimal unknown / current protocols = 1-2 units (200-500 mL)
  - Optimally with neutralizing antibody titers of >1:80

• **Safety/Adverse Reactions**: Infection risk and typical blood product concerns

• **Drug-drug Interactions**: Theoretical lowering of INR for patients on warfarin
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