Convalescent Plasma
A Review of Pertinent Information for SARS-CoV-2

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Data as of April 13th, 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
1892: Diphtheria
1918: Spanish Flu
1920s: Scarlet Fever
1934: Measles outbreak
Up to 1970s: Pertussis, Tetanus
2004: SARS-CoV-1
2009: Influenza A H1N1
2012: MERS-CoV
2015: Ebola

### SARS-CoV-1

<table>
<thead>
<tr>
<th>Population/Intervention:</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>
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<td>• Factors associated with good outcomes:</td>
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<tr>
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<td>• Receipt of convalescent plasma within 14 days of symptom onset.</td>
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<td>• 56% good outcome vs. 15.6% poor outcome patients had admin ≤14 days (p&lt;0.001)</td>
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<td>• PCR positivity with seronegativity at the time of treatment.</td>
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<tr>
<td></td>
<td>• 61% good outcome vs. 21% poor outcome patients had PCR positive/serology negative (p&lt;0.001)</td>
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</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>
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<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>
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<td>(Note: all 10 received antiviral therapy and 6/10 received methylprednisolone)</td>
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<tr>
<td><strong>Results</strong>:</td>
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</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>
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<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>
<tr>
<td></td>
<td>• No deaths</td>
</tr>
</tbody>
</table>

Available Evidence


<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>69 y/o Female</td>
<td>55 y/o Male</td>
<td>73 y/o Female</td>
<td>31 y/o Female</td>
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</tr>
</tbody>
</table>

| Total administered Convalescent Plasma Volume | 900 mL (3 infusions) | 200 mL (1 infusion) | 2400 mL (8 infusions) | 300 mL (1 infusion) |

- 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.

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 28 days prior to donation
  - 2) Complete resolution of symptoms at least 14 days prior to donation + negative PCR
- Eligible to donate blood products
- HLA antibody negative
- Optimally, neutralizing antibody titers >1:80

Refer potential donors to: ccpp19.org or FDA or American Red Cross websites

# 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><strong>- Prophylaxis</strong></td>
<td><strong>- Facility enrollment</strong></td>
<td><strong>- Similar enrollment to expanded access</strong></td>
</tr>
<tr>
<td><strong>- Mild/Moderate</strong></td>
<td><strong>- Lab confirmed COVID-19</strong></td>
<td><strong>- Fill out FDA form 3926 (turn-around: 4-8 hours)</strong></td>
</tr>
<tr>
<td><strong>- Severe</strong></td>
<td><strong>- Patients with severe or life-threatening disease NOT eligible for clinical trials</strong></td>
<td><strong>- Call 1-866-300-4374 (turn-around: &lt;4 hours)</strong></td>
</tr>
</tbody>
</table>


Dosing

Currently available study protocols:

**Prophylaxis:**

1 unit (~200-250 mL)

**Treatment:**

1-2 units (~200-500 mL)

Infusion Rate: 500 mL/hr

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


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

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

Consider:
• Pretreatment with acetaminophen/diphenhydramine
• Slowing infusion

• 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:
  • 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

• Clinicaltrials.gov
  • Currently active clinical trials

• 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