Convalescent Plasma

A Review of Pertinent Information for SARS-CoV-2

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Data as of April 14th, 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


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

1892: Diphtheria
1918: Spanish Flu
1920s: Scarlet Fever
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

<table>
<thead>
<tr>
<th><strong>Duan K, et al.</strong></th>
<th><strong>Shen, et al.</strong></th>
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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>
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<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><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>
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<tr>
<td><strong>Results:</strong></td>
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<tr>
<td>• Improvement in all symptoms within 1-3 days</td>
<td>• Normalization of body temperature within 3 days</td>
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<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>
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Available Evidence

• Case Series: Zhang B, et al.

<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>
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<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>
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<tr>
<td>Convalescent Plasma</td>
<td></td>
<td></td>
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<tr>
<td>Volume</td>
<td></td>
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• 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.

Available Evidence

Cochrane Review of Convalescent Plasma Therapy in COVID-19:

- **8 Studies**
- **32 Patients**
- **Bias: High**
- **Outcome Certainty: Low**

**Efficacy – Mortality:** Reported in all 8 studies. All reported patients survived - Unable to assess

**Efficacy – Symptomatic Improvement:** Reported in 6 studies. All reported symptomatic improvement - Unable to assess

**Efficacy – Time to Hospital Discharge:** Reported in 6 studies. Ranged from 4-35 days post-transfusion – Unable to assess

**Safety – Adverse Events:** 2 ADRs reported. 1 case of anaphylaxis and 1 moderate fever - Unable to assess

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 28 days prior to donation
    • 2) Complete resolution of symptoms at least 14 days prior to donation + negative PCR
  • 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


### Patient Enrollment

<table>
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<tr>
<th>Obtaining Approval for Convalescent Plasma</th>
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<tbody>
<tr>
<td><strong>Enrollment in Clinical Trial</strong></td>
</tr>
<tr>
<td>- Prophylaxis</td>
</tr>
<tr>
<td>- Mild/Moderate</td>
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<tr>
<td>- Severe</td>
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**Clinicaltrials.gov.**

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


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

Adverse Reactions

National Expanded Access Program: April 3\textsuperscript{rd} – May 11\textsuperscript{th}, 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)

• 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

• Uscovidplasma.org
  • US expanded access program website

• Key Reviews:
    http://doi.org/10.1172/JCI138003.
    http://doi.org/10.1172/JCI138745.
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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