Treatment for Emerging Infections: Convalescent Plasma and COVID-19

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Disclosures

I have NO financial disclosure or conflicts of interested with the material presented in this lecture.
Objectives

1. To provide an overview on the current treatment landscape for COVID-19
2. To expound on the mechanisms of action of convalescent plasma therapy (CPT) and potential risks associated with its use
3. To present available evidence regarding efficacy and safety of CPT on treatment of COVID-19
4. To present our institutional protocols regarding the use of CPT and our early experiences
What is Convalescent Plasma?
CPT has multiple plausible mechanisms of action

CPT: Benefits over various phases of COVID-19

Stage I (Early Infection)

Stage II (Pulmonary Phase)

Stage III (Hyperinflammation Phase)

Severity of Illness

Time course

Viral response phase

Host inflammatory response phase

VIRAL NEUTRALIZATION

IMMUNOMODULATION
Antibody therapies for infections over the years

- Diphtheria
- Tetanus
- Spanish influenza
- Pneumococcus
- Meningococcus
- Group A Strep
- Diphtheria
- Tetanus
- Rabies
- Measles
- Anthrax
- Tularemia
- etc

- Tetanus Ig
- Rabies Ig
- Hep B Ig
- Varicella Ig
- CMV Ig
- RSV Ig

- SARS-CoV
- H1N1 influenza
- MERS-CoV
- Ebola
Convalescent Plasma Therapy: Evidence from Other Illnesses
CPT use was associated with lower mortality in Spanish influenza

- Meta-analysis on data during the Spanish influenza era (1918-1925)
- Crude CFR of 16% for those treated with CPT (versus 37% for untreated group)
- Adverse events noted: chills, possible exacerbation of symptoms in few patients

CPT is beneficial in patients with SARS especially when given earlier during the disease course

<table>
<thead>
<tr>
<th>P</th>
<th>Patients with SARS (2003, HK) who deteriorated despite antibiotics, ribavirin and methylprednisolone (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>200-499 ml of CP</td>
</tr>
<tr>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| O | • 30 patients with good outcome (discharged by day 22), noted to have been given CP earlier than those who had poor outcome (11.67 vs 16.04 days)  
  • No immediate adverse effects noted                                                                                          |
| M | Prospective cohort                                                                                                              |

CPT showed mortality benefit among patients with severe H1N1 infection

<table>
<thead>
<tr>
<th>P</th>
<th>Patients aged ≥18 y/o with severe H1N1 2009 infection (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CP, NAT &gt;1:160, obtained by pheresis</td>
</tr>
<tr>
<td>C</td>
<td>Patients who declined plasma treatment</td>
</tr>
<tr>
<td>O</td>
<td>• Mortality: 20.0% vs 54.8%, p=0.01</td>
</tr>
<tr>
<td></td>
<td>• Multivariate analysis: reduction of mortality, OR 0.20 (95% CI 0.06-0.69, p=0.011)</td>
</tr>
<tr>
<td>M</td>
<td>Prospective cohort</td>
</tr>
</tbody>
</table>
CPT did not confer improvement in survival among patients with Ebola virus infection

<table>
<thead>
<tr>
<th>P</th>
<th>Patients of all ages, including 1 pregnant patient (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2x 200-250 ml CP</td>
</tr>
<tr>
<td>C</td>
<td>Historical control (patients treated in center prior to availability of CP)</td>
</tr>
</tbody>
</table>
| O | • From day 3-16, risk of death: 31% vs 38%  
• No significant improvement in survival  
• No SAEs observed |
| M | Non-randomized controlled cohort study                  |
Convalescent Plasma Therapy: Potential Risks
CPT Risks: Transfusion-related reactions

- Transfusion-transmissible infections
- Acute hemolytic transfusion reactions
- Febrile non-hemolytic transfusion reactions
- Allergic/urticarial reactions
- Anaphylactic/anaphylactoid reactions
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated circulatory overload (TACO)
CPT Risks: Immune-related reactions

Antibody-mediated enhancement of infection (ADE)

• Immune-mediated reaction which may occur with several disease (dengue, yellow fever, Zika, etc.)

• Characterized by disease enhancement in presence of certain non-neutralizing antibodies

• Available evidence from use of CPT in SARS and MERS-CoV patients, however, suggest that it is safe

• It remains to be a theoretical concern at present

CPT Risks: Immune-related reactions

Attenuation of immune response

- Attenuation of immune response which may leave recipients vulnerable to subsequent reinfection
- If proven to be real, recipients could be prioritized for vaccination against COVID-19 in the future once these become available

Convalescent Plasma Therapy: Early studies on COVID-19
CPT use in critically-ill COVID-19 patients is safe and associated with clinical improvement and viral load reduction

<table>
<thead>
<tr>
<th>P</th>
<th>Critically ill COVID-19 positive patients with ARDS (n=5), already on antivirals (lopinavir/ritonavir, favipravir, IFN alfa-1b, arbidol, darunavir) and MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CP with anti-SARS-CoV-2 IgG binding Ab titer &gt;1:1000 and NAT &gt;1:40 given between days 10-22</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
</tr>
</tbody>
</table>
| O | • Normalization of body temp within 3 days in 4/5 patients; SOFA score decreased, PaO2/FiO2 increased in 12 days  
  • Viral loads decreased and became negative within 12 days of transfusion  
  • 3 discharged (LOS: 53, 51, 55 days), 2 in stable condition but were still on MV (one off ECMO)  
  • No transfusion-related AEs |
| M | Case series |
CPT use in severe COVID-19 is well-tolerated and associated with clinical, laboratory and radiologic improvements

<table>
<thead>
<tr>
<th>P</th>
<th>Severe COVID-19 (n=10), on maximal supportive care with antivirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1x 200 ml dose of CP, NAT &gt;1:640</td>
</tr>
<tr>
<td>C</td>
<td>Historical controls</td>
</tr>
<tr>
<td>O</td>
<td>• Clinical, laboratory and radiologic improvement in all 10 patients</td>
</tr>
<tr>
<td></td>
<td>• 3 discharged, 7 much improved (control: 3 died, 6 stable, 1 improved)</td>
</tr>
<tr>
<td></td>
<td>• Well-tolerated, no SAEs</td>
</tr>
<tr>
<td>M</td>
<td>Prospective cohort study</td>
</tr>
</tbody>
</table>

CPT use in critically-ill patients is well-tolerated and associated with clinical improvement and viral clearance

<table>
<thead>
<tr>
<th>P</th>
<th>Critically-ill COVID-19 patients (n=4), one is post-partum, all receiving supportive therapy and other agents (arbidol, lopinavir/ritonavir, oseltamivir, ribavirin and IFN-alfa-2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CP, 200 to 2400 mL, no mention of NAT</td>
</tr>
<tr>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| O | • All four patients showed clinical improvement and viral clearance 3-22 days from CP  
• Three eventually discharged  
• No SAEs noted |
| M | Case Series |
Should convalescent plasma therapy be used in the treatment of critically ill patients with COVID-19?

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Date of Review: 03-April-2020 (version 1)
Last Updated: 13-April-2020 (version 4)

This rapid review summarizes the available evidence on the efficacy and safety of convalescent plasma therapy in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

- There is insufficient evidence to support the routine use and efficacy of convalescent plasma on critically ill patients with COVID-19 at this time.

Who are we?

We are a group of physicians and scientists from 57 institutions in 46 states who have self-organized for the purpose of investigating the use of convalescent plasma in the current COVID-19 pandemic. The nucleus of the organization sprung from a coalition of biomedical researchers assembled several years ago to refocus studies of health and disease more squarely on public health priorities.¹

**COVID-19 Convalescent Plasma Project (CCPP19) Leadership Group**

- Arturo Casadevall MD, PhD (Chair), Johns Hopkins University
- Benjamin Chen MD, Mount Sinai School of Medicine
- Brenda J. Grossman, MD, MPH, Washington University School of Medicine
- Michael J Joyner, MD, Mayo Clinic School of Medicine
- Jeffrey P Henderson MD, PhD, Washington University School of Medicine
- Nigel Paneth MD, MPH, Michigan State University
- Liise-anne Pirofski, MD, Albert Einstein College of Medicine
- Shmuel Shoham MD, Johns Hopkins University
Pathways for Use of Investigational COVID-19 Convalescent Plasma

Patient Eligibility

- Adult patients with laboratory confirmed COVID-19
- Severe or immediately life-threatening disease
- Informed consent provided by patient or healthcare proxy

<table>
<thead>
<tr>
<th>Severe Disease</th>
<th>Life-threatening Disease</th>
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</tr>
<tr>
<td>• Lung infiltrates &gt;50% within</td>
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</table>
Clinical Trials on CPT

- CPT for high-risk children (immunocompromised, severe cardiac or pulmonary disease)
- CPT as post-exposure prophylaxis in adults
- CPT for adults with mild/moderate illness
- CPT for adults with severe/critical illness
- CPT for prevention of complications among outpatients with symptomatic illness
Convalescent Plasma Therapy: Newer studies on COVID-19
CPT is safe in hospitalized patients with incidence of SAEs at <1% and 7-day incidence of mortality of 14.9%

<table>
<thead>
<tr>
<th>P</th>
<th>First 5,000 patients of US FDA Expanded Access Program for COVID-19 convalescent plasma (4,051 [81%] had severe or life-threatening disease and 949 judged to have a high risk of progressing to severe or life-threatening disease); 66% admitted to ICU</th>
</tr>
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<tr>
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<td>CPT</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
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</table>
| O | Within 4 hours of CPT, 36 SAEs noted (<1%)
• 15 deaths (0.3%), 4 of which were judged as related (possibly 3, probably 1, definitely 0)
• 21 non-death SAEs: 7 TACO, 11 TRALI, 3 severe allergic reactions
  • All incidences of TACO and TRALI judged as related (possibly 9, probably 7, definitely 2)
Overall 7-day mortality rate 14.9% (95% CI 13.8-16.0%)
• ICU patients: 16.7% (456)
• Non-ICU: 11.2% (146)
7-day mortality rate of 14.9% is not alarming, given CFR of 15-20% among hospitalized patients and 57% among those admitted to ICU |
| M | Prospective cohort study |

CPT was associated with improved survival in non-intubated patients but not in intubated patients

<table>
<thead>
<tr>
<th>P</th>
<th>39 adult patients (FDA eIND indication/severe and life-threatening disease); 87% on non-invasive O₂ delivery and 10% (4 patients) on MV</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>CP: anti-spke Ab titers ≥1:320, 2x 250 mL x 1-2 hours</td>
</tr>
<tr>
<td>C</td>
<td>1:4 matched controls (based on use of HCQ+azithromycin, intubation status and duration, LOS, O₂ requirement on day of transfusion)</td>
</tr>
</tbody>
</table>
| O | • Respiratory status: Day 14, worsened in 18.0% in those on CPT vs 24.3% in control (OR 0.86, 95% 0.75-0.98, p=0.028) [no statistical significant difference in resp status on days 1 and 7]  
• CPT associated with improved survival in non-intubated patients (HR 0.19, 95% CI 0.05-0.72) but not in intubated patients (HR 1.24, 95% CI 0.33-4.67)  
• No evidence that effect of plasma depended on duration of symptoms |
| M | Prospective cohort study |

CPT was associated with clinical improvement in severe disease but not life-threatening disease

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<td>SOC (symptomatic control and supportive care)</td>
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| O | • Clinical improvement within 28 days: **51.9%** in CPT group (43.1% in control); HR 1.40 [95% CI, 0.79-2.49], p=0.26  
  - Severe disease: **91.3%** in CPT group (68.2% in control); HR 2.14 [95% CI, 1.07-3.42], p=0.3  
  - Life-threatening disease: **20.7%** in CPT group (24.1% in control); HR **0.088** [95% CI, 0.30-2.63], p=0.83  
  • No significant difference in 28-day mortality (15.7% vs 24.0%; OR 0.65[95% CI, 0.29-1.46]; p=0.30)  
  • Negative conversion rate of viral PCR at 72 hours: **87.2%** in CPT group (37.5% in control group); OR 11.39[95% CI,, 3.91-33.18]; p<0.001  
  • Two patients in CPT group experienced adverse events within hours (**1 non-severe allergic transfusion reaction** and the other a **possible severe transfusion-associated dyspnea**) |
| M | Open-label, multicenter, randomized clinical trial (7 centers in Wuhan) |

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Convalescent Plasma Therapy: Local Experiences
COVID-19 Convalescent plasma document library

COVID-19 is an infectious disease that is caused by a new coronavirus, SARS-CoV-2. The outbreak has affected almost every country of the World and as of April 9, 2020, a total of 1,503,900 confirmed cases and 89,915 deaths had been reported in 184 countries. As the development of efficient and safe vaccination will require months, quick alternative treatments are sought. Passive immunisation using the plasma of recovered COVID-19 donors for the treatment of severe COVID-19 cases could offer a suitable therapeutic strategy. The plasma of recovered COVID-19 donors contains specific IgG and IgM anti-SARS-CoV-19 antibodies, which can neutralize the virus. However, implementation of a convalescent plasma transfusion programme might need comprehensive planning.

ISBT aims to support those organisations who need guidance with developing their protocol for collecting and processing plasma for the treatment of COVID-19. Therefore, we prepared an open access platform for SHARING protocols from various WHO regions.

If your organisation has a protocol, guideline, guidance or a publication on the collection and processing of COVID-19 convalescent plasma, please upload the documents to share it with those, who might need your help.

Scroll down to submit your document.

Please find here the resources categorized by WHO region

<table>
<thead>
<tr>
<th>International</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points to consider in the preparation and transfusion of COVID-19 convalescent plasma by the ISBT Working Party on Global Blood Safety</td>
</tr>
<tr>
<td>Points to consider in the preparation and transfusion of COVID-19 convalescent plasma in low- and middle-income countries by the Global Blood Safety Working party of the ISBT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eastern Mediterranean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of Convalescence Plasma in the Treatment of Patients Infected with COVID-19 Virus infection, Saudi Arabia</td>
</tr>
<tr>
<td>Protocol for the use of convalescent plasma for the treatment COVID-19 infected patients in Qatar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Western Pacific</th>
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</thead>
<tbody>
<tr>
<td>Guide on the Compassionate Use of Convalescent Plasma Therapy For COVID-19, Philippines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Investigational COVID-19 Convalescent Plasma by FDA</td>
</tr>
</tbody>
</table>
CPT: Compassionate Use in UP-PGH

Eligible adult patients for use of convalescent plasma therapy
- Adult patient with laboratory confirmed COVID-19
- Severe or immediately life-threatening disease

<table>
<thead>
<tr>
<th>Severe Disease</th>
<th>Life-threatening Disease</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
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<td>Respiratory failure</td>
</tr>
<tr>
<td>Respiratory rate ≥30/min</td>
<td>Septic shock and/or</td>
</tr>
<tr>
<td>Oxygen saturation ≤93%</td>
<td>Multiple organ dysfunction or failure</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio &lt;300 and/or</td>
<td></td>
</tr>
<tr>
<td>Lung infiltrates &gt;50% within 24 to 48 hours</td>
<td></td>
</tr>
</tbody>
</table>

- Within 3 to 21 days from onset of symptoms
- Not a diagnosed case of IgA deficiency
- Must be able to provide informed consent (see attached). In the event that the patient cannot provide consent, next of kin or legal surrogate decision maker should provide consent.
CPT: Compassionate Use in UP-PGH

Eligible pediatric patients (0-19 years of age) for use of convalescent plasma therapy

- Children who have baseline immunosuppression
  - Children with cancer undergoing chemotherapy
  - Children diagnosed with primary immunodeficiency syndromes except IgA deficiency
- With laboratory confirmed COVID-19
  - Exception will be given for children with probable COVID-19 who are able to receive first-line immunomodulators while awaiting test results
  - Severe or immediately life-threatening disease

<table>
<thead>
<tr>
<th>Severe Disease (one or more of the following)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>- Dyspnea</td>
<td>- Respiratory failure</td>
</tr>
<tr>
<td>- Elevated Respiratory rate</td>
<td>- Septic shock and/or</td>
</tr>
<tr>
<td>&lt;2 months: ≥ 60/min</td>
<td>- Multiple organ dysfunction or failure</td>
</tr>
<tr>
<td>2 to 11 months: ≥ 50/min</td>
<td></td>
</tr>
<tr>
<td>1 to 5 years: ≥ 40/min</td>
<td></td>
</tr>
<tr>
<td>5 to 16 years: ≥ 30</td>
<td></td>
</tr>
<tr>
<td>- Oxygen saturation ≤ 93%</td>
<td></td>
</tr>
<tr>
<td>- PaO2/FiO2 ratio ≤ 300 and/or</td>
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</table>

- Within 3 to 21 days from onset of symptoms
- Must be able to provide informed consent (see attached). In the event that the patient cannot provide consent, next of kin or legal surrogate decision maker should provide consent.
CPT: Transfusion Protocol

• Choose a type-specific properly-labeled unit using the table below.

<table>
<thead>
<tr>
<th>Recipient Blood Type</th>
<th>Plasma Blood Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A, AB</td>
</tr>
<tr>
<td>B</td>
<td>B, AB</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
</tr>
<tr>
<td>O</td>
<td>O, A, B, AB</td>
</tr>
</tbody>
</table>

• Thaw frozen plasma at 37°C

• Transfuse 2 aliquots of plasma (250 mL x 2) per patient
  • Transfuse first aliquot for 2-3 hours
  • Transfuse 2nd aliquot at same rate 2 hours after completion of first aliquot
  • For pediatric patients, transfuse 10-15 mL/kg IV over 2-3 hours
CPT: Transfusion Protocol

• For patients at **higher-risk for volume overload**, may consider:
  • Increasing interval between two aliquots
  • Given IV dose of diuretics
  • Decreasing total dose to one aliquot (*should be discussed with clinical care team*)

• **Record time** at start and end of each infusion

• **Monitor vital signs** immediately prior to infusion, at 10-20 minutes after start of infusion, at completion of infusion and 30-60 minutes after

• **Pre-treatment to minimize transfusion reactions** may be given per clinical care team discretion
CPT: Transfusion Protocol

• If an **adverse event develops during infusion**, the infusion may be **slowed or stopped** as per clinical care team’s decision. Transfusion of CP should be halted and not restarted if anaphylaxis or severe allergic transfusion reactions develop

• Patients receiving CP **should be closely clinically monitored** using standard pathways to assess effectiveness of intervention. Monitoring may include (but not limited) to the following:
  • Clinical status and vital signs
  • Inflammatory markers (e.g., hSCRP, LDH, ferritin, IL-6)
  • Chest radiographs or CT scan
  • Arterial blood gases to check for PaO2/FiO2 ratio or PFR
CPT: Early Experiences

• CPT is generally well-tolerated. Documented adverse events include transfusion-associated dyspnea which is unlikely to be TRALI/TACO.

• CPT appears to be helpful in:
  • Improving inflammation as evidenced by decreasing trends of inflammatory markers.
  • Improving respiratory status as evidenced by increasing PFR trends and improvements in chest imaging abnormalities.

• CPT appears to be more effective among COVID-19 patients with severe disease compared to those with life-threatening disease.
CPT: Timing in relation with other investigational therapies

• CPT may be given with other investigational drugs

• There are no documented or foreseeable contraindications to giving CPT and tocilizumab together. However, we suggest that if CPT will be given after tocilizumab, that it should be given 24 hours after to provide time for assessment of effect of tocilizumab.

• No timing concerns or schedule adjustments required with regards to hemoperfusion at present (based on UP-PGH Hemoperfusion protocol). There is no theoretical risk for adsorption/removal of antibodies.
CPT: Regulatory Requirements

• CPT protocols should be prepared in compliance with FDA Circular 2020-013 “Guidance for the Monitoring of Drug Products Used for Treatment of COVID-19” and the Administrative Order No. 4 of 1992 “Compassionate Special Permit for Restricted Use of Unregistered Drug and Device Products”

• In compliance with FDA requirements, weekly updates on CPT recipients are submitted online thru email

• Serious adverse events are reported within 24 hours to the FDA using the VigiFlow drug monitoring management system
CPT: Moving Forward

• Continuous updating of CPT protocols as new clinical evidence arises
• Implementation of institutional RCTs on CPT
• Transition to hyperimmune globulins → monoclonal therapies
Summary

• Convalescent plasma therapy is a safe treatment modality which may be used in the management of COVID-19 while we wait for definitive therapies and development of a viable vaccine
  • Works by effecting viral neutralization and immunomodulation
  • Available evidence suggests better outcomes when given earlier during the course of disease (i.e., severe disease, before intubation is required)

• Clinical trials are needed to further elucidate the efficacy and safety of CPT and to identify the best recipients of this intervention
Treatment for Emerging Infections: Convalescent Plasma and COVID-19

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