Strategies to support the COVID-19 response in LMICs

A virtual seminar series
Use of convalescent plasma/transfusions in Low and Middle-income countries (LMICs)

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Disclosures

- As a member of the FDA Blood Product Advisory Committee...
  - Any views or opinions that are expressed in this presentation are my own, based on my own scientific expertise and professional judgement; they do not necessarily represent the views of either the Blood Products Advisory Committee or the formal position of FDA, and also do not bind or otherwise obligate or commit either Advisory Committee or the Agency to the views expressed

- Consultant/speaker
  - Grifols Diagnostic Solutions
  - Terumo, BCT

- Coinvestigator: 2 clinical trials of pathogen reduction using a commercial technology

Disclaimer

Most of what I say could change in days to weeks
Objectives

1. Review evidence behind convalescent plasma
2. Summarize research and clinical trials
3. Describe access to COVID-19 convalescent plasma (CCP)
4. Contextualize related challenges in LMICs
5. Review clinical considerations
6. Ethics

Abbreviations
CCP: COVID-19 Convalescent Plasma
HICs vs LMICs: High- vs. Low and Middle Income Countries
TTIs: Transfusion Transmitted Infections
PPE: Personal Protective Equipment
COVID-19 pandemic
20th May 2020

>5 million cases spanning 188 countries or territories

>325,000 deaths

Case fatality rate: 0.1%-16.3%

Underestimates true burden of disease

Inattention to LMICs in the pandemic
The premise behind convalescent plasma

**Passive transfer** (i.e. transfusion or infusion) of antibodies from **convalescent individual** into a **recipient** at risk of infection or already infected with virus i.e. SARS-CoV-2

“**Passive antibody administration** is the only short-term strategy to confer immediate immunity to susceptible individuals”

**It is NOT** ideal
- It is a **temporizing measure** pending availability of refined strategies for
- **Treatment** e.g. hyperimmune globulin, monoclonal antibodies, direct acting antivirals and/or
- **Prevention** (i.e. vaccination)

Historical precedent and biological plausibility
Convalescent plasma has been used many times... but does it work?

**1918-1919** Spanish Influenza (H1N1)

**Meta-Analysis:** Convalescent Blood Products
Crude case-fatality rate 19% (<4 days) of vs. 59% (if ≥4 days of pneumonia complications)

**1974-1978** Argentine hemorrhagic Fever (n=188)

- **Double blind placebo-controlled trial**
- **Hospitalized patients with Junin virus ≤8 days from onset of symptoms**
  - **Donors:** ≥four-fold rise in titers complement-fixation tests.
- **The case-fatality rate**
  - Immune plasma 1.1% vs Normal plasma 16.5%
Recent examples

**Ebola Virus Disease** (n=84) *(Feb to Aug 2015)*
- **Nonrandomized, comparative study** of patients with EVD
- 2 consecutive transfusions of (200-250 ml) within 2 days of diagnosis
  - Level of neutralizing antibodies **unknown** at the time of administration.
- **Control group:** 418 patients treated at the same center in previous 5m
- **Primary outcome:** risk of death 3 to 16 days after diagnosis
- **Risk of death**
  - 31% in the convalescent-plasma group vs. **38%** in the control group

**No serious adverse reactions**
**Not associated with a significant improvement in survival status** *(primary endpoint)*

Use of convalescent plasma in SARS1 and MERS

SARS

Hong Kong: retrospective chart review (n=80)
- Good clinical outcome in 33 of 80 (41.3%) patients as defined by hospital discharge by day 22; titering not performed
- Improved outcome associated with early administration
- No adverse events

MERS

Seoul, South Korea: case series (n=3)
Uncertain benefit although all 3 patients survived

Riyad, Saudi Arabia
Feasibility study
8/196 (2.7%) suspected confirmed MERS-CoV ELISA+
4/230 (1.7%) exposed healthcare workers ELISA+
- Low proportion with neutralizing antibodies


Use of convalescent plasma for COVID-19

Zhengzhou City, China

- **Retrospective observational study** of 21 subjects contemporaneously admitted: critically ill with COVID-19
- **6 patients received CP** median of 21.5 days after first detection of viral shedding ➔ median 300 mL (Donors IgG positive)

Mortality

5/6 in treatment group vs 14/15 in control group (p = 0.184)

Improvement in clinical status of ALL patients

- Weaning off mechanical ventilation,
- Reduction in viral loads
- Radiological improvement in pulmonary lesions
- Improved oxygenation and clinical stabilization
- and investigational antivirals

Zeng QL et al. J Infect Dis 2020
Summarizing the evidence behind convalescent plasma

• Generally **well tolerated** ➔ Adverse effects are few
• **Strength of the efficacy data is mixed**
  – Deployed in times of emergency
• Studies suffer from **serious methodologic limitations**
  – Lack of blinded, randomized, or placebo-controlled trials
  – Very different infections
• **Early administration** confers better outcomes

Growing literature suggests benefit in treatment of COVID-19
Overview of research: clinical trials

1. Post-exposure prophylaxis
   - High-risk exposure (e.g. health care workers) and/or individuals at high risk of severe disease
   - IND clearance expected to begin shortly

2. Early onset of symptoms: staving off progression

3. “Green Zone” treatment of moderate COVID-19

4. “Hail Mary” Rescue intervention for severe COVID-19

5. Pediatric protocols
   - Safety
   - Post-exposure prophylaxis
   - Early treatment

Outcome measures
   Incidence of infection ➞ hospitalization ➞ hypoxia ➞ intubation and ventilation ➞ death

Other research

Individual patient data and expanded access programs ➞ opportunity to mine data
**Global access to convalescent plasma**

**Compassionate Use**
- Severe and life-threatening COVID-19

**Hybrid models**
- Moderate to life-threatening COVID-19
- National or regional programs that contain reporting requirements
  - Example: Expanded access program in the US
- Participating institutions gain access to plasma through major blood collection agencies

**Research**
- Clinical trials and other investigational applications
CCP workflow: procurement steps

History of COVID-19
• Diagnosis of SARS-CoV-2 infection/COVID-19
  • Positive test for SARS-CoV-2 using an approved molecular assay or
  • Evidence of antibodies against SARS-CoV-2

≥14 days following resolution of symptoms

Donor eligibility

Pre-donation screening

Undertaken by clinical provider*
• Clinical assessment that no active infection (i.e. afebrile, no reported symptoms for ≥14 days)
• Serum collection for anti-SARS-CoV-2

*share donor history questionnaire

Antibody testing
• Ideally, certified lab testing using a validated test (e.g. ELISA) for anti-SARS-CoV-2
Convalescent plasma collections workflow continued...

Seropositive anti-SARS-CoV-2: optimal titer ≥160

Contact donor and coordinate referral to collections site (e.g. blood center)

Collections

Blood center or hospital

Criteria for donation
- Satisfies **ALL eligibility criteria** for community blood donation based on standard donor history questionnaire

Collections
- 450-800mL (if apheresis-collected) plasma (frozen within 24hrs of collection)
- Label quarantine pending results of standard TTI testing
- **Routine donor testing**
  - Transfusion-transmitted infections
  - HLA antibody screening (parous female donors)

Negative routine blood donor screening results

ABO Blood Group compatible
- Needs dedicated recipient consent that explains general risks of blood products/CCP

Transfusion
Major challenges

- **Scale-up and access to products**
  - Recruitment and vetting of donors

- **Changing criteria for eligibility**
  - History of **confirmed COVID-19** ➔ Follow-up negative test 14-27d
  - Requirement for **negative testing** ➔ 30-50%+
  - **Relaxing eligibility criteria**
    - Allowing for antibody detection to qualify donors
    - No longer a requirement for negative testing after 14d post-symptom

Major challenges

Antibody testing: **not widely available or standardized**

- Neutralization assays (gold standard) vs EIA
  - Formal neutralization assays impractical → BSL3 and long TAT
- What **isotypes and/or subclasses** of antibodies are optimally effective?
  - IgM
  - IgG → IgG1 vs IgG2 vs IgG3 vs IgG4
  - IgA vs IgM vs Total antibodies
- What is the **optimal titer?**
- Kinetics of infection → seroconversion 8-21d post-infection
- Variability in the assays and where they are being undertaken
  - Commercial vs in-house assays → Clinical vs research setting
  - Approved vs unapproved
- Practically: can one be that selective anyway?

39 of 40 (97.5%) convalescent individuals in Wuhan study had titers ≥160

Duan K, et al. medRxiv. 2020:2020.03.16.20036145
What do the antibody results mean?

- ELISAs in use target antibodies against
  - Receptor binding domain (RBD)
  - Full-length **spike protein**
- **Good correlation** between ELISA targeting Spike protein and microneutralization
- Absent or **low cross-reactivity** from human coronaviruses

Contextualizing the challenges to CCP procurement in LMICs

Broader challenge of blood safety

Systemic

Includes the World’s poorest countries
- Cultural, ethnic, geographic and economic heterogeneity
- Funding
- Infrastructure

Specific to blood transfusion safety

1. Situational Analysis
   National policy, Organization and oversight

2. Donor recruitment & mobilization

3. Biological testing

4. Rational blood use

5. Quality Assurance + hemovigilance
Recruitment in LMICs for CCP

- A low proportion of the eligible population donate
- Suboptimal donation models given challenges to recruitment
- Voluntary Non-remunerated vs Replacement vs Paid donation
- Knowledge of the motivators for and barriers against donation largely lacking in LMICs → strategies from HICs don’t necessarily apply
- Social media and formal news outlets could be applied broadly.
- Strategies to mine patient records are difficult in LMICs given largely absent electronic medical records and variability in patient registries

Voluntary Non-remunerated

\[ \text{Vs} \] Replacement donation

Stringent “lock-down” policies severely restrict travel of potential donors

Global Health Data
COVID-19 Surveillance and impact to CCP

- Incidence of disease
- Case definitions
- Number of recovered individuals
- Capacity for testing
- Seroprevalence
- Eligibility for testing
- Reporting
Ascertainment of donor eligibility in LMICs

- Capacity for SARS-CoV-2 testing is low in LMICs, even for acutely symptomatic patients.
- Limited **laboratory infrastructure**, availability of testing kits and technical expertise impacts large scale molecular testing and surveillance.

Without testing, the pool of eligible CP donors is uncertain

Most LMICs report <10,000 cases of COVID-19
Most report tens to hundreds of cases → is there a critical mass of tested individuals?

Most report <10,000 cases of COVID-19
Pre-donation screening in LMICs

- **Limited laboratory capacity** to conduct antibody testing for SARS-CoV-2
- **Universal challenges** in regard to optimal testing

*Reporting at titer ≥320 and ≥28d

### Screening convalescent subjects at Johns Hopkins (n=137)

<table>
<thead>
<tr>
<th>Antibodies not present</th>
<th>Borderline</th>
<th>Antibodies present*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>122 (89.1%)</td>
<td>7 (5.1%)</td>
</tr>
<tr>
<td>IgG</td>
<td>43 (31.4%)</td>
<td>9 (6.6%)</td>
</tr>
</tbody>
</table>

*Solution*

Temporarily **forgo testing**

**Biobank retention tubes** pending availability of testing
Collection facilities

**Collection of CCP is NO different from other plasma components**

- **Fixed sites** e.g. hospitals or blood centers
- **Mobile collections NOT widely used** given risks to collections staff
  - may be used to collect CCP in affected communities
- **PPE** (i.e. face shields and masks) are provided to the collections staff.
  - Access to PPE varies greatly ➔ generally limited in LMICs
  - resulting in an increase use of homemade masks, which may be of variable efficacy.
- Screening donors and employees (e.g. symptoms and signs, temperatures)
- Social distancing ≥1.5m (6 feet) challenging for confidential donor interview and collections

Apheresis technology

- Major mode of collection in HICs (incl. CCP)
- Highly efficient ➔ A single donor yield 3 or 4 units (~600-800mL) of plasma

Barriers to adoption in LMICs

High cost, technical expertise and availability of apheresis kits

LMIC status does not bar apheresis

- It was adopted rapidly during the 2014 Ebola outbreak in West Africa
- Logistical barriers were overcome and CCP was collected successfully

Mode of collection

Whole blood collection
Parent product separated into components (i.e. plasma and red blood cells) after collection

Challenges

High prevalence of anemia in LMICs \( \rightarrow \) many will not meet the minimum hemoglobin

Longer deferral periods (e.g. 8-12 weeks) than plasma.

Recent severe illness \( \rightarrow \) not ideal candidates for donation

Possible solutions: relaxing of the inter-donation intervals as long as the donors still meet minimum hemoglobin thresholds.

Clinical considerations

**Inventory management**
- Allocation of scarce resources

**Dose of convalescent plasma**
- Highly variable differences in prevention versus treatment
- Based on studies in SARS1; also experience in COVID-19
- The planned clinical trials
  - **One unit (200-250mL)** for post-exposure prophylaxis:
  - **1-2 units** have been proposed for treatment
  - **Repeated doses** (up to 6) in rescue intervention
  - Pediatric transfusions need to aliquot and dose by body weight

**Administration**
- Appears to be safe Data from China, Italy and US

**Duration of efficacy**
- Unknown likely few weeks to several months

### Risks of convalescent plasma

#### General risks
- Donors must satisfy all criteria for blood donation

#### Specific risks
- **Transfusion-transmitted SARS-CoV-2**
  - Theoretical → recipients already infected *(in context of treatment)*
  - **No reports** of transfusion-transmission of respiratory viruses
  - SARS-CoV-2 RNA rare in blood → donors ≥14 days post-resolution of symptoms
- **Antibody-dependent enhancement (ADE)** → theoretical
  - Antibodies from prior infection exacerbate clinical severity i.e. exposure to other strains of coronavirus
  - **No ADE reported** with use of convalescent plasma for SARS, MERS or COVID-19
- **Coagulation derangements**
- **Blunting the development of a natural immune response**
  - Unknown

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**References**

Safety Data
FDA Expanded access program in the US

Transfusion of ABO-compatible CCP in 5,000 hospitalized adults with severe or life-threatening COVID-19

- 66% of patients in the intensive care unit

- The incidence of all serious adverse events (SAEs) in the first 4 hours after transfusion was <1%

- 36 reported SAEs reported → 25 related SAEs
  - Including mortality (n=4) → mortality rate (0.3%).
  - Transfusion-associated circulatory overload (TACO; n=7)
  - Transfusion-related acute lung injury (TRALI; n=11)
  - Severe allergic transfusion reactions (n=3)

- Only 2 (of 36) SAEs definitely related to CCP

- The seven-day mortality rate was 14.9%

Comparable risk to non-immune plasma transfusion in same population i.e. suggesting safety in hospitalized patients with COVID-19

• **Implementation of a product of unproven efficacy**
  - Potential benefit that has been highly publicized
  - Observational data with potential confounding
  - Triage of compassionate use plasma in the absence of robust data

• **Triage**
  - Clinical trials vs. alternative access pathways
  - Blood center limited access i.e. to 1-2 products per patient
  - Prioritization against other investigational treatments

• **Prevention**
  - Scale up of inventory to ensure sufficient supply
  - What is the minimum inventory?

• **Scarce resource committee**
  - Separate from transfusion service and prescribing providers

• **Lottery system**
  - Weighting requests to ensure equitable access
  - Scoring systems (cf. organ transplantation)
Unmet need for blood in LMICs

Potential to divert resources away from strained services

- WHO: 10 units per 1000 population
- 119 (61%) of 195 countries do not have sufficient blood supply to meet their needs
  - Annual transfusion deficit: 102 359 632 (95% UI 93 381 710–111 360 725) blood product units

“Every country in central, eastern, and western sub-Saharan Africa, Oceania, and south Asia had insufficient blood to meet their needs.”

**Conclusion**

- **A temporizing strategy** pending availability of hyperimmune globulin and vaccines
- Globally scalable using extant blood collection infrastructure
- **Major logistical challenges** → ”unmet need”
  - Ethics and clinical considerations, particularly in LMICs where there is potential to divert resources
- Need for rigorous **research**
  - Wealth of data suggest that it is **safe and offers benefit**

**Resources**

- [https://ccpp19.org/donors/donate.html](https://ccpp19.org/donors/donate.html)
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