

Strategies to support the COVID-19 response in LMICs

A virtual seminar series

Resource Page

Convalescent Plasma Therapy

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Summary/Key Points:

- I. *The premise behind convalescent plasma is passive transfer*
 - Passive transfer (i.e. transfusion or infusion) of antibodies from convalescent individual into a recipient at risk of infection or already infected with virus
 - **“Passive antibody administration is the only short-term strategy to confer immediate immunity to susceptible individuals”**
 - But it is not ideal because it is a **temporizing measure** with pending availability of refined strategies for treatment or prevention (ie vaccination)

Historical precedent and biological plausibility- Does convalescent plasma work?

- Example: Ebola virus disease- Nonrandomized, comparative study of patients with EVD
 - Although there were no serious adverse reactions, it was not associated with a significant improvement in survival status
- Example: SARS- Hong Kong
 - Improved outcome associated with early administration with no adverse events
- Example: MERS- Seoul, South Korea
 - Uncertain benefit although all 3 patients survived; low proportion with neutralizing antibodies. In a feasibility study in Riyadh, Saudi Arabia, there was a low proportion of either recovered or exposed with neutralizing antibodies, which questioned the feasibility of convalescent plasma therapy use.

Use of convalescent plasma for **COVID-19**: In all three studies, all patients had other competing therapies (ie steroids, traditional Chinese remedies, antimicrobials)

- Wuhan, China
 - Uncontrolled case series in which patients received convalescent plasma in which those units were well characterized with high titers, with no significant adverse events
- Shenzhen, China

- Uncontrolled case series, like the one in Wuhan: noticed improvements in clinical status of all patients as evidenced by weaning of mechanical ventilation, reduction in viral loads, radiological improvements in pulmonary lesions, and improved oxygenation and clinical stabilization
- Zhengzhou City, China
 - Retrospective study: between the treatment group and the control group, there was non-significant

Summarizing the evidence behind convalescent plasma: Generally well tolerated -> adverse effects are few

Weakness: the strength of the efficacy data is mixed

- Since the therapy is often deployed in times of emergency, the results of the studies suffer from significant methods of logic limitation. The lack of blinded, randomized, or placebo-controlled trials in which the data refers to vary based on type of infections (bacterial or viral)

Strength: early administration confers better outcomes

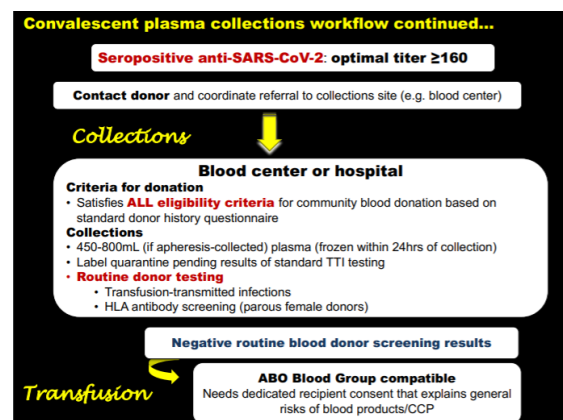
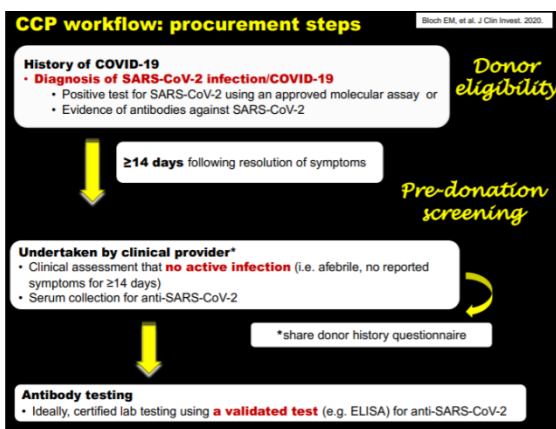
II. *Overview of research: clinical trials*

Outcome measures: incidence of infection -> hospitalization -> hypoxia -> intubation and ventilation -> death

1. Post-exposure prophylaxis
 - a. High exposure and/or individuals at high risk of severe disease
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
 - a. Safety, post-exposure prophylaxis, early treatment

III. *Global Access to convalescent plasma*

- Compassionate Use: for severe and life-threatening COVID-19
- Hybrid Models: for moderate to life-threatening COVID-19
 - a. National or regional programs that contain reporting requirements
 - b. Participating institutions gain access to plasma through major blood collection agencies



- People should not be qualified, based on their history of COVID-19 only to be deferred for something unrelated at a blood center.
- The mainstay in high income countries is that we collect using apheresis technology that is highly efficient.
- Routine donor testing (transfusion transmitted infections): collected in mostly high-income countries, this includes HLA antibody screening of females who report, having previously been pregnant, and for the purposes of mitigation of transfusion related acute lung injury
- If results are negative, that unit is then released the hospital for transfusion

Major Challenges:

- Scale-up and access to products
 - Recruitment and vetting of donors
- Changing criteria for eligibility (most of these changes have been favorable)
 - relaxing of eligibility criteria include allowing for antibody detection to qualify donors, and that there is no longer a requirement for negative testing after 14 days post-symptom
- **Antibody testing- not widely available or standardized**
 - We still do not know what isotypes and/or subclasses of antibodies are optimally effective or the optimal titer.

IV. *Contextualizing the challenges to COVID-19 Convalescent Plasma procurement in LMICs* 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 and mobilization
 - a. Recruitment in LMICS for COVID-19 Convalescent Plasma (CCP) is either voluntary non-remunerated, replacement, or paid donation
 - i. Low proportion of the eligible population donate, and stringent "lock-down" policies severely restrict travel of potential donors
 - b. The capacity for SARS-CoV-2 testing is low in LMICs, and it is difficult to implement large scale molecular testing/surveillance due to limited laboratory infrastructure, availability of testing kits and technical expertise
 - i. **Solution:** temporarily forgo testing
3. Biological testing
4. Rational blood use
5. Quality assurance and hemovigilance

Collection

- Collection of COVID-19 Convalescent Plasma is no different from other plasma components. Collection is at fixed sites, mobile collections are not widely used, and there is variation in access to PPE
- Mode of collection: Apheresis technology
 - Barriers to adoption in LMICS: high cost; requires technical expertise and availability of apheresis kits
 - Alternative solution: Whole blood collection, but this solution has high prevalence of anemia; longer deferral periods; recent severe illnesses

V. *Clinical considerations*

- Inventory management of scarce resources
- Dose of convalescent plasma
- Administration
- Unknown duration of efficacy

Risk of convalescent plasma

- General risks: Donors must satisfy all criteria for blood donation
 - Non-infectious risks: allergic transfusion reactions
 - Infectious risk: low in US and high-income countries
 - The infectious risk is very different in HIC and LMICs, because in LMICs, there is a higher incidence and prevalence of transmitted infections and testing is enormously variable.
- Specific risks:
 - Transfusion-transmitted SARS-CoV-2
 - Antibody-dependent enhancement (antibodies from prior infection exacerbate clinical severity, or exposure to other strains of coronavirus)
 - Coagulation derangements
 - Blunting the development of a natural immune response

VI. *Ethics and proposed solutions*

- Implementation of a product of unproven efficacy (triage of compassionate use of plasma in the absence of robust data)
- Triage (Prioritization against other investigational treatments)
- Prevention (Scale up of inventory to ensure sufficient supply)
- Scarce resource committee (Separate from transfusion service and prescribing providers)
- Lottery system (Weighting requests to ensure equitable access-> scoring systems)

Conclusion

- A temporizing strategy pending availability of hyperimmune globulin and vaccines that could be globally scalable by using extant blood collection infrastructure
- **Major logistical challenges -> “unmet need”**
 - Ethics and clinical considerations, particularly in LMICs where there is potential to divert resources
 - Unmet need for blood in LMICs: potential to divert resources away from strained services. The solution is to supplement the annual transfusion deficit of product units with convalescent plasma, in these regions that have insufficient blood to meet their needs.
 - Need for rigorous research
 - Wealth of data suggest that it is safe and offers benefit

Online resources:

<https://ccpp19.org/donors/donate.html>

<https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>