Convalescent plasma to prevent or treat COVID-19
How, what and why?

Indian Country COVID-19 ECHO
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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, Abbott Laboratories, Terumo BCT

- Coinvestigator
  - DoD-funded clinical trial of pathogen reduction using a commercial technology
  - DoD-funded clinical trials e.g. **CSSC 001 and 004 (CCP prophylaxis and early treatment)**

Abbreviation

**CCP**: COVID-19 Convalescent Plasma  
**nAbs**: Neutralizing antibodies
Objectives

1. **How** did prior experience motivate for use of CCP?
2. **What** have we learned about CCP?
   - Logistical/operations
   - Scientific
   - Clinical
3. **Why** might the lessons be important beyond COVID-19?

Disclaimer
20min is very short
Convalescent plasma emerged early as a leading treatment for COVID-19

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

**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)

Biological plausibility and historical precedent for use of convalescent plasma

- Historical and modern examples
- Well tolerated
- **Post-exposure prophylaxis** e.g.
  - Hepatitis, mumps, polio, measles, rabies
- **Treatment** e.g.
  - Spanish Influenza (H1N1)
  - Argentine hemorrhagic fever
  - Severe Influenza A and B
  - Ebola
  - SARS
  - MERS
  - COVID-19

Administration of convalescent plasma early in disease course consistently better

Logistics unprecedented access to CCP

Research
Restricted access to study e.g. to clinical trials

Ethical considerations
Scientific yield

Emergency/compassionate use
Hospitalized patients with predominantly severe and life-threatening COVID-19

1. Emergency/Individual provider
2. Expanded Access Program
   - Government-initiated (Mayo clinic DCC)
   - Scale up and safety
   - Efficacy data? Outcomes better <4d of diagnosis and high titer
3. Emergency Use Authorization: relax criteria

Practicality
Public health need

Daily new confirmed COVID-19 cases
Shown is the rolling 7-day average. The number of confirmed cases is lower than the number of actual cases; the main reason for that is limited testing.

- **Changing epidemiology**
  - Record cases in South/western US
  - Waning reserves

- **Scale-up and access to products**
  - Recruitment and vetting of donors
  - Definition of eligibility
  - Pre-donation screening
  - Antibody testing and interpretation
  - Uncertainty about safety

- **Exponential phase**
  - Demand, complacency

- **Emergency Use Authorization**
  - Donor qualification, supply

Source: European CDC – Situation Update Worldwide – Last updated 19 November, 10:06 (London time)
Wealth of observational data
Case reports, uncontrolled case series and matched control studies

• Generally safe/ well tolerated

• Improvement in clinical status → Weaning off ventilation, improved oxygenation, reduced viral loads, radiological improvement, decreased mortality

• Early administration confers better outcomes
  – EAP: ≤3 days of diagnosis and high titer confers significantly lower mortality

We need more clinical trials

150 studies of convalescent plasma listed on clinicaltrials.gov

The overwhelming majority of studies are targeting a hospitalized patient population, which is less likely to benefit

Studies differ with respect to
1. Design e.g. single arm vs blinded RCTs
2. Timing of administration
3. Primary outcomes
4. Characterization of intervention (e.g. titer)
5. Control (e.g. plasma vs crystalloid vs SOC)
Trials that are currently underway

Prophylaxis

Early disease

Pediatrics

Moderate disease

Adults

Severe/life-threatening

Results expected soon

Only 2 outpatient studies to evaluate CCP for early treatment and 1 study as prophylaxis in adults
**Wuhan, China**
Severe and Life-threatening COVID-19
CCP + SOC (n = 52) vs SOC alone (n = 51)
**NO** significant difference...but **underpowered (103/200)**

**Netherlands**
Moderate to severe COVID-19
300ml of CCP with nAbs ≥1:80
**No difference in mortality**, hospital stay or day-15 disease severity
BUT...study **underpowered**: 86 (20%) of targeted 426 patients enrolled
44/56 (79%) had neutralizing antibodies titers~ to donors

**Spain**
Moderate COVID-19
- SOC ± 250-300ml of CCP with anti-SARSCoV-2 IgG+
- Study **underpowered** Incidence waned \( \Rightarrow 81/278 \) (29%)
- **Clinical progression** 0/38 (0%) in CCP vs 6/43 (14%) control
- **Mortality rates** 0% in CCP vs 9.3% of control at days 15 and 29


Baghdad, Iraq
Moderate COVID-19; First 3 days in respiratory care unit
CCP (n=21) vs age- and sex- matched individuals (n=28) SOC
CCP anti-SARSCoV-2 IgG index ≥1.25
**Reduced duration of infection by 4 days**
**Reduction in mortality:** 1/21 versus 8/28 in control group

Bahrain (n=40)
Moderate COVID-19
**No significant differences in the primary outcome** (ventilation) although fewer patients in CCP arm required ventilation and those that did had shorter duration

Argentina
Mild to moderate COVID-19: ≤72hrs of symptoms (n=160)
High titer CCP to patients ≥65yrs with comorbid disease or ≥75yrs
13/80 (16.2%) CCP vs. 25/80 (31.2%) placebo had severe respiratory disease \[\text{RR (95\%CI)} = 0.52 (0.29,0.94); p=0.026\]
61% reduction in need for oxygen

Variable quality, with mixed signals
Encouraging data from Argentina
India
Hospitalized, moderately ill confirmed COVID-19 (n=464)
SOC± 2 doses of 200 mL CP transfused 24 hours apart
Non-significant differences between trial arms
Primary outcome: Composite of progression to severe disease (PaO2/FiO2<100) or all cause mortality at 28 days
High proportion had units with low titer of nAbs

Summary
Multiple trials
Differences by target population: Age i.e. Adult vs Pediatric
characterization of products, intervention (e.g. timing) and outcomes→limitations

Negative finding but key limitation
Overall summary: The impact of human convalescent plasma therapy on COVID-19 patient mortality

Immunology of COVID-19

Antibodies ➔ Class ➔ Subclass ➔ epitope specificity

Neutralizing vs non-neutralizing antibodies

Testing: A rate limiting step

Optimal titers

Predictors of seroreactivity
Ancillary benefits

Screening convalescent subjects at Johns Hopkins (n=292)

<table>
<thead>
<tr>
<th></th>
<th>Antibodies not present</th>
<th>Borderline</th>
<th>Antibodies present*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>263 (90.1%)</td>
<td>13 (4.5%)</td>
<td>16 (5.5%)</td>
</tr>
<tr>
<td>IgG</td>
<td>88 (30.1%)</td>
<td>18 (6.2%)</td>
<td>186 (63.7%)</td>
</tr>
</tbody>
</table>

*Reporting at titer ≥320 and ≥28d
Convalescent individuals (donors) offer insight into a novel pathogen

- **Antibody testing**
  - Neutralization assays (gold standard) impractical ➔ BSL3 and long TAT
    - **Variable performance** of clinical assays
    - Good — albeit imperfect — correlation between ELISA targeting Spike protein and microneutralization
    - “varying degrees of accuracy in predicting nAb activity”
- **Kinetics of infection** ➔ seroconversion 8-21d post-infection
  - Most develop antibodies ➔ ~1/3 are not high titer ➔ variable persistence
  - **Wuhan: 39/40 (97.5%)** convalescent individuals had titers ≥160
  - Avidity ➔ peak 1-4 weeks (ICU vs non-ICU)
- **Optimal titer is not known**
  - Higher titers better ➔ older age, male sex and hospitalization status
- What **isotypes and/or subclasses** of antibodies are optimally effective?

**Practically, can one be that selective anyway?**
Clinical considerations

**Dose of convalescent plasma** ➔ Highly variable

- Based on *studies in SARS1*
  - 5 mL/kg of plasma at a titer of ≥160 was utilized ~250 mL/a standard unit
  - Variability in titers between products
  - Incomplete characterization of antibodies

- **The 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

**Duration of efficacy**

- Unknown ➔ likely few weeks to several months

**ABO compatible recommended but variable practice**

- E.g. Group A

**Single vs multiple units?**

Hedge your bets given variable antibody titers?
Do we know what is **optimally informative**?
Is there sufficient **inventory** to support multiple units?
Safety Data
FDA Expanded access program in the US
April 3 to June 2, 2020

Transfusion of ABO-compatible CCP in **20,000** hospitalized adults with severe or life-threatening COVID-19

- 58% of patients in the intensive care unit

**The incidence of all serious adverse events (SAEs)** in the first 4 hours after transfusion was **<1% (n=146)**
- Deaths (n=63; 0.3%) → 13 related → 12 possible; 1 probable; 0 definite

**Thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3% → vast majority unrelated**

**The seven-day mortality rate was 8.6%**

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

Making sense of the role of convalescent plasma: Heath vs Research vs Time

**Observational studies**

**Case reports**
- 20 January 2020: 1st case reported in the US

**Case series**
- April 2020

**IND for Convalescent plasma**
- April 2020

**Matched case control**
- 12 October 2020

**EUA for Convalescent plasma**
- 23 August 2020

**EUA for Bamlanivimab**
- 9 November 2020

**Clinical trials**
- 11 November 2020: First Phase 3 vaccine results


7.7 million cases of SARS-CoV-2
206,597 deaths in the US alone
Rigorous research is critical— it has proved to be enormously challenging

- **Major logistical challenges**
- **Rapidly changing** landscape of activities
- **Need for greater harmonization** in efforts i.e. creativity/innovation
  - Examples of ingenuity in this regard e.g. COMPILE

Data support **early administration, high titer**

- **There are studies underway that should provide clarity**
  - If definitive: there would be a role for convalescent plasma in future outbreaks and pandemics
  - **Globally scalable** intervention
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