JOHNS HOPKINS
MEDICINE

Convalescent plasma to prevent or treat COVID-19

How, what and why?

Indian Country COVID-19 ECHO

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Evan M Bloch, MD, MS

Associate Professor of Pathology
Associate Director, Transfusion Medicine Division
Johns Hopkins University School of Medicine
International Health (Joint appt.)
Johns Hopkins Bloomberg School of Public Health
Johns Hopkins Hospital
ebloch2@jhmi.edu

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

1 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)

Bloch EM, et al. J Clin Invest. 2020.

Biological plausibility and historical precedent for use of convalescent plasma *Does it work?*

- **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

Casadevall A, et al. Clin Infect Dis. 1995;21(1):150-61. Casadevall A, et al. Nat Rev Microbiol. 2004;2(9):695-703. Sahr F, et al. J Infect. 2017;74(3):302-9. Stokes J, Jr., et al. American Journal of Diseases of Children. 1935;50(3):581-95. Zhou B, et al. N Engl J Med. 2007;357(14):1450-1. Hung IF, et al. Clin Infect Dis. 2011;52(4):447-56. Luke TC, et al. Ann Intern Med. 2006;145(8):599-609. Maiztegui JI, et al. Lancet. 1979;2(8154):1216-7. Cheng Y, et al. Eur J Clin Microbiol Infect Dis. 2005;24(1):44-6; Ko JH, et al. Antivir Ther. 2018;23(7):617-22.. Bloch EM, et al. J Clin Invest. 2020.

2 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**

Over 90,000 transfused

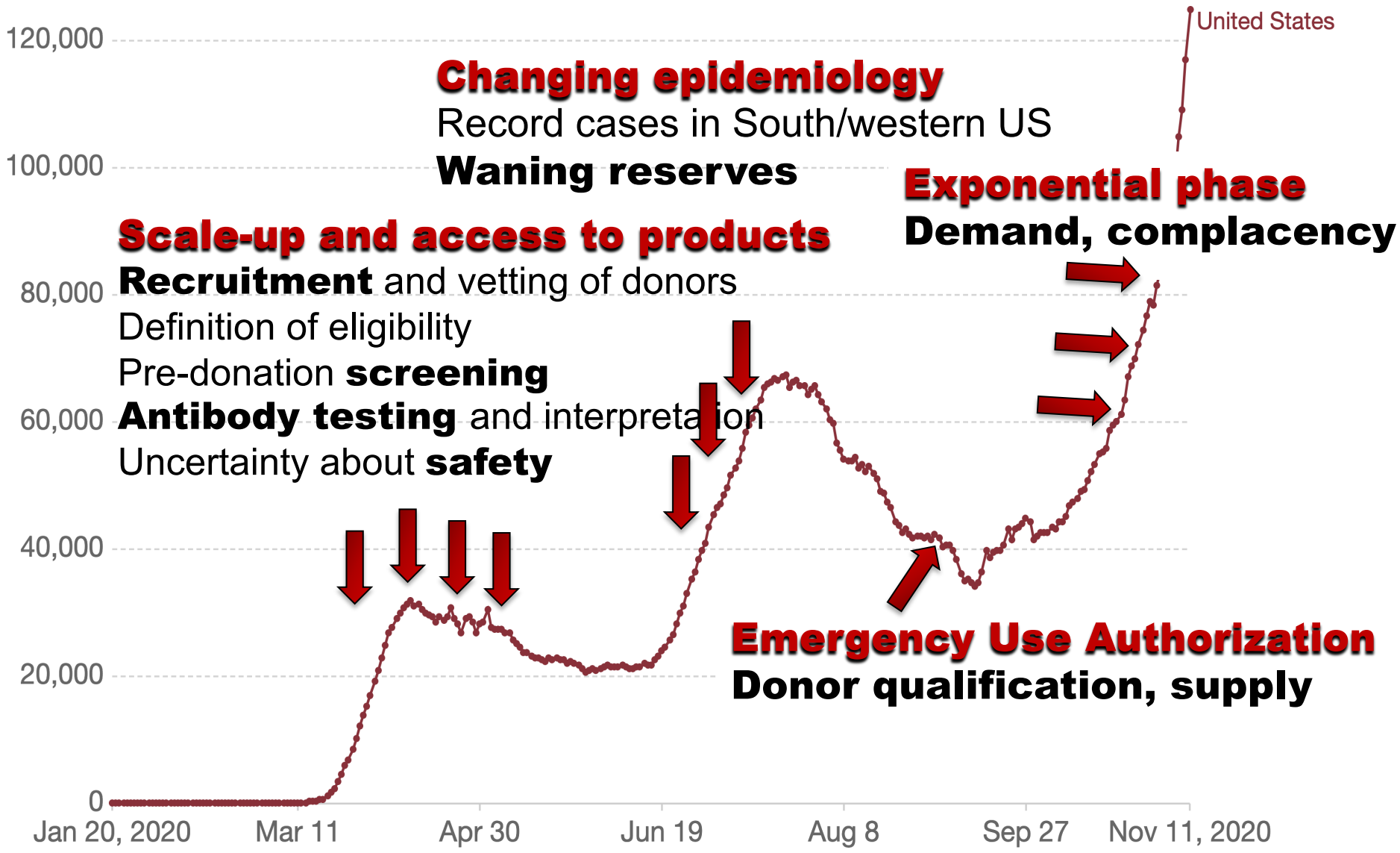
Practicality
Public health need

Joyner M, et al. Mayo Clin Proc 2020.
Joyner MJ, et al. J Clin Invest 2020.

Daily new confirmed COVID-19 cases

CCP navigating the obstacles

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.



Source: European CDC – Situation Update Worldwide – Last updated 19 November, 10:06 (London time)

CC BY

Science

The evidence behind CCP

Wealth of observational data

Case reports, uncontrolled case series and matched control studies

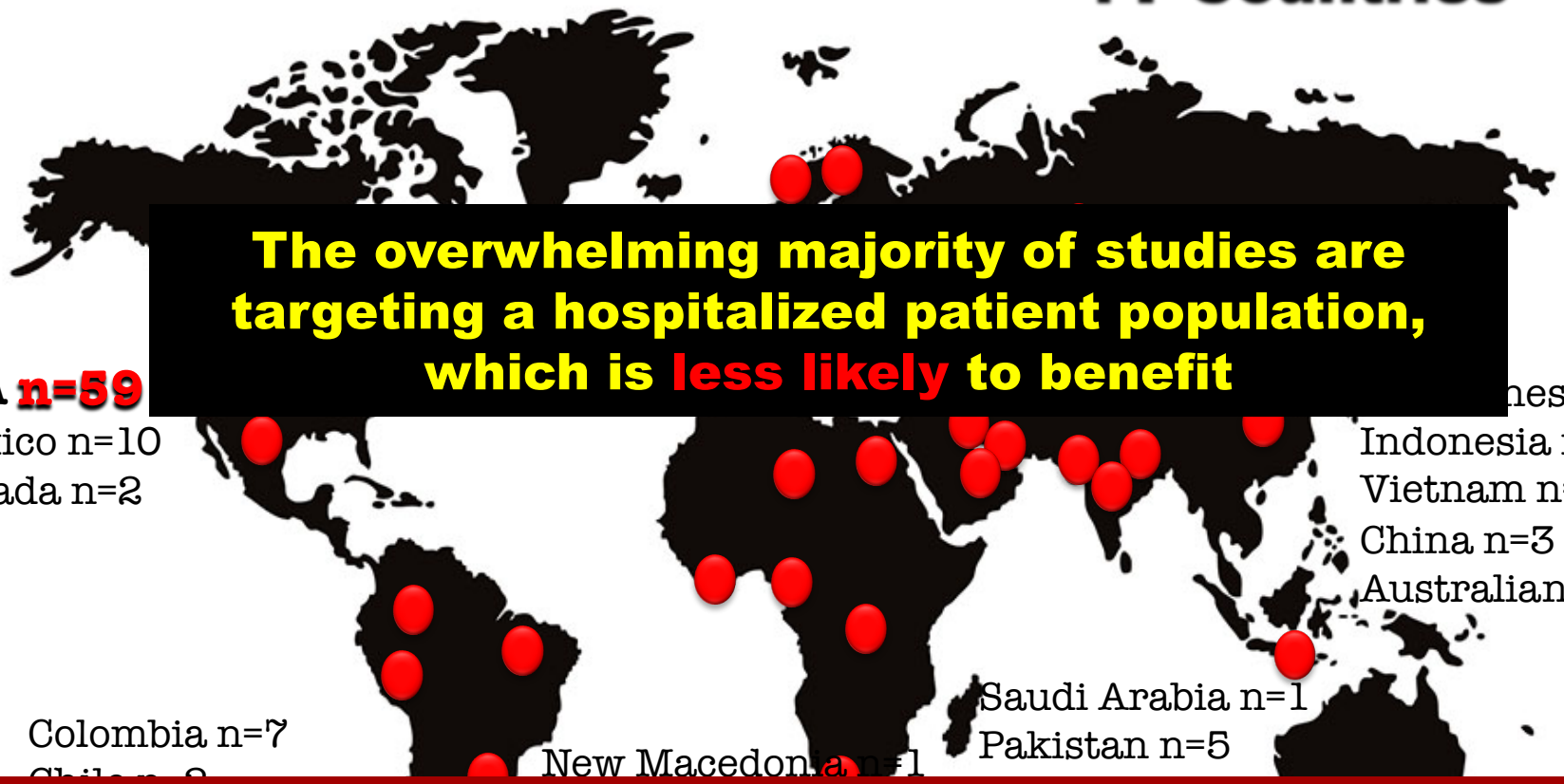
- **Generally safe/ well tolerated**
- **Improvement in clinical status** ➔Weaning off ventilation, improved oxygenation, reduced viral loads, radiological improvement, **decreased mortality**
- **Early administration** confers better outcomes
  - EAP: **≤3 days of diagnosis and high titer** confers significantly lower mortality

Shen C, et al. JAMA. 2020.; Duan K, et al Proc Natl Acad Sci U S A. 2020 Apr 28;117(17):9490-6. Zeng QL et al. J Infect Dis 2020; Liu STH, et al. Nature Medicine. 2020 2020/09/15. Gharbharan A, et al. medRxiv 2020: 2020.07.01.20139857. Li L, et al. *JAMA*. 2020 Joyner MJ, et al. medRxiv. 2020:2020.08.12.20169359.

150 studies of convalescent plasma listed on clinicaltrials.gov

"We need more clinical trials"

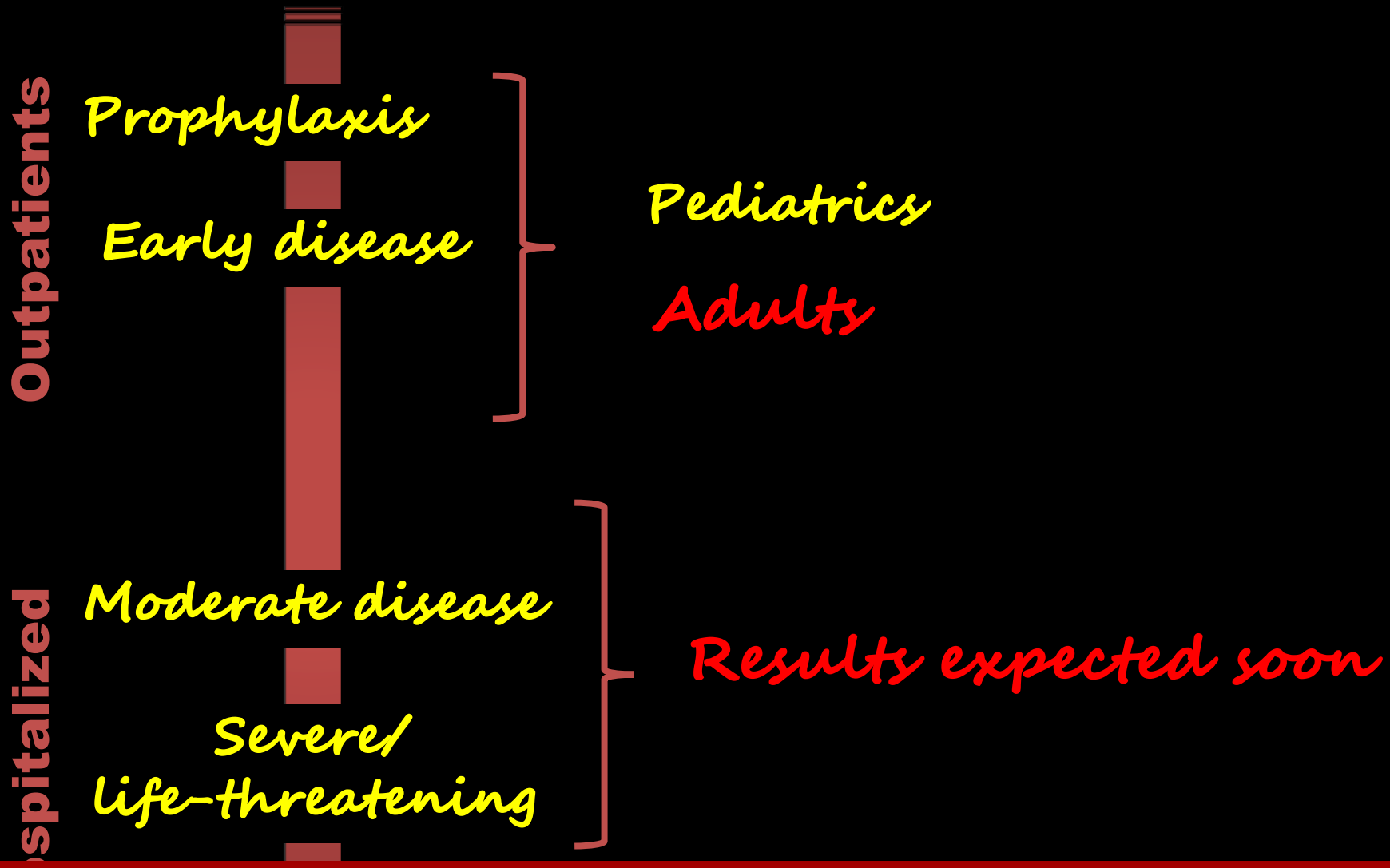
41 Countries



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



Only **2 outpatient studies** to evaluate CCP for **early treatment** and **1 study as prophylaxis in adults**

Clinical trials

Wuhan, China

Li L, et al. *JAMA*. 2020.

Severe and Life-threatening COVID-19

CCP + SOC (n = 52) vs SOC alone (n = 51)

NO significant difference…but **underpowered (103/200)**

Hospitalized patients, some positive signals but underpowered

Netherla

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

Avendano-Sola C, et al. medRxiv 2020: 2020.08.26.20182444.

Moderate COVID-19

- SOC ± 250-300ml of CCP with anti-SARSCoV-2 IgG+
- Study **underpowered** Incidence waned ➔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

Rasheed AM, et al. Infez Med. 2020;28:357-366.

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)

AlQahtani M,, et al. medRxiv. 2020:2020.11.02.20224303.

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

Libster R,et al.. medRxiv 2020: 2020.11.20.20234013.

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 [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

Agarwal A, et al. BMJ. 2020;371:m3939.

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 ($PaO_2/FiO_2<100$) or all cause mortality at 28 days

High proportion had units with low titer of nAbs

Negative finding but key limitation

Summary

Multiple trials

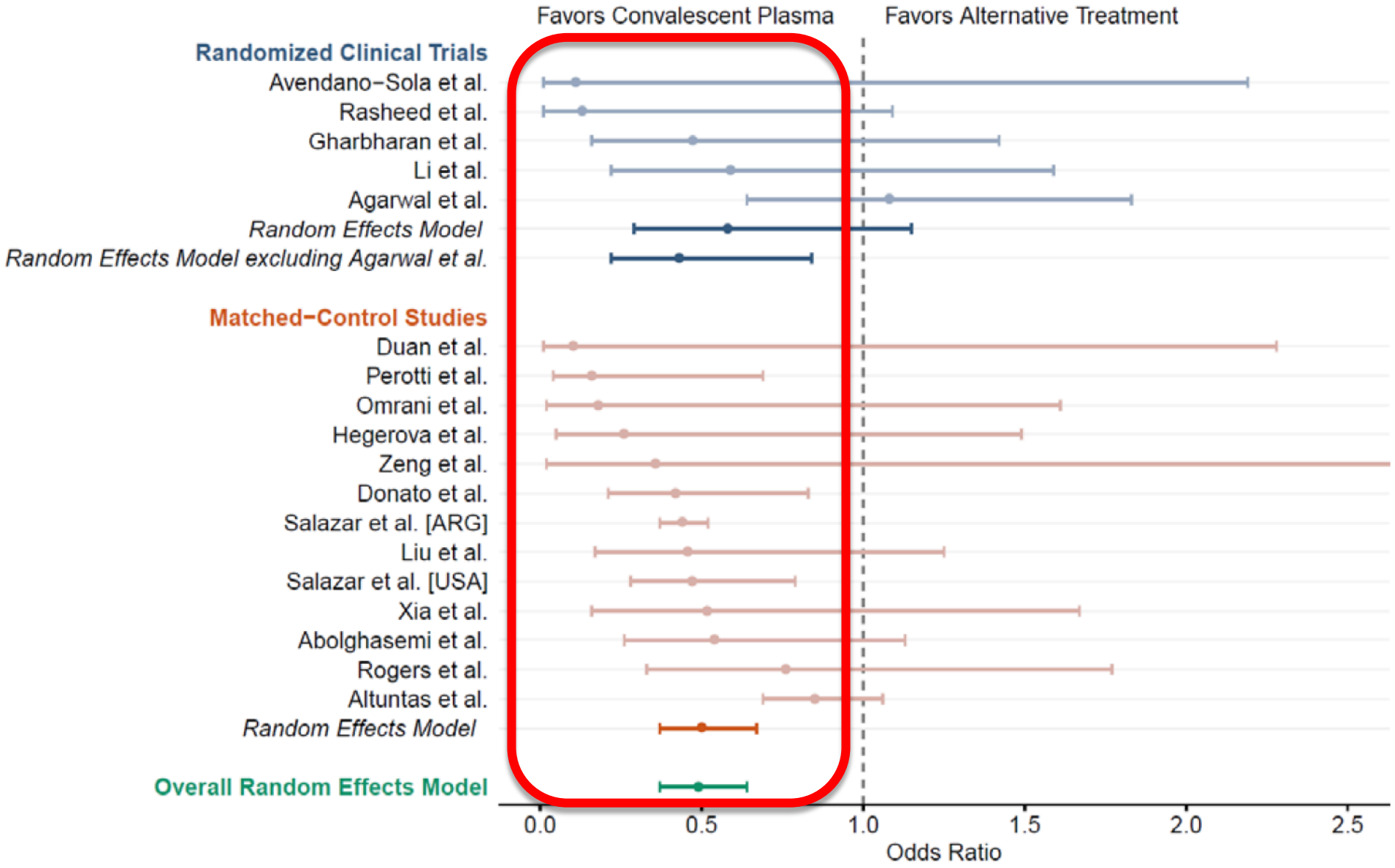
Differences by

target population: *Age i.e. Adult vs Pediatric*

characterization of products, intervention (e.g. timing) and outcomes→limitations

Overall summary: The impact of human convalescent plasma therapy on COVID-19 patient mortality

Figure 1



Klassen SA, et al. medRxiv. 2020:2020.07.29.20162917.

Immunology of COVID-19

The Atlantic

HEALTH

Immunology Is Where Intuition Goes to Die

Which is too bad because we really need to understand how the immune system reacts to the coronavirus.

ED YONG AUGUST 5, 2020

Antibodies→Class→Subclass→ *epitope specificity*

Neutralizing vs *non-neutralizing* antibodies

Testing: A rate limiting step

Optimal titers

Predictors of seroreactivity

Ancillary benefits

Recruitment of convalescent individuals affords key insight into the immunopathogenesis of SARS-CoV-2 infection

- **Donor recruitment**
  - Self-identification, referrals, testing databases, news, social media
- **Pre-donation specimen collection and testing**

Donor qualification
Antibody testing
Scheduling of collections

Sample repository
Testing: Validation, Comparison
Correlation of sample types

Functional aspects of convalescent plasma

Immunology
Cellular response

humoral response: kinetics, avidity, cytokines

Screening convalescent subjects at Johns Hopkins (n=292)

	Antibodies not present	Borderline	Antibodies present*
IgA	263 (90.1%)	13 (4.5%)	16 (5.5%)
IgG	88 (30.1%)	18 (6.2%)	**186 (63.7%)**

***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?

Okba NMA, et a l. Emerg Infect Dis. 2020;26(7):1478-1488..;Luo YR, et al.. medRxiv. 2020:2020.2007.2030.20165522.;Guo L, et al. Clin Infect Dis. 2020.; Duan K, et al. Proc Natl Acad Sci U S A. 2020;117(17):9490-9496.; Robbiani DF, et al. Nature. 2020.; Klein S,, et al J Clin Invest. 2020 Aug 7. Benner SE, et al. The Journal of infectious diseases. 2020:jiaa581. Amanat F,et al. Nature Medicine. 2020;26(7):1033-1036.Ou X, et al. Nature Communications. 2020

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 4hrs 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

Joyner M, et al.. Mayo Clin Proc. 2020.
Joyner MJ, et al. J Clin Invest. 2020.
Busch MP, et al. *Blood.* 2019;133(17):1854-64.
Hendrickson JE, et al. Anesth Analg. 2009;108(3):759-69.
Wang W, et al. JAMA. 2020.
Tetro JA. Microbes Infect. 2020;22(2):72-3.

3

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

Observational studies

Shen C,, et al. JAMA. 2020.

Holshue ML, et al. New England Journal of Medicine. 2020;382(10):929-36.

20 January 2020

1st case reported in the US

Case reports
Case series

April 2020

IND for
Convalescent plasma

Clinical trials

Matched case control

23 August 2020

EUA for
Convalescent plasma

12 October 2020

Agarwal A, et al. BMJ. 2020;371:m3939.

7,7 million cases of SARS-CoV-2
206,597 deaths in the US alone

EUA for Bamlanivimab

9 November 2020

11 November 2020

First Phase 3 vaccine results

"We must not be left wondering whether the intervention worked after the pandemic wanes."

- 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

Bloch EM. *Blood.* 2020;136(6):654-655.

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