CONVALESCENT PLASMA - LATEST FINDINGS

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DEPARTMENTAL SEMINAR
EPIDEMIOLOGY AND BIOSTATISTICS
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HOW DID A PERINATAL EPIDEMIOLOGIST GET INVOLVED WITH CONVALESCENT PLASMA?

A LITTLE HISTORY

2015 - 2020

ORIGINS OF THE ANTI-PRECISION MEDICINE PROJECT

For some years, I have been increasingly concerned with the direction biomedical research, including epidemiology, was taking, and especially the inordinate focus on the human genome.

And then I read an OP-ED in the NYT – *Moonshot Medicine Will Let Us Down.* The author was Michael J Joyner MD, anesthesiologist at the Mayo Clinic. Michael ended his piece with this:

> *"Like most "moonshot" medical research initiatives, precision medicine is likely to fall short of expectations…..We would be better off directing resources to better understanding what it takes to solve messy problems about how humans behave as individuals and in groups. Ultimately we have more control over how much we exercise, eat, drink and smoke than over our genomes." (Jan 29,2015)*

THE ANTI PRECISION MEDICINE PROJECT: EVOLUTION OF A DISCUSSION FORUM

- I wrote to Michael and we began to think about collaborating and identifying like-minded thinkers.

- In 2016 a group of us met in Boston. In addition to the two of us, we were joined by Arturo Casadevall (JHU), Greg Fink (MSU), Sui Huang (Institute for Systems Biology) and our hosts from Tufts, Carlos Sonnenschein and Ana Soto – all academics, largely involved in laboratory science.

- Continued interaction in email discussion forum, ultimately including some 30 people from a wide range of disciplines – medicine, laboratory science, social science, and including two deans of public health - Sandro Galea of Boston University and Sten Vermund of Yale.

- We wrote viewpoints and reviews and ultimately were invited to edit a special issue of *Perspectives in Biology and Medicine*

PERSPECTIVES IN BIOLOGY AND MEDICINE AUTUMN 2018 ISSUE

THE PRECISION MEDICINE BUBBLE

Special Issue on the Precision Medicine Bubble
Autumn 2018
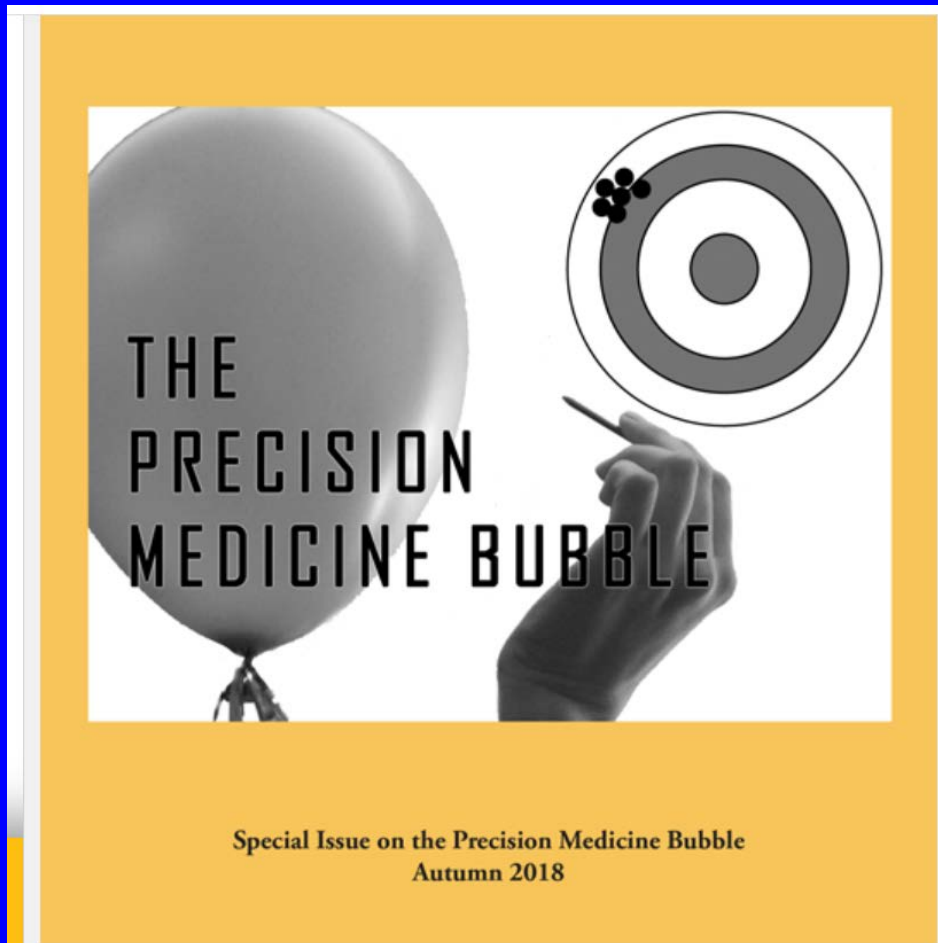
10 articles addressing different aspects of precision medicine and its problems.

Edited by MJ Joyner and N Paneth

Cover art courtesy of Mark Watrich

SOME BACKGROUND TO CONVALESCENT PLASMA: THE THREE FORMS OF PASSIVE IMMUNIZATION

By passive immunization we mean the transfer of pre-formed antibodies to a recipient to prevent or cure disease. Must be distinguished from active immunization, where we use vaccines to stimulate the immune system to produce its own antibodies and to have immunologic memory. Passive immunization provides only temporary protection.

The three forms of passive immunization are:

- HYPERIMMUNE GLOBULIN

- CONVALESCENT PLASMA

- MONOCLONAL ANTIBODIES

HYPERIMMUNE GLOBULIN

Von Behring and Kitasato discovered in the 1890's that serum from rabbits recovering from diphtheria and tetanus had something in their serum that could prevent or cure disease in susceptible animals.

They were able to show that the active agent was an antitoxin, effective against the toxins created by these bacteria. Behring and colleagues mass-produced this antitoxin and provided it to treat, effectively, people with these diseases.

"Saviour of Children"

ANTIDIPHTHERIC SERUM

Emil von Behring
(15 March 1854 -31 March 1917)
German physiologist
He was awarded the first
Nobel Prize in Physiology or
Medicine in 1901
for his discovery of
diphtheria antitoxin

www.butrossfoundation.com

Von Behring established Behringwerke in 1904, which eventually merged with an Australian firm, Commonwealth Serum Laboratories (established in 1914) to form CSL Behring, which today makes several immunoglobulins and coagulation factors

HYPERIMMUNE GLOBULINS
or POLYCLONAL ANTIBODIES

## Licensed Polyclonal Antibody Products for Infectious Diseases

Product name	Polyclonal Product Description	Infection	Indication
BIG	Botulinum Immune Globulin	*C. botulinum* toxin	Treatment of infants
CMV-IGIV	Cytomegalovirus Immune Globulin	CMV	Prevention in Organ Transplants
HBIG	Hepatitis B Immune Globulin	Hepatitis B	Post Exposure Needle Stick Prevention in Organ Transplants
HRIG	Rabies Immune Globulin	Rabies	Post Exposure
ISG	Immune Serum Globulin	Hepatitis A Hepatitis B Measles	Prevention in travelers/exposure Prevention in travelers/exposure Post Exposure
RSV-IGIV	Respiratory Syncytial Virus Immune Globulin	RSV	Prevention in High Risk Infants
TIG	Tetanus Immune Globulin	Tetanus	Post Exposure and Treatment
VIG	Vaccinia Immune Globulin	Vaccinia	Post Exposure
VZIG	Varicella Zoster Immune Globulin	Varicella Zoster	Post Exposure

HYPERIMMUNE GLOBULIN IN COVID-19

- A coalition of plasma fractionating companies have agreed to merge resources and create a generic hyperimmune globulin derived from patients.

- The group is called the CoVIg Plasma Alliance. https://www.covig-19plasmaalliance.org

- A trial of this product has just begun enrolling patients

- PI is William Mezzanotte MD of CSL-Behring

- Trial is supported by Gates and NIH

CONVALESCENT PLASMA
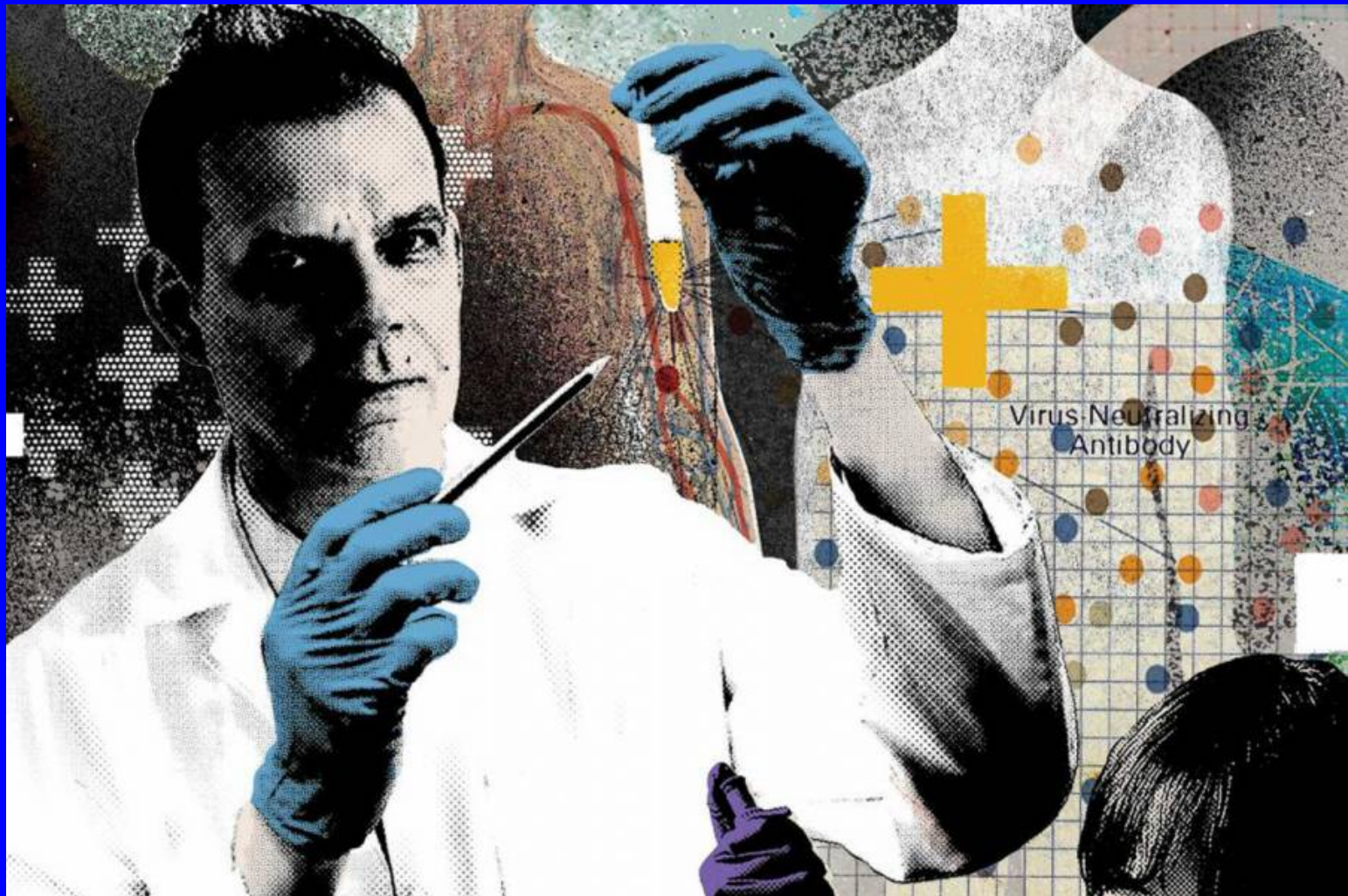
CONVALESCENT PLASMA

- Unlike hyperimmune globulin, is not manufactured in bulk, but is plasma obtained from recovered patients for use in a sick patient

- Because, unlike other antibody preparations, no manufacturing is involved, CP can be used nearly immediately in an epidemic situation.

- Substantial history of apparent success in early 20th century in bacterial meningitis, pneumococcal pneumonia and 1918 influenza.

- Today CP is obtained by plasmapheresis with return of red cells to donor, permitting weekly repeat donations.

- Each donation can have as much as 600 cc of plasma which can serve 3 patients if a 200 cc unit contains sufficient antibody

MONOCLONAL ANTIBODIES

- Developed 45 years ago by Kohler and Millstein (Nobel prize in 1984)

- Technique involves fusing an immortal cell (e.g. myeloma cell line) with an antibody producing white cell to create an immortal producer of a single clone of antibodies

- Mostly used in cancer and auto-immune disorders

- Only three approved monoclonals for infections so far

  – For treatment of Respiratory Syncytial Virus infections in high-risk infants

  – Post-exposure prevention of Anthrax

  – Treatment of C. Difficile infections

MONOCLONAL ANTIBODIES IN COVID 19

- Eli Lilly and Regeneron are both actively developing monoclonal antibody preparations and are conducting human trials.

- All we know as of this date is from news releases by the companies – no data have been published.

- The Regeneron product is two antibodies (one derived from a human-mouse chimera, the other from recovered patients) both virus-neutralizing and active against the spike protein. The exact composition of the Lilly antibody has not been released.

- Each product has been used in just one patient outside of clinical trials – The Regeneron product in President Trump and the Lilly product in Governor Christie

Returning to our anti P-M group

Some of the discussion in our anti-precision medicine group revolved around the question:

We know what we are against, but what are we for?

THEN COVID HIT

THE KEY PAPER THAT ENERGIZED OUR GROUP

Arturo Casadevall, Liise-anne Pirofski: The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130(4):1545-1548. MARCH 13, 2020

Arturo and Liise-anne argued that absent any other treatments for COVID-19, it would be wise to consider convalescent plasma, a form of passive immunity used successfully in the past against many respiratory and other serious infections.

Arturo Casadevall also wrote an op-ed in the Wall Street Journal -

OPINION | COMMENTARY

How a Boy's Blood Stopped an Outbreak

A school physician's approach to measles in 1934 has lessons for the coronavirus.

By Arturo Casadevall
Feb. 27, 2020 6:48 pm ET

THE NATIONAL COVID 19
CONVALESCENT PLASMA PROJECT
WAS ESTABLISHED

ABBREVIATED AS:

CCPP19

CCPP19 ORGANIZATIONAL ARRANGEMENTS THAT SPRUNG UP IN WEEKS

- Development of national group of several hundred physician-scientists
- Large scale meetings by phone
- Need for communications led to the establishment of an-MSU supported website on March 26th
- MSU IT collaborated with Amazon Web Services (who donated their time) to put up a website ccpp19.org in less than 48 hours.

National COVID-19 Convalescent Plasma Project

Search...

Health Care Providers   Donating Plasma   Seeking Treatment   Key Scientific Papers   News   Who are we?

News

Please see Statement from CCPP19 Leadership in Response to Emergency Use Authorization below.

Ask a question

National convalescent plasma group
https://ccpp19.org

Michael Joyner
Mayo Clinic

Arturo Casadevall
Johns Hopkins

Nigel Paneth
Michigan State

Brenda Grossman
Wash U

Jeffrey Henderson
Wash U

Shmuel Shoham
Johns Hopkins

Lisse-anne Pirofski, Einstein

AND THEN, JUST AS WE WERE GETTING ORGANIZED, A MAJOR DEVELOPMENT

ON APRIL 6TH THE FDA ANNOUNCED ITS EXPANDED ACCESS PROGRAM (EAP) FOR CONVALESCENT PLASMA, CONDUCTED JOINTLY WITH THE MAYO CLINIC

THE THREE FDA AUTHORIZATIONS OF CONVALESCENT PLASMA USE IN THE US

COVID-19 convalescent plasma is viewed as an experimental biologic product and its legal use in the US requires approval by the FDA division of biologics

1. MARCH 22 - FDA authorizes use of CP for compassionate use on a case-by-case basis

2. APRIL 6 – FDA authorizes EXPANDED ACCESS PROGRAM (EAP) a research study to establish the safety, and if possible, measures of effectiveness, of CP. Mayo Clinic agrees to coordinate the study.

3. AUGUST 23 - FDA announces EMERGENCY USE AUTHORIZATION, supplanting the EAP and bringing enrollment in the study to an end.

THE EXPANDED ACCESS PROGRAM

- Approved as a single arm observational study by the Mayo Clinic IRB and funded by a contract with BARDA (MJ Joyner, PI).

- Lasted from April 6 – August 23. A total of 139 days – just under 20 weeks. Mayo website: uscovidplasma.org

- This registry obtained detailed information, including clinical status, mortality, complications, on nearly 85,000 patients treated with CP from all 50 states.

- The Mayo IRB also authorized obtaining data on all patients (both treated and untreated with CP) from hospitals participating in the EAP, using a study design from MSU, to compare outcomes in CP treated and untreated patients

- Working with 56 blood banks, obtained remnant serum samples from transfused plasma and measured antibody levels to assess in relation to outcome

RESEARCH EFFORTS UNDERTAKEN BY CCPP19

- Initiated by MSU
  - Patient trajectories after transfusion
  - Treatment-Control Study
  - Mortality in COVID-19
- Initiated by Mayo Clinic
  - Safety studies
  - Meta-analysis of the literature
  - Effect of antibody level on mortality
- Initiated by Hopkins and Einstein
  - Randomized trials

MSU CCPP19 RESEARCH TEAM

- MSU FACULTY MEMBERS
  - Chenxi Li, Mat Reeves
- FROM THE ECHO PROJECT
  - Breanna Kornatowski, Teng Fei Ma
- GRADUATE ASSISTANT (SUMMER 2020)
  - Ra'ed Hailat
- INDEPENDENT STUDY STUDENTS (SUMMER 2020)
  - Villisha Gregoire, Barrett Montgomery, Megan Eagle, Alyssa Vanderziel, Alicynne Glazier, Erica Leidy, Sara Campbell (MSU); Rachel Thompson, Thomas Goralski (GVSU); Kathy Sliwinski (UM); Vikram Dillon (DMC intern). This group also contributed substantially to the website

PATIENT TRAJECTORIES

- Devised to obtain information on treated patients quickly by requesting very simple daily reports (email or text) from treating physicians as to whether patient was better, the same or worse than the previous day and whether on ventilator, in ICU, died or was discharged alive.

- Programmed by Amazon Web Services, initially on our website, but transferred to Mayo site to link to EAP

- Ordinal Scoring: Death = -2, Worse = -1, Same = 0, Better = +1, Discharged Alive = +2

- Based on 7,180 patients in the EAP. 4,435 discharged alive, 1,659 died.

- Patterned on work of Lawther in UK who examined self-reported daily scores (compared to previous day) of patients with COPD and showed that ordinal scores correlated with specific air pollutants.

# TRAJECTORIES BY PATIENT STATUS AT TRANSFUSION

First authors:
Teng Fei Ma,
Chad Wiggins
(post-doc,
Mayo)
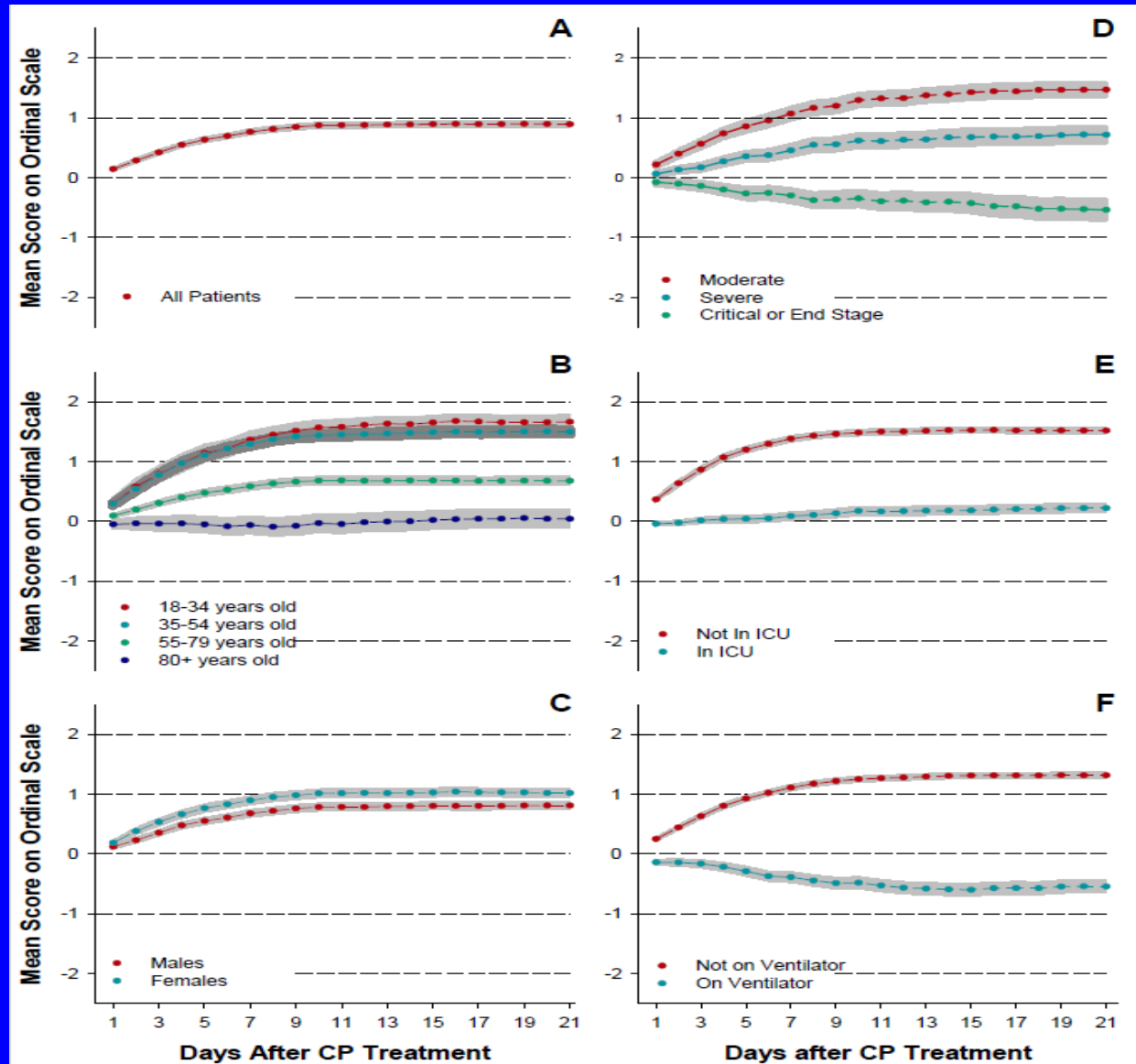
TREATMENT CONTROL STUDY

- Initial design by Chenx-Li and me
- Hospitals using EAP could forward data to Mayo on their COVID-19 patients.
- Phase 1: Mayo biostatistics unit matches untreated controls to treated patients on sex, age, race, hospital, respiratory severity (on hospitalization day corresponding to the day of treatment of CP recipient)

- Phase 2: After matching, we obtain more data on background risk factors on treated and controls. Protocol approved by Mayo IRB

- We are assisted by MITRE corporation in developing protocols; Breanna Kornatowski responsible for all communications with hospitals.

- Design now being replicated by several major hospital systems in US, including VA system.

- Current status: still enrolling hospitals, signs of efficacy in early treated patients
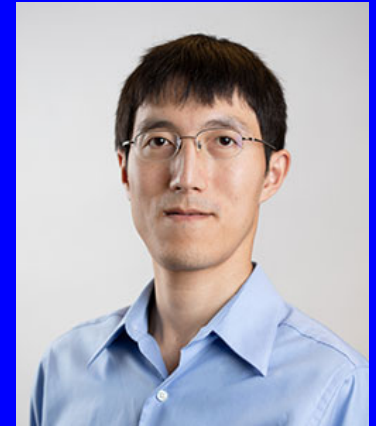
MORTALITY PATTERNS IN COVID-19

- Meta-analysis of all large published data on mortality in hospitalized COVID-1.

- Project initiated in summer independent study with students

- Purpose is to see if a standardized mortality pattern emerges which can be used to compare to CP recipients

- Effort is being led by Mat and Ra'ed

SAFETY STUDIES

- Some 4-5 million units of plasma are used in the US annually. Convalescent plasma differs from usual plasma only in its derivation from people who have recovered from COVID-19 and have been asymptomatic for at least 14 days.

- Residual virus in plasma after recovery does not seem to be a problem.

- Analysis of 20,000 Mayo patients*:
  - TRALI = 0.10%
  - TACO = 0.18%
  - OTHER ALLERGIC REACTION = 0.19%
  - ALL OTHER POSSIBLY RELATED SEVERE ADVERSE EVENTS = 0.8%

*Joyner MJ et al: Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clinic Proceedings 2020; PMID: 32861333

META-ANALYSIS FINDINGS

Joyner MJ et al: Evidence Favoring the efficacy of convalescent plasma for COVID-19 therapy

On the med archive server

doi: https://doi.org/10.1101/2020.07.29.20162917

STUDIES COMPARING MORTALITY IN CP-TREATED TO UNTREATED PATIENTS: COUNTRIES OTHER THAN US

	1st AUTHOR, LOCATION	CP DEATHS	CONTROL DEATHS	RISK RATIO
1	Skrip, Burkina Faso	NA	NA	0.52
2	Perotti, Italy	3/40 = 7.5%	6/17 = 35%	0.15
3	Abolghasemi, Iran	17/114 = 14.8%	18/74 =24.3%	0.61
4	Zeng, China	5/6 = 83.3%	14/15 = 93.3%	0.89
5	Duan, China	0/10 = 0%	3/10 = 30%	< 0.33
6	Xia, China	3/138 = 2.2%	59/1,371 = 4.1%	0.51
POOLED*		**25/170= 14.7%**	**41/116 = 35.3%**	**0.42**

* Skrip excluded because no usable data; Xia excluded because control sample too large. P value for the RR of 0.42 is < .01

US STUDIES COMPARING CP-TREATED TO UNTREATED PATIENTS

	1st AUTHOR, LOCATION	CP DEATHS	CONTROL DEATHS	RISK RATIO
1	Liu, NYC	5/39 = 12.8%	54/230 = 23.5%	0.49
2	Donato, NJ	11/47 = 23.4%	565/1340=42.2%	0.55
3	Hegerova, Seattle	2/20 = 10%	6/20 = 30%	0.22
4	Salazar, Houston	5/136 = 3.7%	19/251 = 7.6%	0.49
5	Rogers, Providence	8/64 = 12.5%	28/177 = 15.8%	0.79
POOLED*		**31/306 = 10.1%**	**107/678 = 15.8%**	**0.64**
Donato excluded because control sample too large				

RANDOMIZED TRIALS OF CONVALESCENT PLASMA

	1st AUTHOR, LOCATION	DEATHS/ TREATED	DEATHS/ UNTREATED	RISK RATIO
1	Li, China	8/51 = 15.7%	12/50 = 24.0%	0.75
2	Gharbharan, Holland	6/43 = 14.0%	11/43 = 25.6%	0.47
3	Avendano-Sola, Spain	0/38 = 0%	4/43 = 9.3%	< 0.25
4	Agarwal, India*	34/235 = 14.6%	31/229 = 13.7%	1.06
5	Rasheed, Iraq	1/21 = 4.7%	8/28 = 28.9%	0.16
ALL 5 POOLED		**49/388 = 12.6%**	**66/393 = 16.8**	**0.75****

*only trial with just 30% of donors having high antibody titers

**p = 0.10; Excluding Agarwal RR = 0.46, p < .01

EFFECT OF ANTIBODY LEVELS IN PLASMA

- Perhaps the single most important study to emerge from the EAP

- Required going back to blood banks to retrieve remnant serum samples from transfused units and have them sent them to Mayo for antibody testing (some also sent to Broad Institute via the FDA).

- 56 blood banks participated. Mayo received 3,082 samples, FDA/Broad got 4,330.

- Antibody levels are the active principle in convalescent plasma, and we assume that the higher the antibody titer in the plasma the better the therapeutic response

- Since antibody levels were unknown at time of transfusion, findings difficult to confound

ANTIBODY FINDINGS FROM MAYO STUDY USING ORTHO IgG SARS-CoV-2 SPIKE SUBUNIT 1 PROTEIN

- Lower mortality in recipients of high titer plasma top 20th percentile) than low titer plasma (lowest 20th percentile), significant in some models, not in others. But powerful interaction noted.

- High vs low antibody in ventilated patients

  - Unadjusted 30-day mortality – 0.97

  - Adjusted* 30-day mortality – 1.02

- High vs low antibody in unventilated patients

  - Unadjusted 30-day mortality – 0.57

  - Adjusted* 30-day mortality – 0.61

*Adjustment factors: treated before or after 5/15, age, race, obesity classification, p/f ratio < 300, >50% lung infiltrates, use of hydroxychloroquine.

FDA DATA BASED ON BROAD INSTITUTE
VIRAL NEUTRALIZATION ASSAY DICHOTOMIZED AS HIGH VS LOW

	7-DAY MORTALITY			28-DAY MORTALITY		
PATIENT CATEGORY	ALL	NOT INTUB	NOT INTUB	ALL	NOT INTUB	NOT INTUB
AGE AND TREATMENT TIME	ALL	ALL	≤80 y, ≤72 h	ALL	ALL	≤80 y, ≤72 h
SAMPLE SIZE	4,330	2,488	932	2,817	1,238	485
LOWER TITER	15.0%	14.0%	11.3%	49.6%	49.4%	46.6%
HIGHER TITER	13.6%	11.0%	6.3%	46.2%	41.5%	33.2%
ABSOLUTE REDUCTION	1.4%	3.0%	5.0%	3.4%	8.0%	13.4%
RELATIVE REDUCTION	9%	21%	44%	7%	16%	29%
P VALUE	NS	0.03	.008	NS	0.004	0.004

IN ADDITION

A small Israeli study found the RR for mortality in high-Ab transfused patients was 0.45 (2/19 vs 7/30)

THESE ANTIBODY FINDINGS, COMBINED WITH THE SAFETY DATA CONVINCED THE FDA TO ISSUE THE EMERGENCY USE AUTHORIZATION ON AUGUST 23RD

AND THEN THE POLITICS!

- White House shows interest in convalescent plasma

- FDA Division of Biologics carefully analyzed EAP data focusing especially on antibody levels in plasma to consider whether to grant emergency use authorization (EUA).

- EUA requires evidence of safety, and evidence that the product "might be effective". Extends only to hospitalized patients during current state of emergency. Considerably lower standard than licensing. EUA also requires labelling convalescent plasma as having high or low antibody.

- NYT reports that NIH (Fauci, Collins) opposed to EUA, and further reports that Trump called Collins and said that CP must be approved by 8/21.

- When EUA was issued 8/23, assumption was made by some that it was made because of WH pressure. This issue is critical because the Division of Biologics is the agency that must approve any COVID vaccine

OUR VIEW

- Having worked with the FDA division of Biologics and its director Peter Marks for some months, the CCPP19 leadership team unanimously thought that the decision to issue the EUA was based on sound science.

- Arturo and I authored two media pieces
  - The first in Bloomberg News, just after the FDA issued the EUA, defending the FDA decision as based on good science
  - The second, nearly a month later in the Wall Street Journal, explaining why the FDA and the NIH could disagree on matters of scientific interpretation
  -

FDA Made the Right Call on Covid Plasma Treatment

The agency has been accused of playing politics in approving transfusions from coronavirus survivors. It was following the science.

By Arturo Casadevall and Nigel Paneth
August 28, 2020, 12:50 PM EDT

A Little Debate on Plasma Is Healthy for Science

The FDA says it's likely effective, while NIH urges caution. The answer: Get more data from trials.

By Arturo Casadevall and Nigel Paneth   Sept. 22, 2020 11:54 am ET

TRIALS ON THE HORIZON

- Still not a single US trial published on CP!
- Liise-anne Pirofski (Einstein) directs the largest current US hospital trial of CP. Sample size now over 300. First look at the data by DSMB at about n = 150 encouraged continuing the trial
- Liise-anne worries that many enrollees in April and May were too sick to benefit from CP
- Shmuel Shoham (JHU) directs a trial of uninfected people at high risk of exposure (e.g. health care workers) and participates in another trial of outpatient mild to moderate illness.
- All US trials we know of are listed on our website

HOW COULD WE DO ALL THIS AND STILL RETAIN OUR DAY JOBS?

IN MY CASE, THE ANSWER IS

GREAT COLLABORATORS AND GREAT RESEARCH STAFF!

CO-PRINCIPAL INVESTIGATORS OF OUR ECHO PROJECT

Patti McKane MDHHS

Jean Kerver MSU

Douglas Ruden WSU
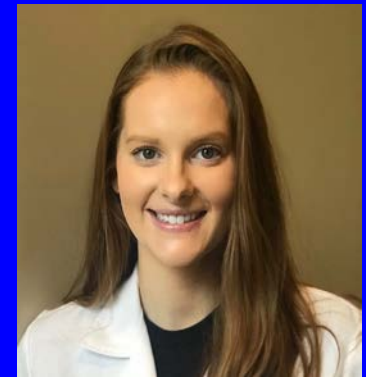
Michael Elliott, U of M

Charles Barone HFHS

ECHO STUDY OFFICE AT MSU

1. Alexa Krueger
2. Tracy Thompson
3. Breanna Kornatowski

4. Teng-Fei Ma
5. Kristen Schmidt
6. Kylie Voorhis

7. Shelly Ross
8. Brie Frasher
9. Janel Gryc

CONCLUSIONS

- Even absent a large randomized trial, it is hard not to see powerful evidence, from a variety of sources, of convalescent plasma efficacy in reducing mortality

- The data showing the dose-response relationship of antibody levels unknown at the time of treatment to mortality is hard to explain away.

- Early treatment is clearly better than waiting until disease is more severe and complications have ensued.

- IF I WERE TO GET COVID-19, I WOULD WANT HIGH-TITER CONVALESCENT PLASMA AS SOON AS POSSIBLE

AND AS FOR PRECISION MEDICINE

We still await a measurable therapeutic or preventive advance in COVID or any other disease from precision medicine approaches.

And as we watch the progress of the epidemic and its dependence on failure to wear masks and to socially distance, and the reluctance to give up, even temporarily, parties and other mass gatherings, the words of Mike Joyner from 2015 continue to ring true:

"We would be better off directing resources to better understanding what it takes to solve messy problems about how humans behave as individuals and in groups."