Convalescent Plasma For COVID-19 Disease

https://www.uscovidplasma.org/

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Disclaimer

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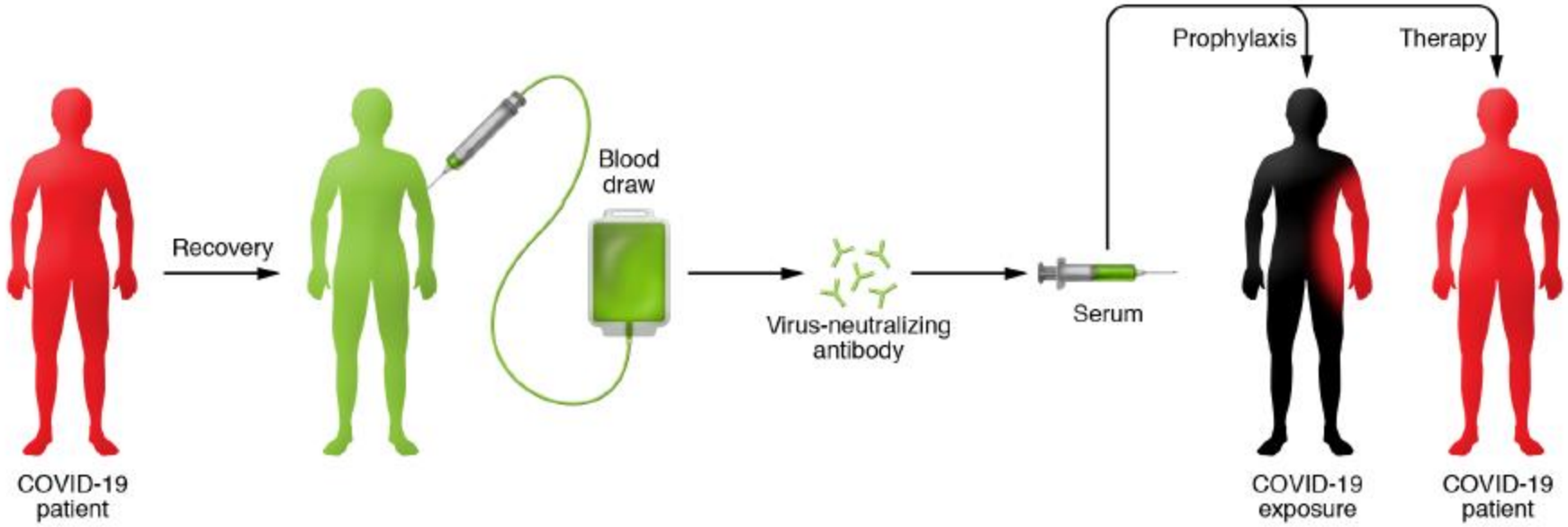
What is convalescent plasma?

- Relies on principles of passive immunity
- ***1st "best shot" on biological goal***
- Transfer of antibodies from a recovering patient or animal
  - Post exposure to prevent disease
  - To treat disease
- Long history

Conceptual Model



Casadevall & Pirofski JCI 2020

1. Use in 1918

THE USE OF CONVALESCENT HUMAN SERUM IN INFLUENZA PNEUMONIA—A PRELIMINARY REPORT.*

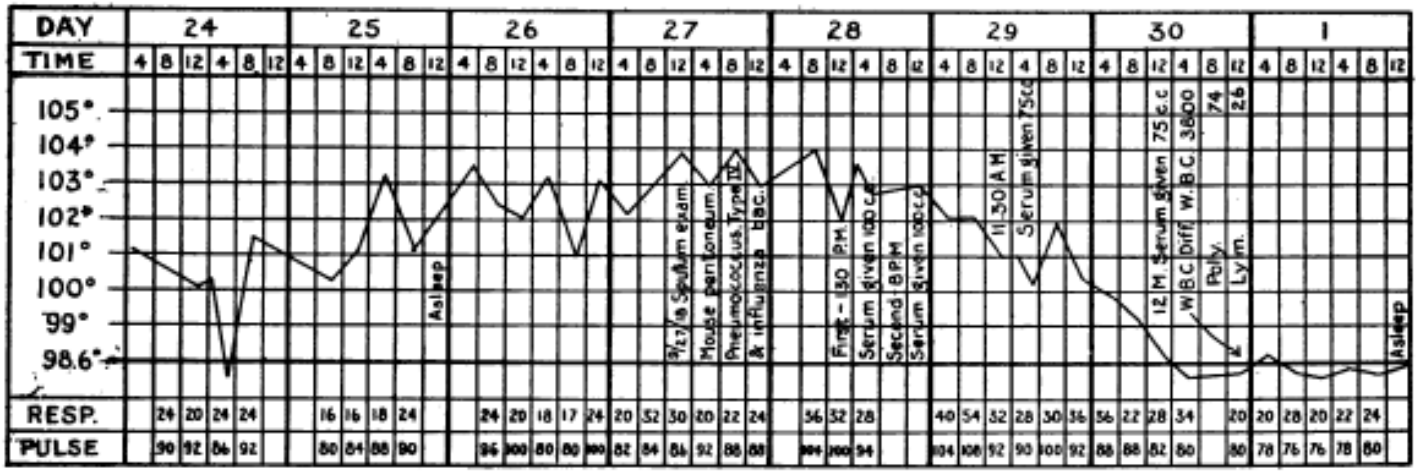


FIG. 1. Temperature Chart of Officer.

McGuire & Redden AJPH 1918

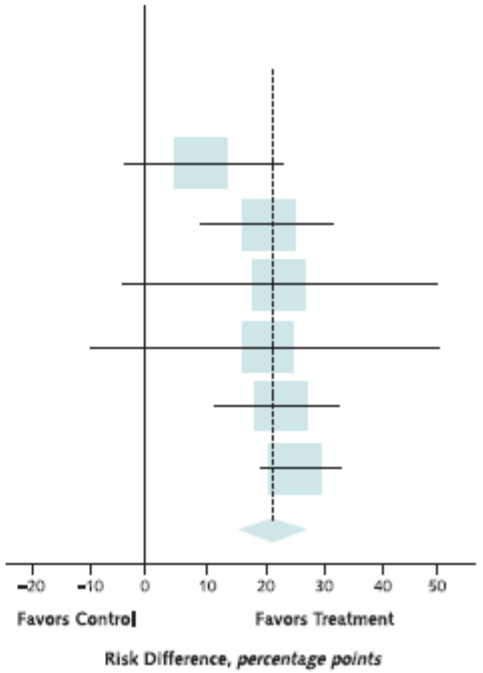
2. Meta Analysis 1918

Annals of Internal Medicine | Review

Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

Figure 2. Absolute risk differences in mortality among patients treated with convalescent blood products and controls.

Study (Reference)	Mortality Rate, *n/n (%)*		Risk Difference (95% CI), *percentage points*
	Treatment Group	Control Group	
Stoll (17)	25/56 (45)	201/379 (53)	8 (–6 to 22)
O'Malley and Hartman (18)*	3/46 (7)	28/111 (25)	19 (8 to 29)
Ross and Hund (19, 20)	6/28 (21)	9/21 (43)	21 (–5 to 47)
Kahn (21)	12/25 (48)	12/18 (67)	19 (–11 to 48)
Gould (22)	2/30 (7)	82/290 (28)	22 (11 to 32)
McGuire and Redden (23, 24)*	6/151 (4)	120/400 (30)	26 (21 to 31)
Overall	54/336 (16)	452/1219 (37)	21 (15 to 27)



Luke et al Ann Int Med 2006

3. Argentine Hemorrhagic Fever

Double blind trial with immune plasma: Between 1974 and 1978, a double blind placebo-controlled study was performed among patients with a clinical diagnosis of AHF hospitalized in Pergamino with less than 8 days from onset of symptoms. The patients were randomly allocated to receive intravenously either 500 ml of immune plasma or normal plasma. Ultimately, 188 cases with a laboratory confirmation of infection with Junin virus entered in the trial. The case-fatality rate among cases treated with normal plasma was 16.5% while the rate in those patients treated with immune plasma was 1.1% (Maiztegui et al., 1979).

Enria et al Antiviral Res 2008

4. SARS early 2000s

Y. Cheng · R. Wong · Y. O. Y. Soo · W. S. Wong · C. K. Lee · M. H. L. Ng · P. Chan · K. C. Wong · C. B. Leung · G. Cheng

Use of convalescent plasma therapy in SARS patients in Hong Kong

Abstract In order to evaluate the efficacy of convalescent plasma therapy in the treatment of patients with severe acute respiratory syndrome (SARS), 80 SARS patients were given convalescent plasma at Prince of Wales Hospital, Hong Kong, between 20 March and 26 May 2003. Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death or hospitalization beyond 22 days. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; $P<0.001$) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; $P=0.001$).

Summary: Has it worked in the past?

- Yes
- Prophylaxis – many examples
- Early use seems better
- Rescue therapy?
- Concentrated products follow plasma

WSJ February 27, 2020

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

It isn't every day that a school physician's work gets published in a medical journal. But it happened in 1934, and the story contains a lesson for the coronavirus epidemic.

Arturo is a friend of mine……

Use of Convalescent Measles Serum to Control Measles in a Preparatory School

J. ROSWELL GALLAGHER, M.D.

School Physician, The Hill School, Pottstown, Pa.

SUMMARY

1. In a threatened outbreak of measles in a group of preparatory school boys, 66 of whom had not had measles, convalescent measles serum was used prophylactically. Only 3 cases of measles, all decidedly attenuated, subsequently developed in this group. On the basis of past experience, at least 25 per cent of this group might have been expected to develop measles.

2. The use of convalescent measles serum is suggested as the most practical method of controlling an outbreak of measles among adolescents in a preparatory school or in a similar situation. A dose of 10 c.c. is considered adequate for members of this age group.

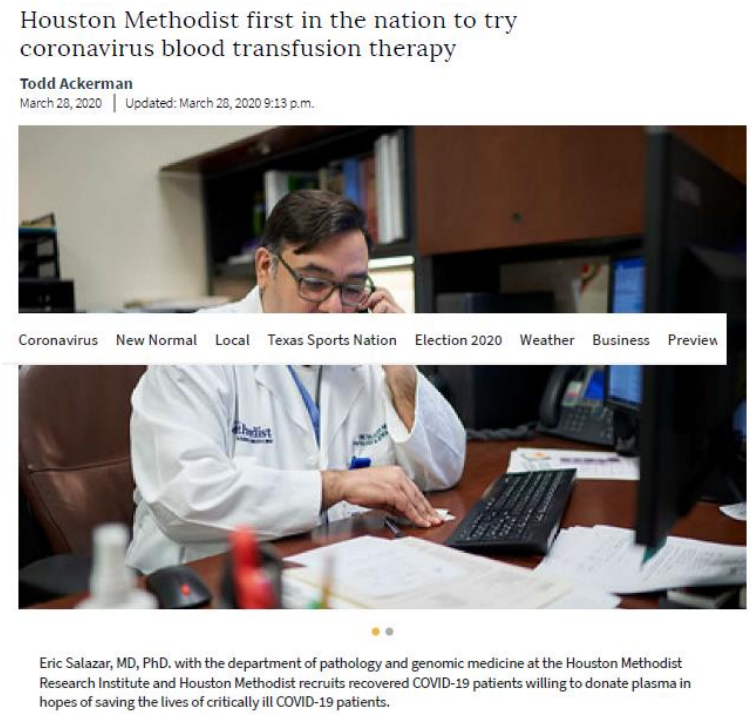
Am J PH 1935

Mid-March

- Network self-assembles around the idea of CP
- Many members know each other as a result of there shared concerns about excessive reductionism in biomedical research
- Hopkins generates prophylactic protocol
- Mayo adapts for early treatment

Late March:
Lots of Interest Nationally

- FDA announces eINDs for compassionate use
- Houston Methodist & NY Mt Sinai use it
- Blood bankers get mobilized
- Demand for eINDs overwhelms FDA
- Expanded Access Program (EAP) developed



Houston Methodist first in the nation to try coronavirus blood transfusion therapy

Todd Ackerman

March 28, 2020 | Updated: March 28, 2020 9:13 p.m.

Coronavirus New Normal Local Texas Sports Nation Election 2020 Weather Business Preview

Eric Salazar, MD, PhD. with the department of pathology and genomic medicine at the Houston Methodist Research Institute and Houston Methodist recruits recovered COVID-19 patients willing to donate plasma in hopes of saving the lives of critically ill COVID-19 patients.

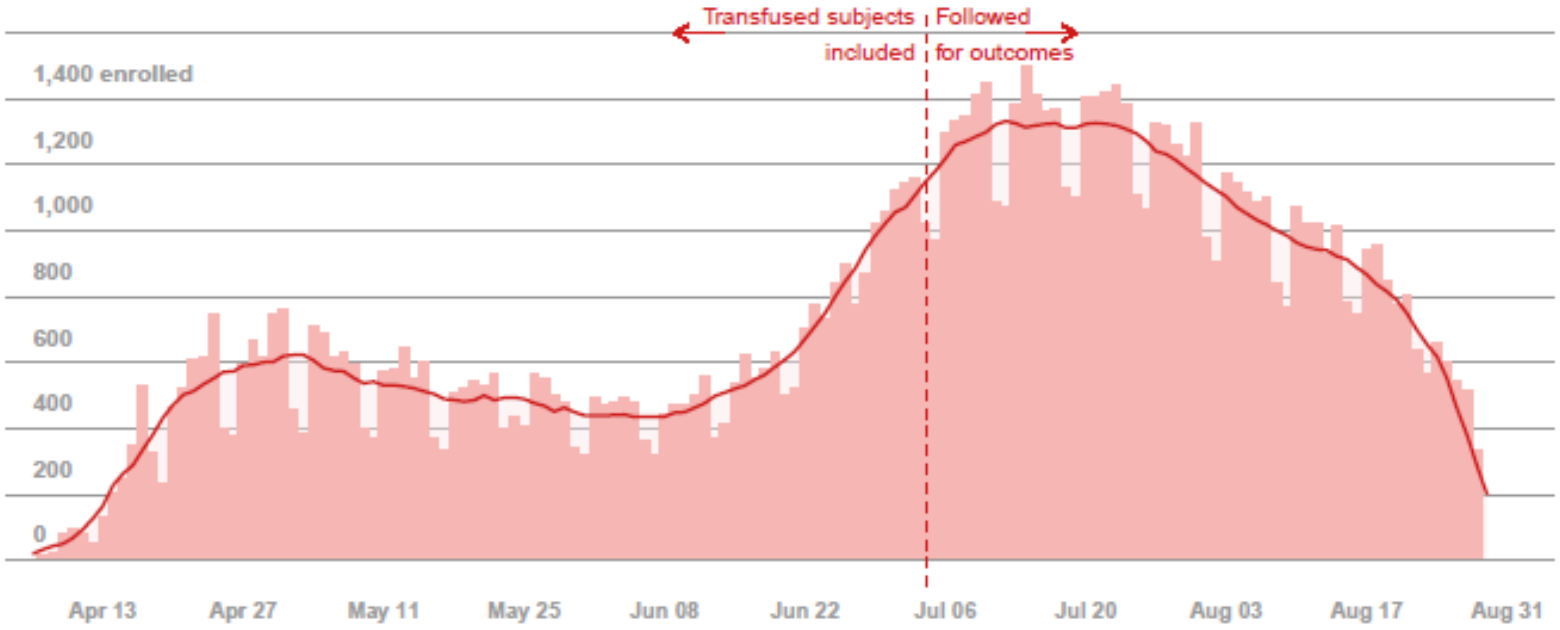
EAP Timeline

- **3/30** FDA contacts Joyner/Mayo about EAP
- **4/1** Mayo IRB approves EAP & is central IRB with e
- **4/1** ***Enrollment Cap set at 5000,↑ many times***
- **4/3** Website roll-out Including:
  - Site, MD, and patient enrollment
  - Workflow
  - Navigator and FAQ functions
  - Case report tools
  - Full-service communication center
- **4/7** **1st patient transfused**
- **8/24** **Emergency Use Authorization (EUA) issued**
- **8/28** ***Enrollment Stops***

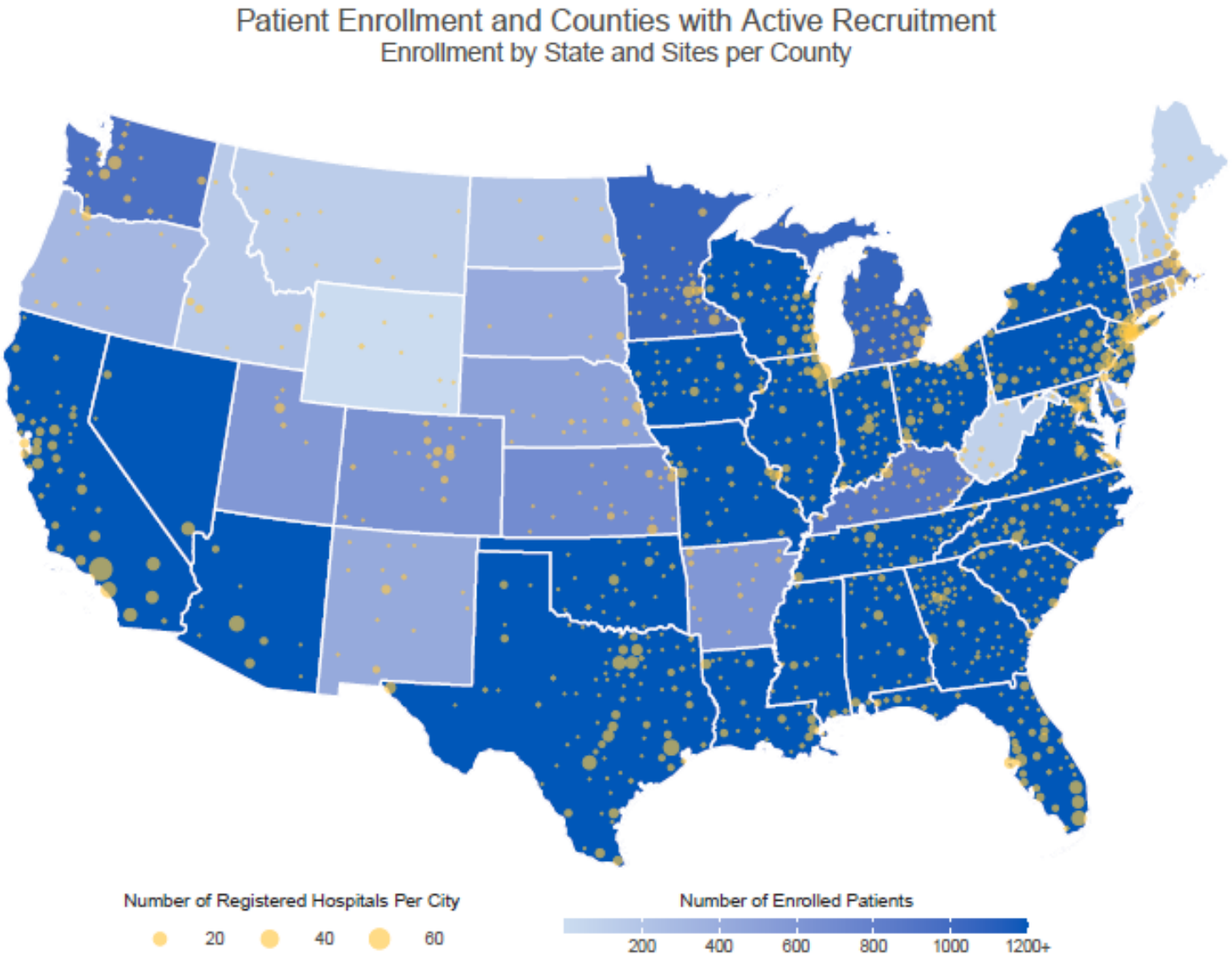
Enrollment Ends Late August

Enrollment Summary

2,764	14,513	105,880	78,774
Total Sites Registered	Total Physicians Registered	Total Patients Consented	Total Patients Transfused



~2800 Hospitals Throughout the US



Teamwork & Repurposing Skill Sets Made it Happen

1. **Casadevall** – idea
2. **Joyner** – could be done at scale
3. **FDA** – need for EAP
4. **Wright** – Mayo IRB & novel ideas about streamlining trials
5. **Fairweather & Bruno** – web based forms
6. **Carter** – Rapid data analysis
7. **Lab** – novel assays developed and done at scale under great time pressure
8. **Fellows, Jr Clinicians & Analytics Staff** – repurpose and generate novel solutions to problems on a daily basis
9. **Administrative & Compliance Staff** – strong and flexible support throughout
10. **Institutional Leadership** – very supportive
11. **BARDA funding**
12. **Philanthropy** - assay development & covers gaps like food and coffee for individuals working nights and weekends

EAP - Our Charge

1. Provide *broad* access to COVID-19 Convalescent Plasma

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

2. Perform Robust Safety Analysis

Objectives:	Primary Objective:	Provide access to COVID-19 convalescent plasma
	Secondary Objectives:	Safety
Endpoints:	Primary Endpoint:	Availability of convalescent plasma
	Secondary Endpoints:	Serious adverse events

3. Explore Efficacy

Access: Plasma Supply Key

METRO

Thousands of Orthodox Jewish New Yorkers donate plasma to fight coronavirus

By Amanda Woods

April 23, 2020 | 1:04pm

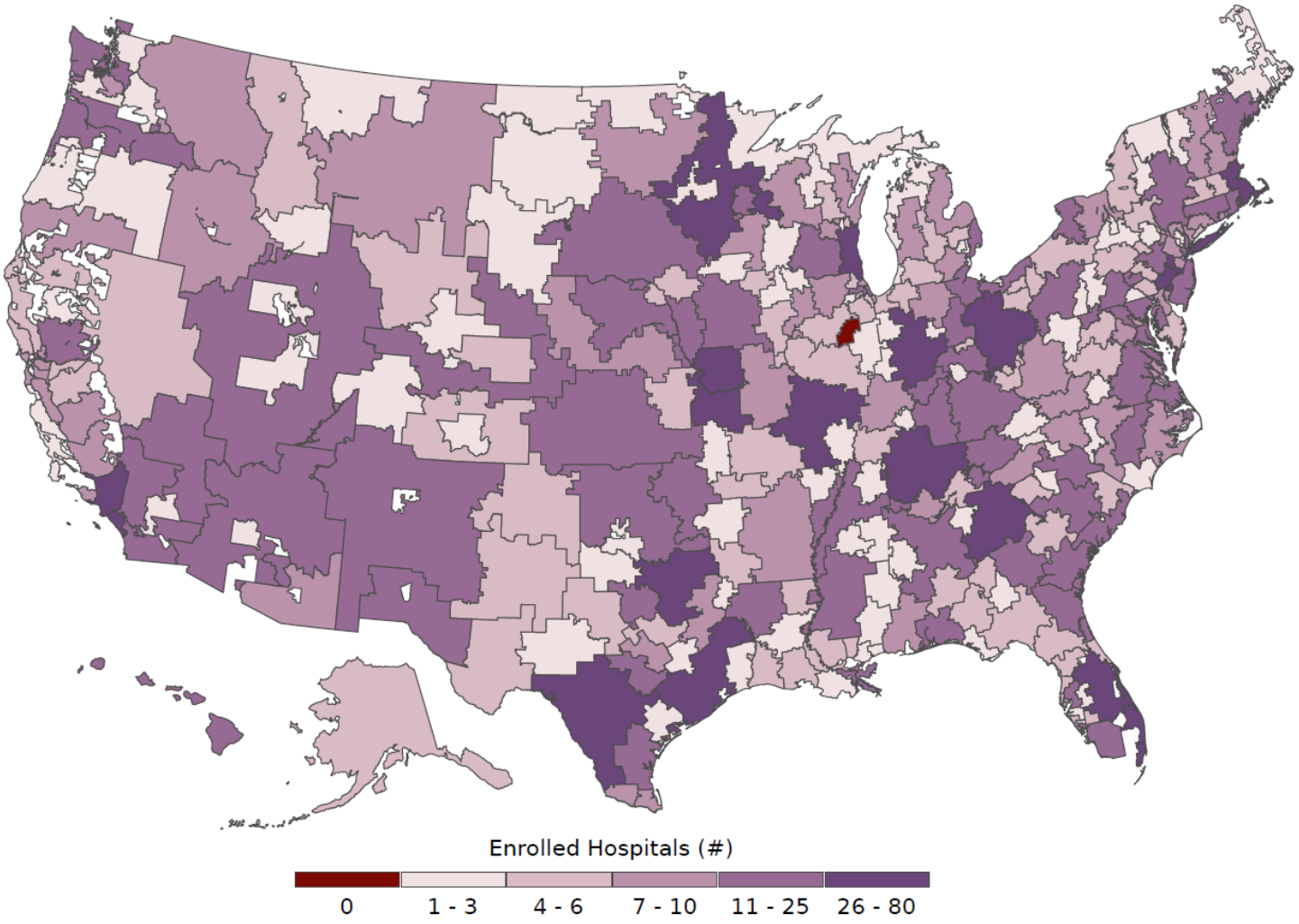
A member of the Orthodox Jewish community get evaluated as a potential plasma donor.
Shmuel Sholham via Twitter

NY Post 4/23

Access: Every Referral Region But 1

Enrolled Hospitals by Hospital Referral Regions

HRR's specify a market within which people generally go to the same hospitals



Safety: *Very Low Rates of TACO & TRALI*

CLINICAL MEDICINE

The Journal of Clinical Investigation

Early safety indicators of COVID-19 convalescent plasma in 5000 patients

Michael J. Joyner,[1] R. Scott Wright,[2,3] DeLisa Fairweather,[4] Jonathon W. Senefeld,[1] Katelyn A. Bruno,[4] Stephen A. Klassen,[1] Rickey E. Carter,[5] Allan M. Klompas,[1] Chad C. Wiggins,[1] John R.A. Shepherd,[1] Robert F. Rea,[2] Emily R. Whelan,[4] Andrew J. Clayburn,[1] Matthew R. Spiegel,[5] Patrick W. Johnson,[5] Elizabeth R. Lesser,[5] Sarah E. Baker,[1] Kathryn F. Larson,[1] Juan G. Ripoll,[1] Kylie J. Andersen,[1] David O. Hodge,[5] Katie L. Kunze,[6] Matthew R. Buras,[6] Matthew N.P. Vogt,[1] Vitaly Herasevich,[1] Joshua J. Dennis,[1] Riley J. Regimbal,[1] Philippe R. Bauer,[7] Janis E. Blair,[8] Camille M. Van Buskirk,[9] Jeffrey L. Winters,[9] James R. Stubbs,[9] Nigel S. Paneth,[10,11] Nicole C. Verdun,[12] Peter Marks,[12] and Arturo Casadevall[13]

Table. Convalescent Plasma Transfusion Reactions

Four Hour Reports	Estimate (95% CI)
Transfusion-Associated Circulatory Overload (TACO)	0.14% (0.07%, 0.29%)
Transfusion-Related Acute Lung Injury (TRALI)	0.22% (0.12%, 0.39%)
Severe allergic transfusion reaction	0.06% (0.02%, 0.18%)

Explore Efficacy

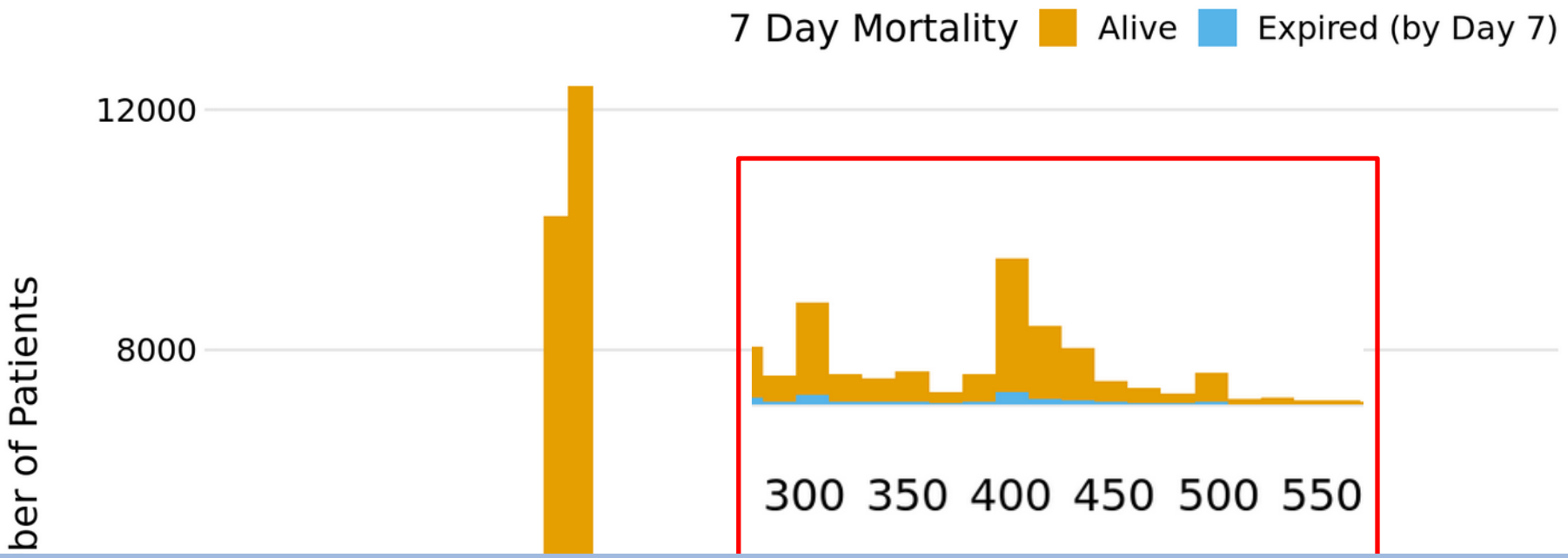
Disclaimers – Not an RCT

- A guesstimate dose
- An uncharacterized product
- Diverse group of hospitalized patients
- Many with disease stages least likely to show a positive effect
- Any hospital
- Teams with no training
- ***Many elements of plane built while flying it***

Nevertheless:
Potential Signals of Efficacy

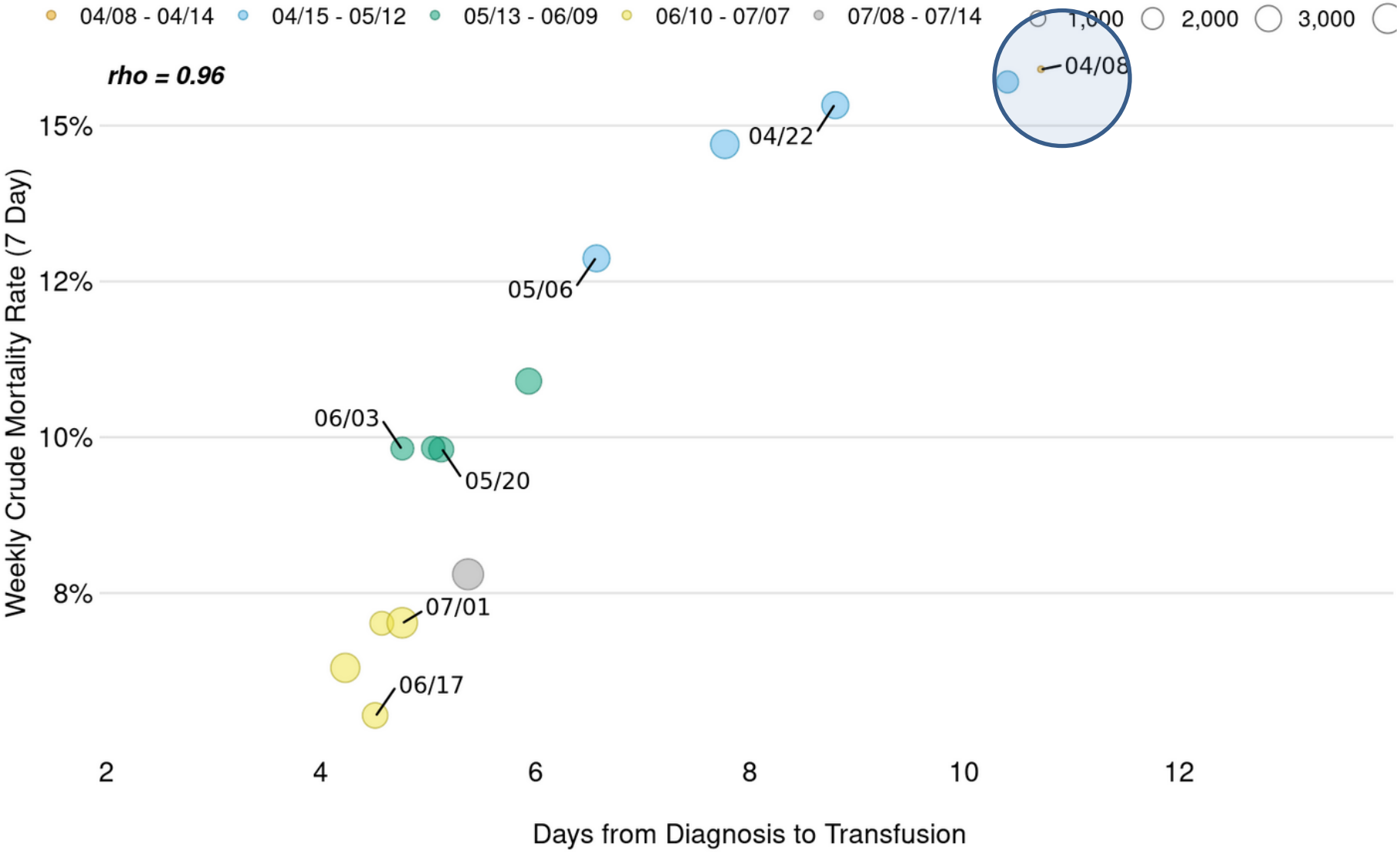
1. **Embedded in Enrollment & Safety Data**
   - Volume Administered
   - Time to Treatment
2. **Exploratory analysis using antibody titers**
3. **Volume, Time, and Abs are variable & have elements of randomization**
4. **Other supportive data**

Volume Administered Varied

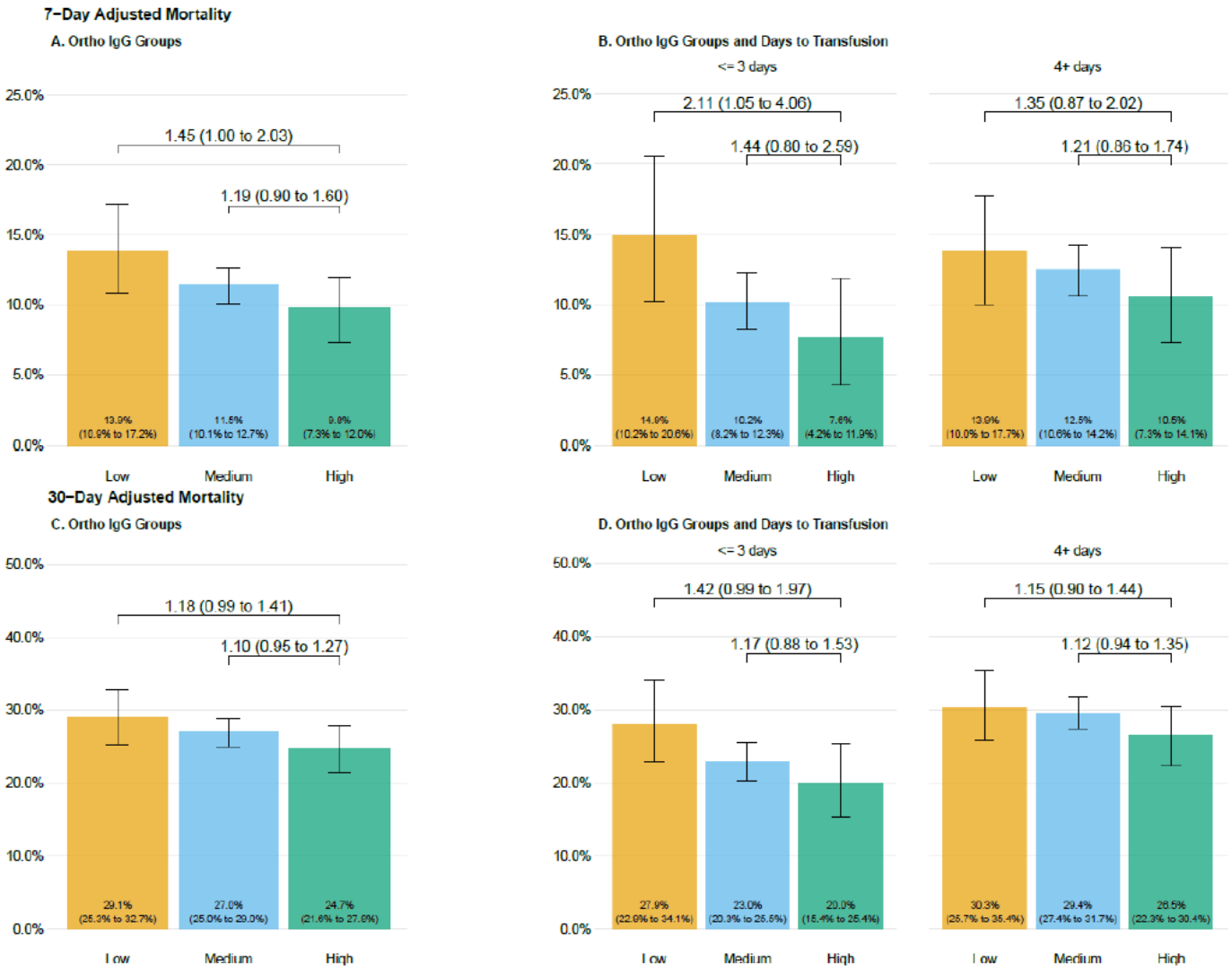


Volume	7 Day Crude Mortality			0.0016	30 Day Crude Mortality			<0.0001
<50	167	19	11.4% (7.4%, 17.1%)		128	33	25.8% (19.0%, 34.0%)	
50 - 149	325	32	9.8% (7.1%, 13.6%)		241	49	20.3% (15.7%, 25.9%)	
150 - 250	30,196	3,138	10.4% (10.1%, 10.7%)		23,560	5,990	25.4% (24.9%, 26.0%)	
251 - 500	9,019	820	9.1% (8.5%, 9.7%)		6,677	1,495	22.4% (21.4%, 23.4%)	
501+	618	44	7.1% (5.3%, 9.4%)		460	100	21.7% (18.2%, 25.7%)	
Missing	399	42	10.5% (7.9%, 13.9%)		354	84	23.7% (19.6%, 28.4%)	
Volume (Grouped)				0.0003				<0.0001
One unit	30,196	3,138	10.4% (10.1%, 10.7%)		23,560	5,990	25.4% (24.9%, 26.0%)	
Two units	9,019	820	9.1% (8.5%, 9.7%)		6,677	1,495	22.4% (21.4%, 23.4%)	

Time to Tx


04/08 - 04/14
04/15 - 05/12
05/13 - 06/09
06/10 - 07/07
07/08 - 07/14
1,000
2,000
3,000
rho = 0.96
15%
12%
10%
8%
Weekly Crude Mortality Rate (7 Day)
04/08
04/22
05/06
06/03
05/20
07/01
06/17
2
4
6
8
10
12
Days from Diagnosis to Transfusion

Antibodies, Time & Mortality



Interim Summary

- Give early
- Give enough
- Give higher titers
- ***Data can help frame RCTs***
- ***Needs additional validation***

Other Supportive Data: *Animal Models*

Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development

At the end of 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) was detected in Wuhan, China, that spread rapidly around the world, with severe consequences for human health and the global economy. Here, we assessed the replicative ability and pathogenesis of SARS-CoV-2 isolates in Syrian hamsters. SARS-CoV-2 isolates replicated efficiently in the lungs of hamsters, causing severe pathological lung lesions following intranasal infection. In addition, microcomputed tomographic imaging revealed severe lung injury that shared characteristics with SARS-CoV-2–infected human lung, including severe, bilateral, peripherally distributed, multilobular ground glass opacity, and regions of lung consolidation. SARS-CoV-2–infected hamsters mounted neutralizing antibody responses and were protected against subsequent rechallenge with SARS-CoV-2. Moreover, passive transfer of convalescent serum to naïve hamsters efficiently suppressed the replication of the virus in the lungs even when the serum was administrated 2 d postinfection of the serum-treated hamsters. Collectively, these findings demonstrate that this Syrian hamster model will be useful for understanding SARS-CoV-2 pathogenesis and testing vaccines and antiviral drugs.

Imai et al PNAS 2020

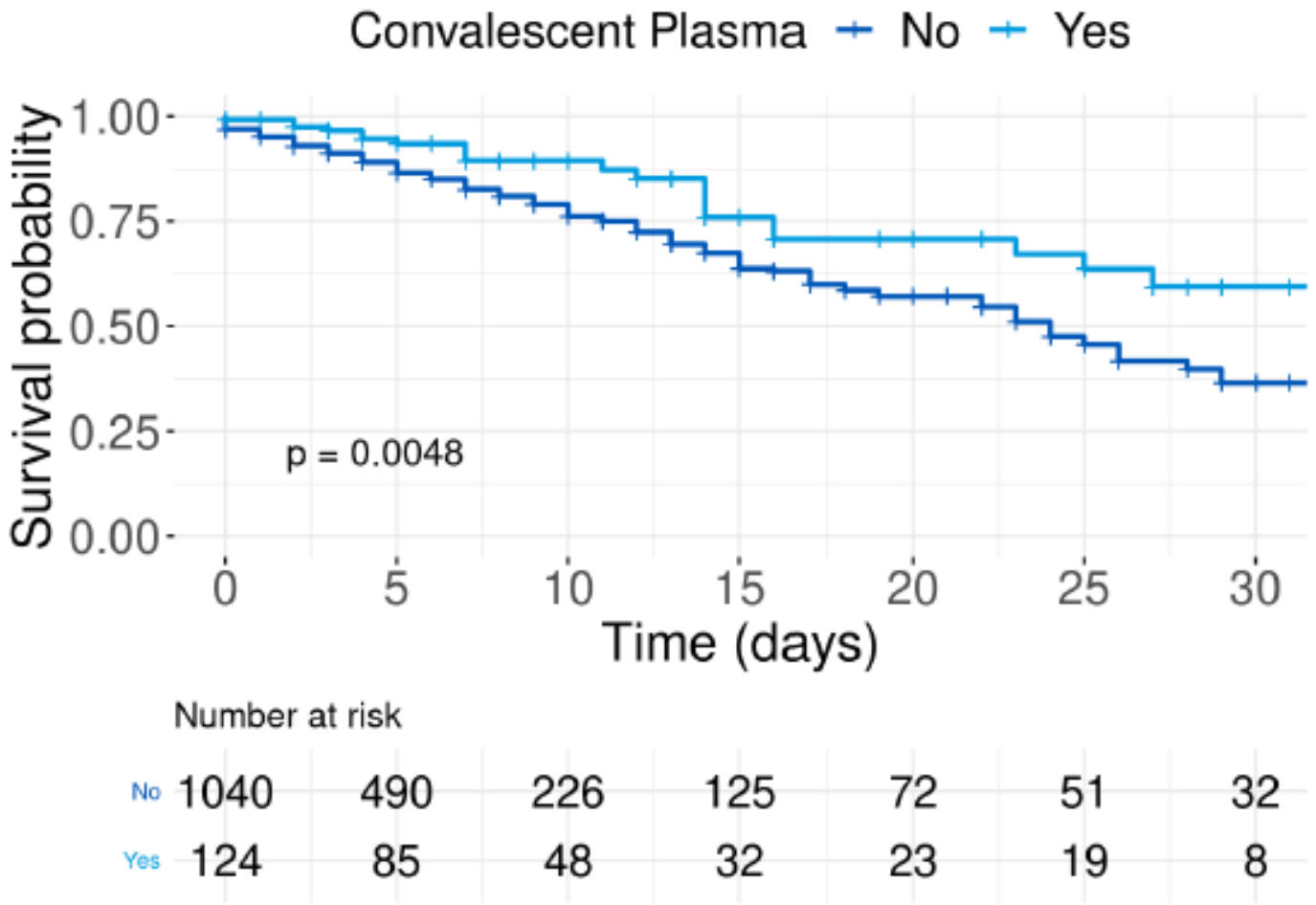
Other Supportive Data: Pooled Studies

Table 1 | Mortality Rates in Hospitalized COVID-19 Patients

Study	Location	Convalescent Plasma			Control			Statistics	
		Survivor	Non-Survivor	Mortality	Survivor	Non-Survivor	Mortality	*OR*	*P*
Clinical Trials - Randomized									
Avendano-Sola et al.	ESP	38	0	0%	39	4	9%	0.11	0.15
Gharbharan et al.	NLD	37	6	14%	32	11	26%	0.47	0.18
Li et al.	CHN	43	8	16%	38	12	24%	0.59	0.30
Fixed Effect Model		118	14	11%	109	27	20%	0.49	0.049
Clinical Trials - Randomized by availability									
Rasheed et al.	IRQ	20	1	5%	20	8	29%	0.13	0.06
Abolghasemi et al.	IRN	98	17	15%	56	18	24%	0.54	0.10
Fixed Effect Model		118	18	13%	76	26	25%	0.46	0.03
Clinical Trials Fixed Effect Model		236	32	12%	185	53	22%	0.48	<0.01
Matched-Control Studies									
Duan et al.	CHN	10	0	0%	7	3	30%	0.10	0.15
Perotti et al.	ITA	43	3	7%	16	7	30%	0.16	0.01
Hegerova et al.	Washington, USA	18	2	10%	14	6	30%	0.26	0.13
Zeng et al.	CHN	1	5	83%	1	14	93%	0.36	0.50
Donato et al.	New York, USA	36	11	23%	775	565	42%	0.42	0.01
Liu et al.	New York, USA	35	5	13%	118	38	24%	0.44	0.11
Salazar et al.	Texas, USA	131	5	4%	232	19	8%	0.47	0.14
Xia et al.	CHN	135	3	2%	1371	59	4%	0.52	0.27
Fixed Effect Model		409	34	8%	2534	711	22%	0.39	<0.001
Overall Fixed Effect Model		645	66	9%	2719	764	22%	0.42	<0.001

OR, odds ratio

Preliminary Electronic Health Record "Data Mining"



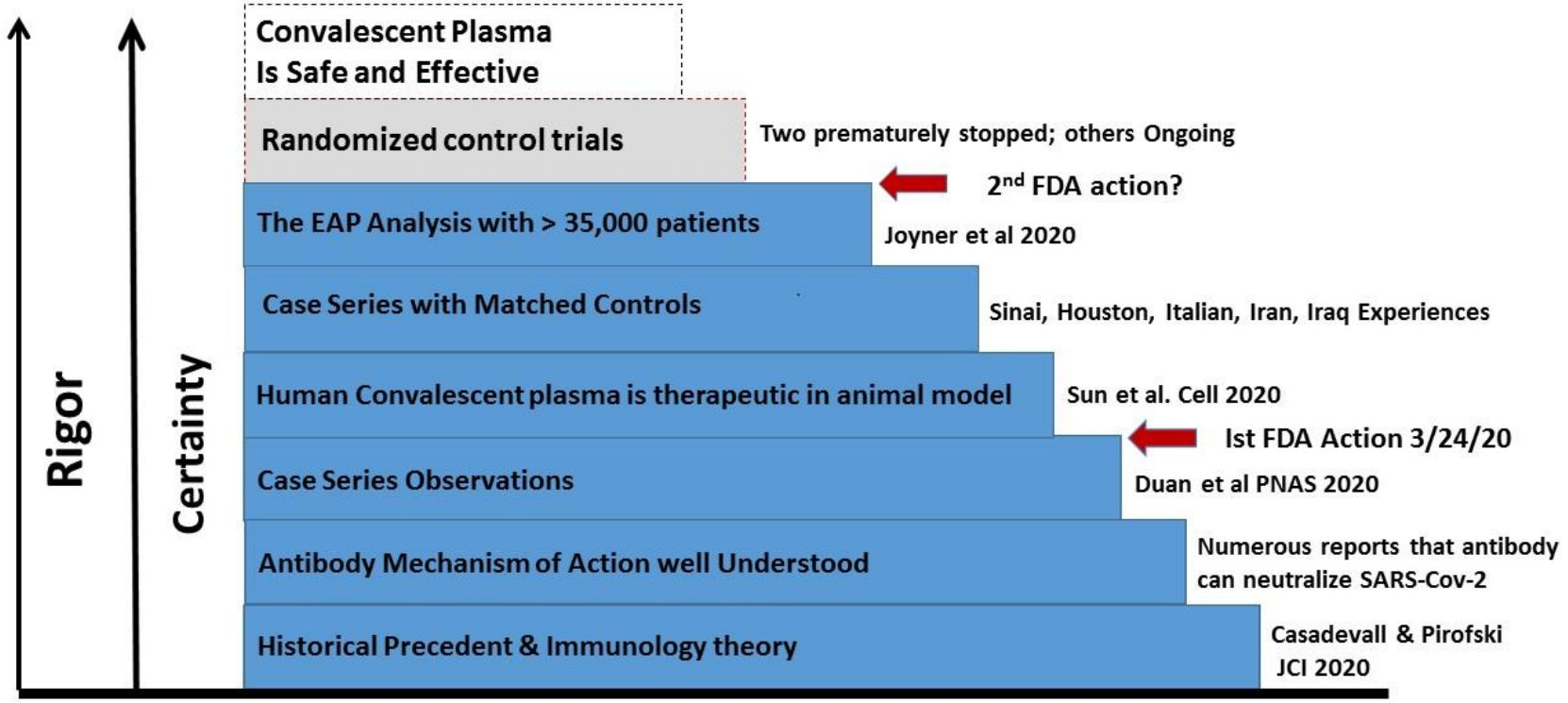
Summary – Not an RCT

- Dosing left to discretion of treating physicians – 1 to 2 units and could be repeated
- No pre-clinical data
- CP did not have any pre-administration measure of nAB or other immune activity

Arturo Casadevall notes:

"Remarkably, in the EAP, signals of efficacy break through despite many potential confounders."

The Epistemic Climb To Establishing Efficacy



Discussion

What Would Cecil Say?

EFFECTS OF VERY EARLY SERUM TREATMENT IN PNEUMOCOCCUS TYPE I PNEUMONIA

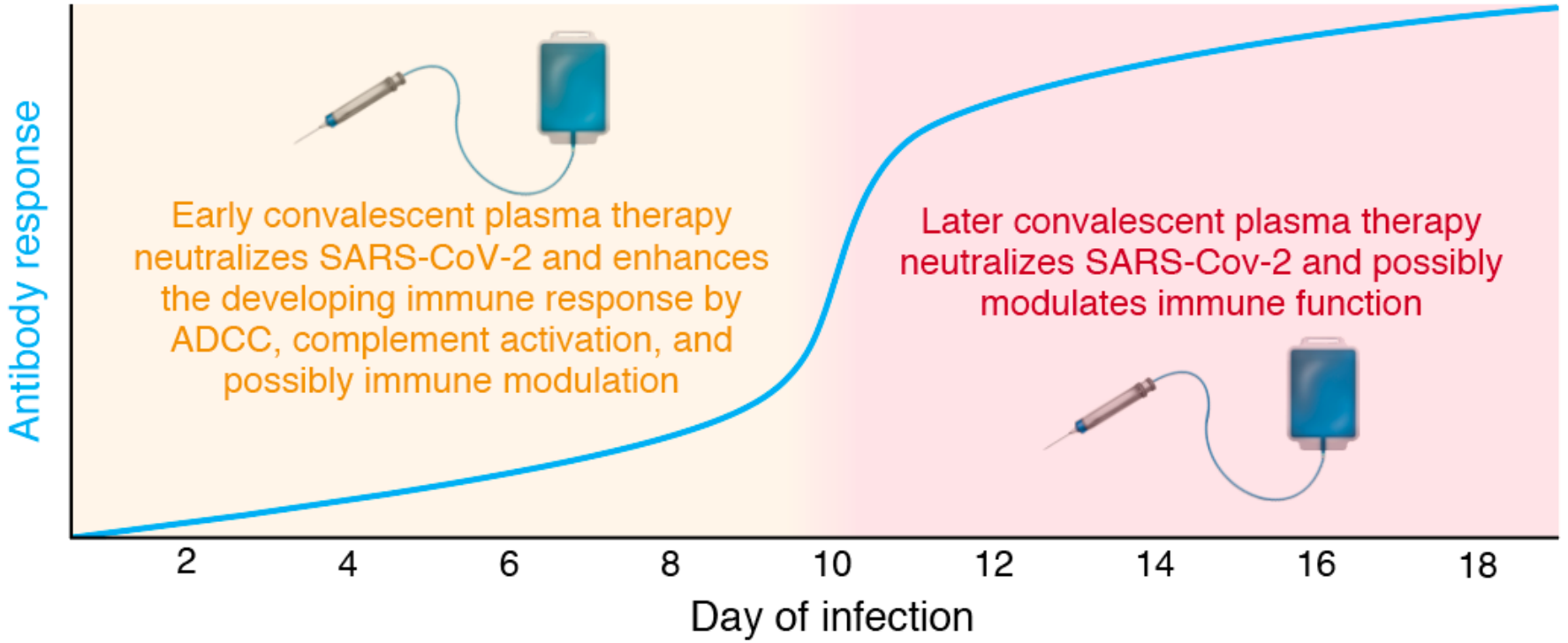
RUSSELL L. CECIL, M.D.
NEW YORK

It is a fundamental principle in all serum therapy that to obtain the best results the serum must be given early in the disease. This statement holds true regardless of whether one is using antitoxic or antibacterial serum.

Cecil JAMA 1937

Antibodies & Timing:

Conceptual Model Confirmed



Casavedall, Joyner & Pirofsky JCI in press