COVID -19 Update August 19

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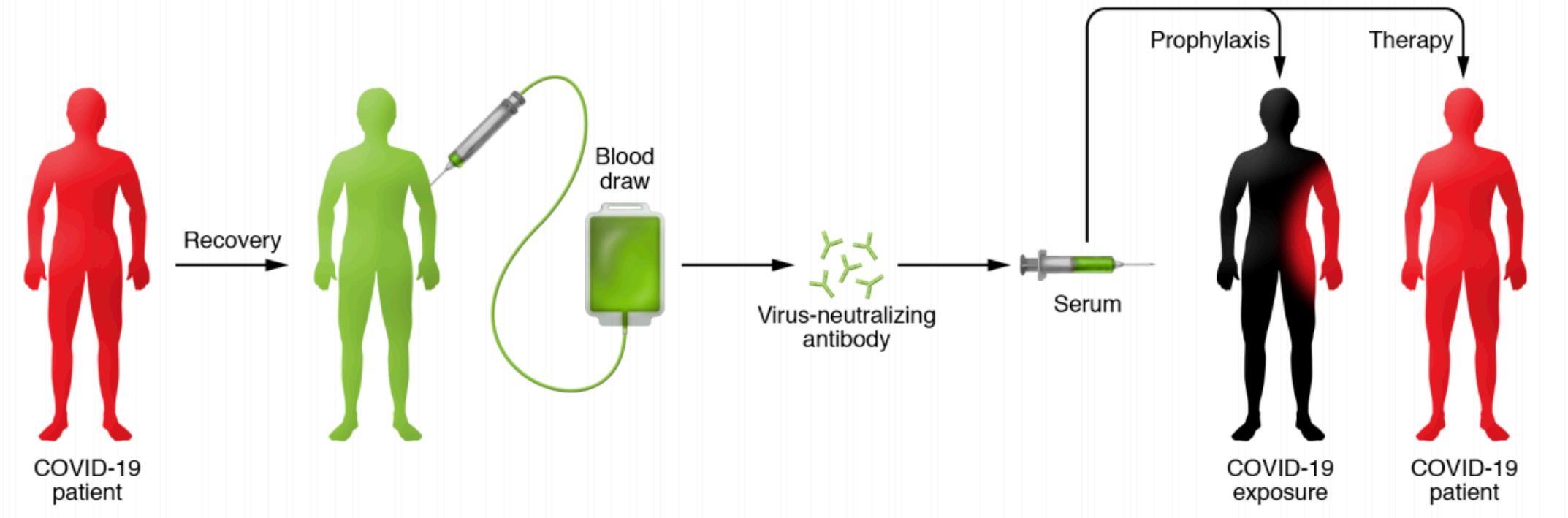
Convalescent Plasma for COVID-19

- What is convalescent plasma
- How does it work
- Historical use
- Data for COVID-19

The Convalescent Sera Option for Containing COVID-19



Passive Antibody Therapy: Administration of antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent

Casadevall A, Pirofski LA, J Clin Invest. 2020;130(4):1545-1548. https://doi.org/10.1172/JCI138003.

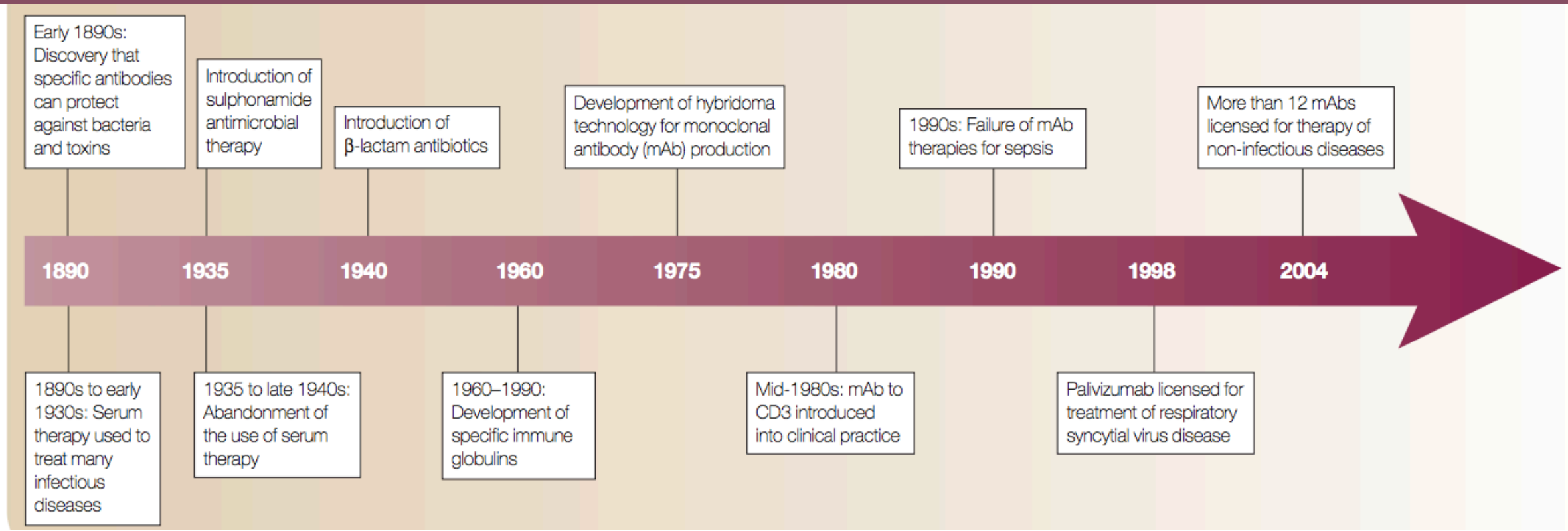
Passive Antibody Therapy

General Principles

- More effective for prophylaxis than treatment
- More effective when used early
- A sufficient amount needs to be administered
- Variables to consider
  - Volume of transfusion
  - Time to transfusion
  - Antibody titers in plasma

Historical Sequence

- Human convalescent plasma (only available now)
- Concentrates (Immunoglobulin)
  - Rabies
  - Hep B
  - RSV
  - VZV
- Monoclonal antibodies
  - (RSV; palivizumab)
- Human antibodies derived from genetically engineered cows

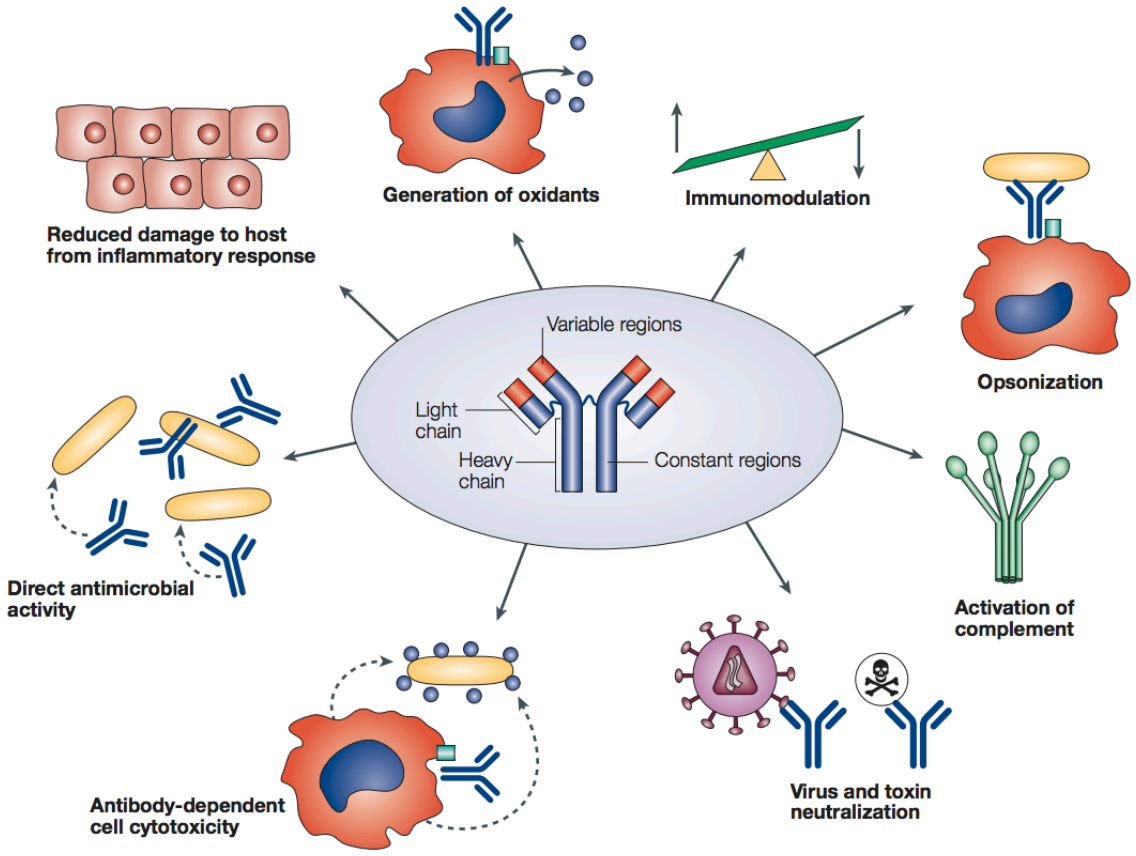


Timeline of Passive Antibody Therapy

Casadevall A, et al. Nat Rev Microbiol. 2004;2(9):695-703

PASSIVE ANTIBODY THERAPY FOR INFECTIOUS DISEASES

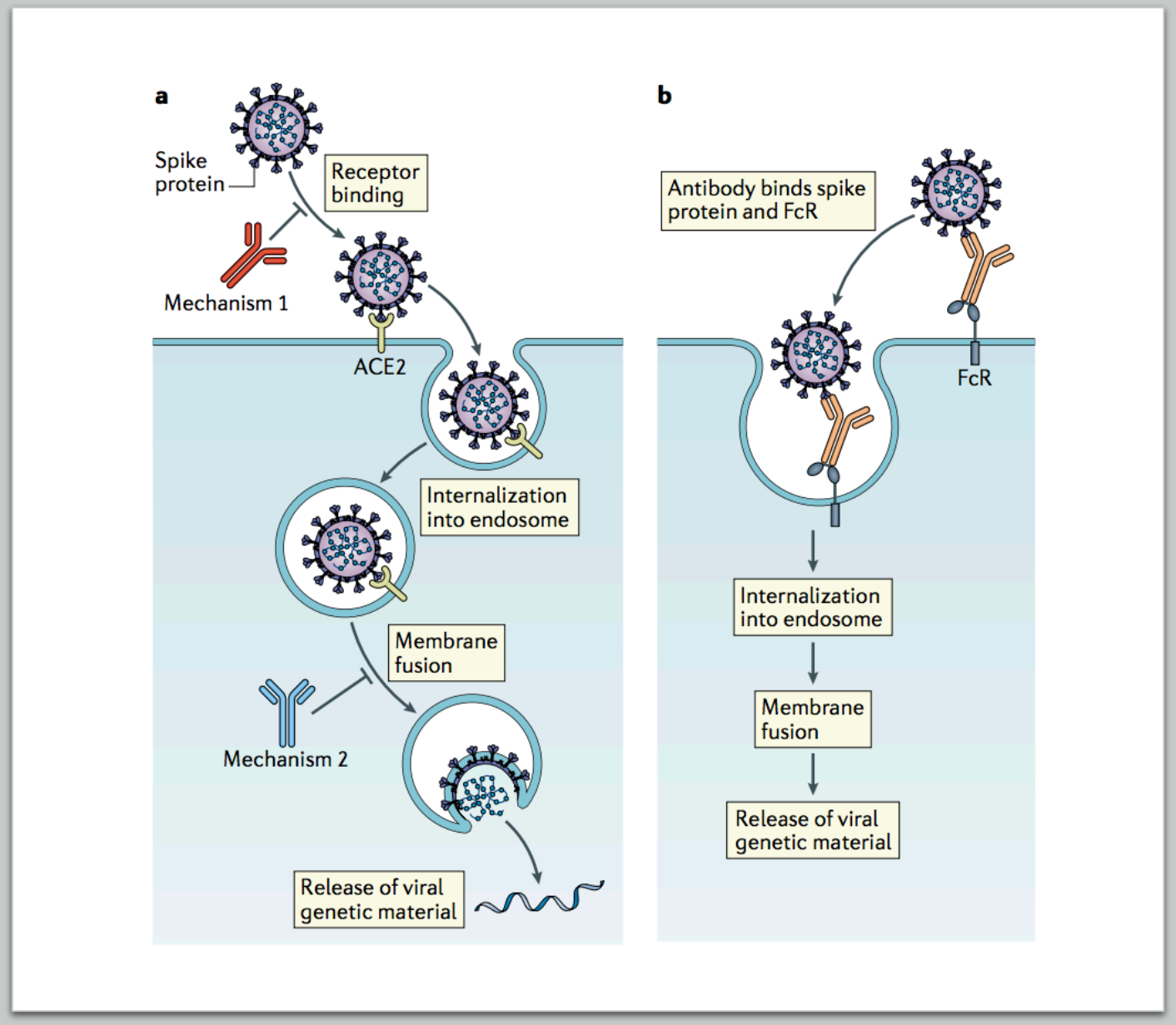
The different biological effects of antibodies. Toxin and virus neutralization, complement activation and direct antimicrobial functions such as the generation of oxidants are independent of other components of the host immune system, whereas antibody-dependent cellular cytotoxicity and opsonization depend on other host cells and mediators.



Casadevall A, et al. Nat Rev Microbiol. 2004;2(9):695-703

Passive antibody therapy in COVID-19

- Potential mechanisms of coronavirus antibody neutralization and antibody enhancement of infection. a | Mechanism
  - Neutralizing antibodies could block viral infection by binding to the viral spike protein and preventing it from interacting with the cellular receptor angiotensin-converting enzyme 2 (ACE2). Mechanism
  - Neutralizing antibodies could bind to the viral spike protein and block the conformational changes that the spike protein must undergo to facilitate fusion of the viral and host cell membranes. b | Antibodies could enhance viral entry into immune cells by binding to the viral spike protein with their Fab portion and to Fc receptors (FcRs) with their Fc domain.



Nature Reviews in Immunology , 402 | July 2020 | volume 20

PASSIVE ANTIBODY THERAPY FOR INFECTIOUS DISEASES

Table 1. Infectious diseases that were treated with antibody-based therapies in the preantibiotic era.

References	Disease	Class, organism
		Bacteria
[7]	Pneumonia	*Streptococcus pneumoniae*
[7]	Meningitis	*Neisseria meningitidis*
[8–10]	Meningitis	*Haemophilus influenzae*
[11–17]	Erysipelas; scarlet fever	Group A *Streptococcus*
[18–20]	Whooping cough	*Bordetella pertussis*
[21]	Anthrax	*Bacillus anthracis*
[22]	Botulism	*Clostridium botulinum*
[16]	Gas gangrene	*Clostridium perfringens*
[23, 24]	Tetanus	*Clostridium tetani*
[25]	Brucellosis	*Brucella abortus*
[26,27]	Dysentery	*Shigella dysenteriae*
[28]	Tularemia	*Francisella tularensis*
[11]	Diphtheria	*Corynebacterium diphtheriae*
		Viruses
[29, 30]	Measles	Measles
[31, 32]	Poliomyelitis	Poliomyelitis
[33, 34]	Mumps	Mumps
[33, 35]	Chickenpox	Varicella zoster

NOTE. This is not a complete list.

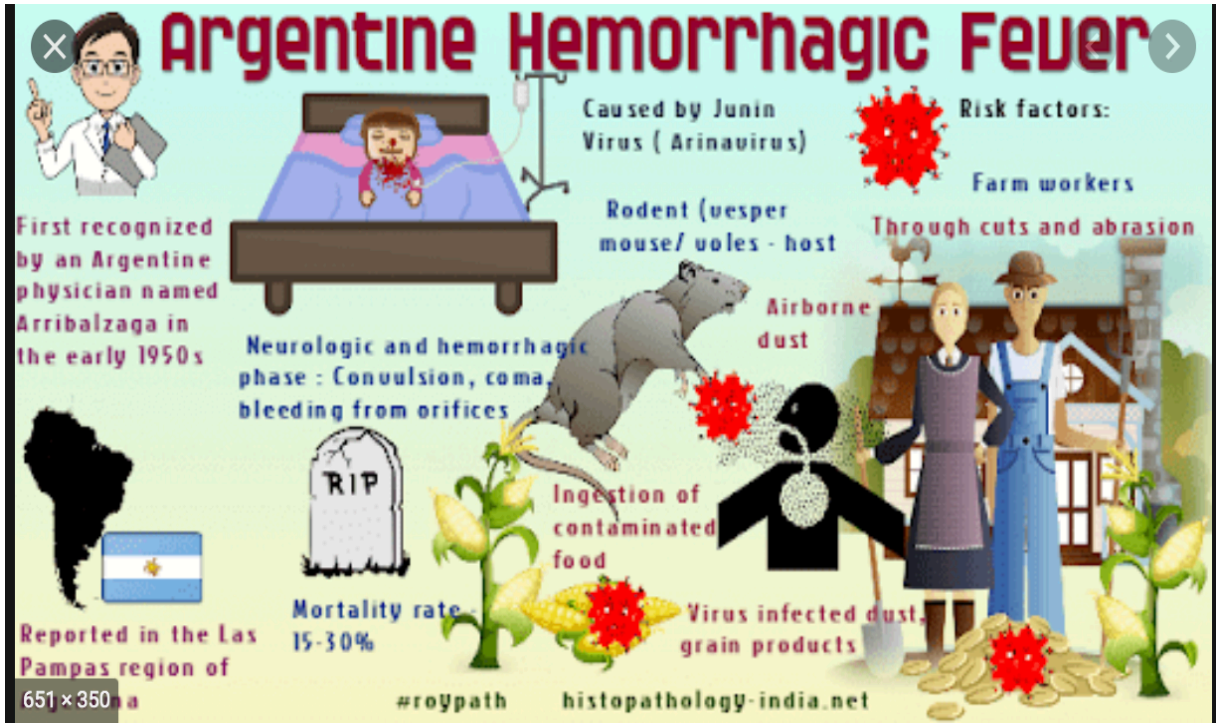
Table 2 | **Microorganisms against which antibody has been used to target human diseases***

Microorganism	Disease in humans	References
Bacillus anthracis	Anthrax	50
Bordetella pertussis	Whooping cough	51
Clostridium tetani	Tetanus	52
Clostridium botulinum	Botulism	53
Cryptococcus neoformans	Cryptococcosis	54
Cryptosporidium parvum	Cryptosporidiosis	55
Enterovirus	Gastrointestinal-tract infections	56
Group A streptococci	Several illnesses including sore throats, necrotizing fasciitis	57
Hepatitis B virus	Hepatitis B	58
Measles virus	Measles	59
Mycobacterium tuberculosis	Tuberculosis	60
Neisseria meningitidis	Meningitis	2,61
Parvovirus	Aplastic anaemia	62
Rabies virus	Rabies	63
Respiratory syncytial virus (RSV)	RSV infection	64
Streptococcus pneumoniae	Pneumonia	2
Varicella–zoster virus	Shingles, chickenpox, pneumonia	65
Variola major	Smallpox	66

*This is not a complete list.

Has Convalescent Plasma Worked in the Past?

- The best evidence comes from a randomized trial in patients with Argentine hemorrhagic fever (caused by Junin virus, an arenavirus), in which 217 patients were assigned to receive 500 mL of convalescent plasma or control plasma within eight days of symptom onset.
- Mortality was lower in the convalescent plasma group (1 versus 16.5 percent). In comparison, patients treated after nine or more days from symptom onset did not have a survival benefit.



Has Convalescent Plasma Worked in the Past?

THE RESULTS OF THE SERUM TREATMENT IN THIRTEEN HUNDRED CASES OF EPIDEMIC MENINGITIS.*

By SIMON FLEXNER, M.D.

(*From the Laboratories of The Rockefeller Institute for Medical Research, New York.*)

J Exp Med. 1913 May 1;17(5):553-76. doi: 10.1084/jem.17.5.553.

TABLE I.

Mortality of Serum-Treated Cases.

No. of cases.	Recovered.	Died.	Per cent. died.
1,294	894	400	30.9

TABLE II.

Mortality according to the Period of Injection of the Serum.

Period of injection.	No. of cases.	Recovered.	Died.	Per cent. recovered.	Per cent. died.
1st to 3d day	199	163	36	81.9	18.1
4th to 7th day	346	252	94	72.8	27.2
Later than 7th day	666	423	243	63.5	36.5
Totals	1,211	838	373	69.2	30.8

TABLE VII.

Serum-Treated Cases of the Grecian Epidemic, 1911–12.

Period of injection.	No. of cases.	Recovered.	Died.	Per cent. died.
1st to 3d day	100	87	13	13.0
4th to 7th day	54	40	14	25.9
Later than 7th day	32	17	15	47.0
Totals	186	144	42	22.6

February 27, 1937

EFFECTS OF VERY EARLY SERUM TREATMENT IN PNEUMOCOCCUS TYPE I PNEUMONIA

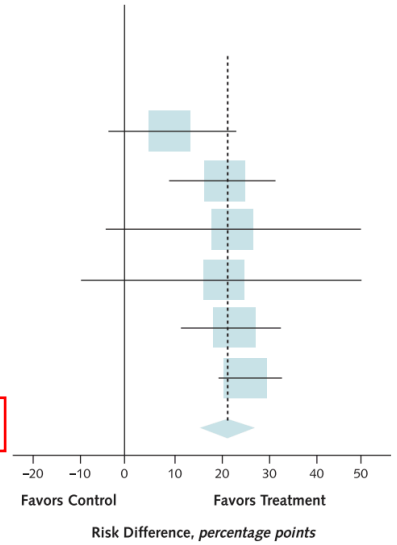
RUSSELL L. CECIL, M.D.

It is a fundamental principle in all serum therapy that to obtain the best results the serum must be given early in the disease.

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)

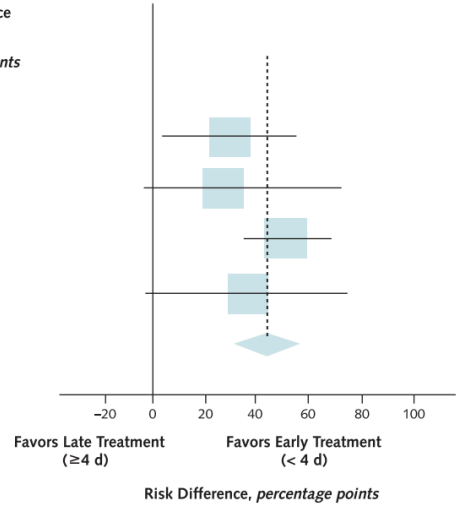


Results favor treatment with convalescent blood products ($z = 7.1$; $P < 0.001$), and there was no statistical evidence of large heterogeneity ($Q = 7.0$; $I^2 = 29.3\%$; $P = 0.22$). The pooled estimate should be interpreted with caution and should not be generalized to other strains of virulent influenza without further study. Percentages have been rounded to the nearest whole integer. *In 2 studies with low mortality rates in the treatment group, the majority of patients were treated within 48 hours after pneumonia complicating influenza was diagnosed (18, 23, 24). McGuire and Redden (23, 24) reported a range of mortality rates of 30% to 60% among controls, and 30% was used in the analysis.

Figure 3. **Absolute risk difference in mortality among patients who received early versus late treatment with convalescent blood**

Download

Study (Reference)	Mortality Rate, *n/n (%)*		Risk Difference (95% CI), *percentage points*
	Early Treatment	Late Treatment	
Stoll (17)	10/31 (32)	15/25 (60)	28 (2 to 53)
Ross and Hund (19, 20)*	3/22 (14)	2/5 (40)	26 (–2 to 72)
Sanborn (25)	6/55 (11)	28/46 (61)	50 (34 to 66)
Maclachlan and Fetter (26)	9/40 (23)	4/7 (57)	35 (–4 to 74)
Overall	28/148 (19)	49/83 (59)	41 (29 to 54)



Results favor treatment with convalescent blood products ($z = 6.50$; $P < 0.001$), and there was no statistical evidence of heterogeneity ($Q = 2.76$; $I^2 = 0\%$; $P = 0.43$). The pooled estimate should be interpreted with caution and should not be generalized to other strains of virulent influenza without further study. Percentages have been rounded to the nearest whole integer. *The treatment day of a fatal case could not be determined and was excluded from analysis of early versus late treatment (19, 20).

Annals of Internal Medicine. 2006; 145(8):599-609. doi:10.7326/0003-4819-145-8-200610170-00139

Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection FREE

Ivan FN Hung, Kelvin KW To, Cheuk-Kwong Lee, Kar-Lung Lee, Kenny Chan, Wing-Wah Yan, Raymond Liu, Chi-Leung Watt, Wai-Ming Chan, Kang-Yiu Lai ... Show more

Clinical Infectious Diseases, Volume 52, Issue 4, 15 February 2011, Pages 447–456,
https://doi.org/10.1093/cid/ciq106

Conclusions. Treatment of severe H1N1 2009 infection with convalescent plasma reduced respiratory tract viral load, serum cytokine response, and mortality.

Convalescent Plasma and COVID-19

?

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial.

Methods

- 103 patients with severe COVID-19 to receive SC plus CP or SC alone.
- **The interval between development of symptoms and plasma administration was long (median, 30 days).**
- Titer of of Ab to the spike protein (S) of 1:640 was used
- The plasma dose was approximately 4 to 13 mL/kg of recipient body weight.

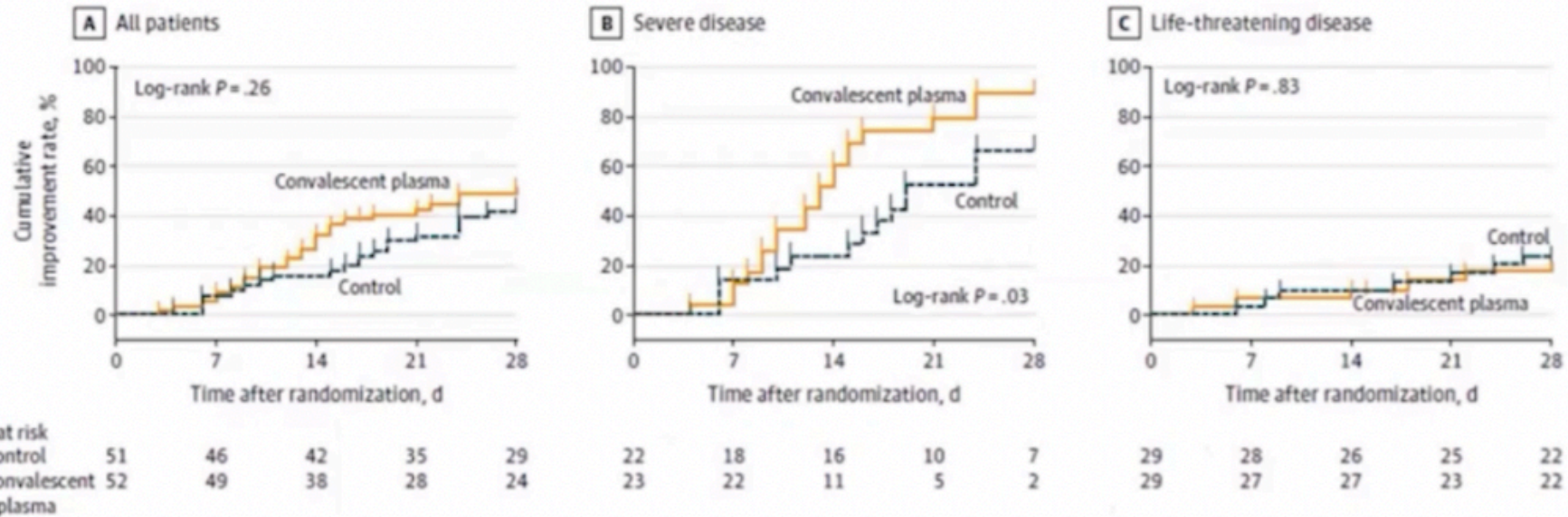
RESULTS

- Lower 28-day mortality (24 versus 16 percent; p = 0.30; odds ratio [OR] 0.59; 95% CI 0.22-1.59)
- Greater likelihood of hospital discharge by 28 days (36 versus 51 percent; p = 0.13)
- Faster improvement (2.2 days shorter; 95% CI, 5.3 days shorter to 1 day longer)
- Greater likelihood of improvement (43 versus 52 percent; hazard ratio [HR] 1.40; 95% CI 0.79-2.49)

Le et al. JAMA 2020

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial.

Figure 2. Time to Clinical Improvement in Patients With COVID-19



No. at risk															
Control	51	46	42	35	29	22	18	16	10	7	29	28	26	25	22
Convalescent plasma	52	49	38	28	24	23	22	11	5	2	29	27	27	23	22

Li et al JAMA 2020

Observational studies of convalescent plasma in cohorts of patients hospitalized with COVID-19:

- **Lower mortality** (2.2 percent, versus 4.1 percent in controls) in a study involving 138 patients treated with convalescent plasma and 1430 controls; the likelihood of clinical improvement showed a correlation with less-severe disease and a non-significant association with higher antibody titers in the plasma.
- **Lower mortality** (10 percent, versus 30 percent in controls) in a study involving 20 patients treated with convalescent plasma and 20 controls; there were no deaths in patients who received plasma prior to seven days of hospitalization.
- **Lower mortality** (6.5 percent, versus 30 percent in controls) in a study involving 46 plasma-treated individuals and 23 matched controls).
- **Reduced viral shedding** (but no effect on mortality, which was very high overall) in study involving six individuals in the intensive care unit (ICU) treated with convalescent plasma and 15 who were not.

Xia X, Li K, Wu L, et al. Blood. 2020;136(6):755.
Hegerova L, Gooley TA, Sweerus KA, et al. Blood. 2020;136(6):759.
Perotti C, Baldanti F, Bruno R, et al. Haematologica. 2020
Zeng QL, Yu ZJ, Gou JJ, J Infect Dis. 2020;222(1):38.
Bloch EM SOBlood. 2020;136(6):654.

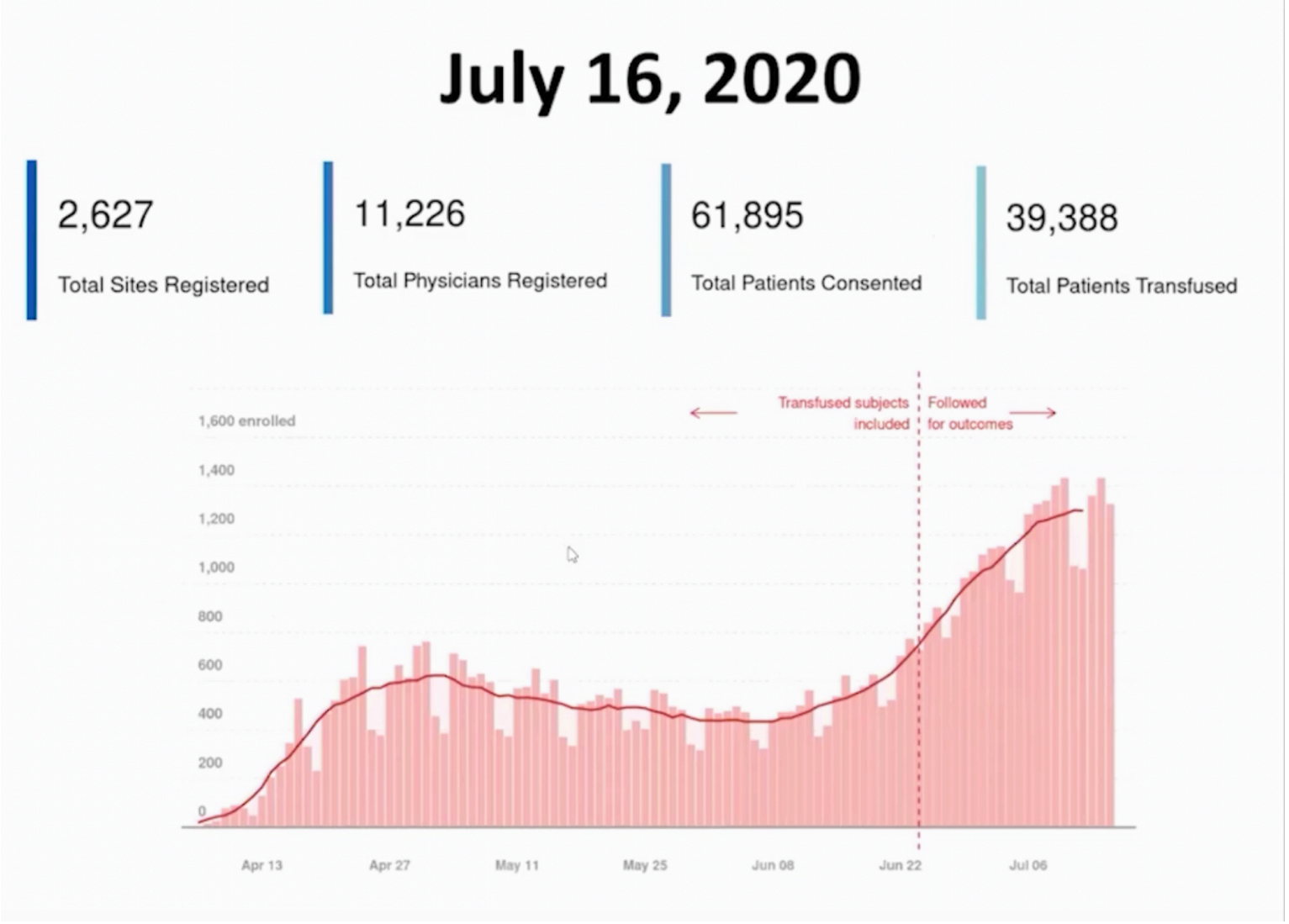
Convalescent Plasma and COVID-19

Seven RCTs or Controlled Case Series Report Reduced Mortality

Study	Location	Type	CP (Alive/Dead)	Control (Alive/Dead)	Mortality	P value (Chi Square)
Li et al. (1)	Wuhan	RCT (Terminated early)	43/8 (18%)	38/12 (32%)	-43%	0.295
Gharbharan et al. (2)	Netherlands	RCT (Terminated early)	37/6 (16%)	32/11 (34%)	-53%	0.176
Rhasheed et al. (3)	Iraq	RCT	20/1 (5%)	20/8 (40%)	-88%	0.033
Liu et al. (4)	Sinai, NYC, USA	Matched controls	35/5 (14%)	118/38 (32%)	-43%	0.120
Perotti et al. (6)	Pavia, Italy	Matched controls	40/3 (7.5%)	16/7 (43%)	-82%	0.11
Xia et al. (7)	Nanjing, China	Matched controls	135/3 (2%)	1371/51 (3.7%)	-54%	0.056
Yoon et al (8)	Bronx, NY	Matched Controls	74/29 (39%)	337/206 (61%)	-36%	0.059
Total (minus Xia, outlier with very low mortality)			254/52 (20%)	563/282 (50%)	-40%	0.00001
Salazar et al (8)	Houston TX	Case Series	24/1	NA		NA
Hartman et al. (9)	Madison, USA	Case Series	27/1	NA		NA

[1] Li et al JAMA 2020; [2] medRxiv https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1; [3] medRxiv https://doi.org/10.1101/2020.06.24.20121905
[4] medRxiv https://doi.org/10.1101/2020.05.20.20102236; [5] medRxiv https://doi.org/10.1101/2020.06.04.20119784
[6] medRxiv https://doi.org/10.1101/2020.05.26.20113373; [7] medRxiv https://doi.org/10.1101/2020.06.19.20135830
[8] Blood. 2020 Jun 19. pii: blood.2020006964. doi: 10.1182/blood.2020006964; [9] Blood. 2020 J un 23. pii: blood.2020007079. doi: 10.1182/blood.2020007079

Mayo Clinic COVID-19 Convalescent Plasma Program



Effect of Convalescent Plasma (CP) on Mortality among 2 Hospitalized Patients with COVID-19: Initial Three-Month Experience

medRxiv preprint doi: https://doi.org/10.1101/2020.08.12.20169359.this version posted August 12, 2020

- **Objective**: To explore signals of efficacy of COVID-19 CP.
- **Design**: Open-label, Expanded Access Program for the treatment of COVID-19 patients with human CP.
- **Setting:** Multicenter, including 2,807 acute care facilities in the US and territories.
- **Participants:** Adult participants enrolled and transfused with CP between April 4 and July 4, 2020 who were hospitalized with (or at risk of) severe or life threatening acute COVID-19 respiratory syndrome.
- **Intervention**: Transfusion of at least one unit of human COVID-19 convalescent plasma during hospitalization.

Effect of Convalescent Plasma (CP) on Mortality among 2 Hospitalized Patients with COVID-19: Initial Three-Month Experience: RESULTS: N= 35,322 Patients Transfused

- High proportion of critically-ill patients
  - 52.3% in the intensive care unit (ICU)
  - 27.5% receiving mechanical ventilation at the time of plasma transfusion.
- **The 7-day mortality rate**
  - **8.7%** [95% CI 8.3%-9.2%] in patients transfused within 3 days of COVID-19 diagnosis
  - **11.9%** [11.4%-12.2%] in patients transfused 4 or more days after diagnosis
- The 30-day mortality 21.6% vs. 26.7%, $p<0.0001$
- **Mortality in relation to IgG antibody levels** in the transfused plasma.
  - High IgG plasma seven-day mortality was **8.9%** (6.8%, 11.7%)
  - Medium IgG plasma mortality was **11.6%** (10.3%, 13.1%)
  - Low IgG plasma mortality was **13.7%** (11.1%, 16.8%) (p=0.048)

Table 2: Early safety indicators of COVID-19 convalescent plasma in 5000 patients

Table 2. Serious adverse event characteristics (*n* = 5,000)

Four-hour reports	Reported (*n* = 36)	Related[A] (*n* = 25)	Estimate (95% CI)
Mortality	15	4	0.08% (0.03%, 0.21%)
Transfusion-associated circulatory overload	7	7	0.14% (0.07%, 0.29%)
Transfusion-related acute lung injury	11	11	0.22% (0.12%, 0.39%)
Severe allergic transfusion reaction	3	3	0.06% (0.02%, 0.18%)
Seven-day reports			
Mortality	602		14.9% (13.8%, 16.0%)[B]

[A]This category of serious adverse events (SAE) reports the aggregate total of possibly, probably and definitely related SAEs, as attributed based on the site investigator's determination. The estimate is based on the number of related SAEs relative to the denominator of 5,000. [B]The estimated 7-day mortality rate is based on a Kaplan-Meier estimate using all reported deaths. See Methods for further estimation details including handling of censoring due to ongoing data collection.

RESULTS. The incidence of all serious adverse events (SAEs), including mortality rate (0.3%), in the first 4 hours after transfusion was <1%. Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (*n* = 4), transfusion-associated circulatory overload (*n* = 7), transfusion-related acute lung injury (*n* = 11), and severe allergic transfusion reactions (*n* = 3). However, only 2 of 36 SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. The 7-day mortality rate was 14.9%.
CONCLUSION. Given the deadly nature of COVID-19 and the large population of critically ill patients included in these analyses, the mortality rate does not appear excessive. These early indicators suggest that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19.

J Clin Invest DOI: 10.1172/JCI140200

Conclusions

- Convalescent Plasma may work for COVID-19
    - If it works, the earlier it is given the better
    - If it works, the higher titers of antibodies against SARS-COV-2 the better
- Convalescent Plasma for COVID-19 seems to be safe
- Randomized trials are ongoing
- Until we have an effective vaccine it is the only immunotherapy available