Convalescent plasma for COVID-19

Mountain States COVID-19 Infectious Disease ECHO Program
September 29, 2020

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COVID-19 convalescent plasma (CCP)

- **What is it?** Plasma donated from a patient recently recovered from COVID-19 that contains antibodies to the SARS-CoV-2 virus

- **Rationale:** When administered to patients exposed to or infected with SARS-CoV-2, antibodies in CCP neutralize the virus and 1) protect from infection or 2) prevent/mitigate progression of existing infection

Limitations and caveats

- Observational studies > randomized trials
- Randomized trials underpowered
- Not all studies peer reviewed
- Heterogeneity of patients and treatment
- Rapidly emerging literature

Early reports out of China

JAMA | Preliminary Communication

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Chenguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; Yang Yang, MD; Jinxiu Li, MD; Jing Yuan, MD; Fuxiang Wang, MD; Delin Li, PhD; Minghui Yang, PhD; Li Xing, MM; Jinli Wei, MM; Haixia Xiao, PhD; Yan Yang, MM; Jiuxin Qu, MD; Ling Qing, MM; Li Chen, MD; Zhixiang Xu, MM; Ling Peng, MM; Yanjie Li, MM; Haixia Zheng, MM; Feng Chen, MM; Kun Huang, MM; Yujing Jiang, MM; Dongjing Liu, MD; Zheng Zhang, MD; Yingxia Liu, MD; Lei Liu, MD

Published online March 27, 2020

Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Bin Zhang, MD, PhD; Shuyi Liu, MD, PhD; Tan Tan, MD; Wenhui Huang, MD, PhD; Yuhao Dong, MD; Luyan Chen, MD; Qiuying Chen, MD; Lu Zhang, MD, PhD; Qingyang Zhong, MD; Xiaoping Zhang, MD, PhD; Yujian Zou, MD; and Shuixing Zhang, MD, PhD

Chest , published online March 31, 2020

Effectiveness of convalescent plasma therapy in severe COVID-19 patients

Kai Duan[a,b,1], Bende Liu[c,1], Cesheng Li[d,1], Huajun Zhang[e,1], Ting Yu[f,1], Jieming Qu[g,h,i,1], Min Zhou[g,h,i,1], Li Chen[j,1], Shengli Meng[b], Yong Hu[d], Cheng Peng[e], Mingchao Yuan[k], Jinyan Huang[l], Zejun Wang[b], Jianhong Yu[d], Xiaoxiao Gao[e], Dan Wang[k], Xiaoqi Yu[m], Li Li[b], Jiayou Zhang[b], Xiao Wu[d], Bei Li[e], Yanping Xu[g,h,i], Wei Chen[b], Yan Peng[d], Yeqin Hu[b], Lianzhen Lin[d], Xuefei Liu[g,h,i], Shihe Huang[b], Zhijun Zhou[d], Lianghao Zhang[b], Yue Wang[d], Zhi Zhang[b], Kun Deng[d], Zhiwu Xia[b], Qin Gong[d], Wei Zhang[d], Xiaobei Zheng[d], Ying Liu[d], Huichuan Yang[a], Dongbo Zhou[a], Ding Yu[a], Jifeng Hou[n], Zhengli Shi[e], Saijuan Chen[l], Zhu Chen[l,2], Xinxin Zhang[m,2], and Xiaoming Yang[a,b,2]

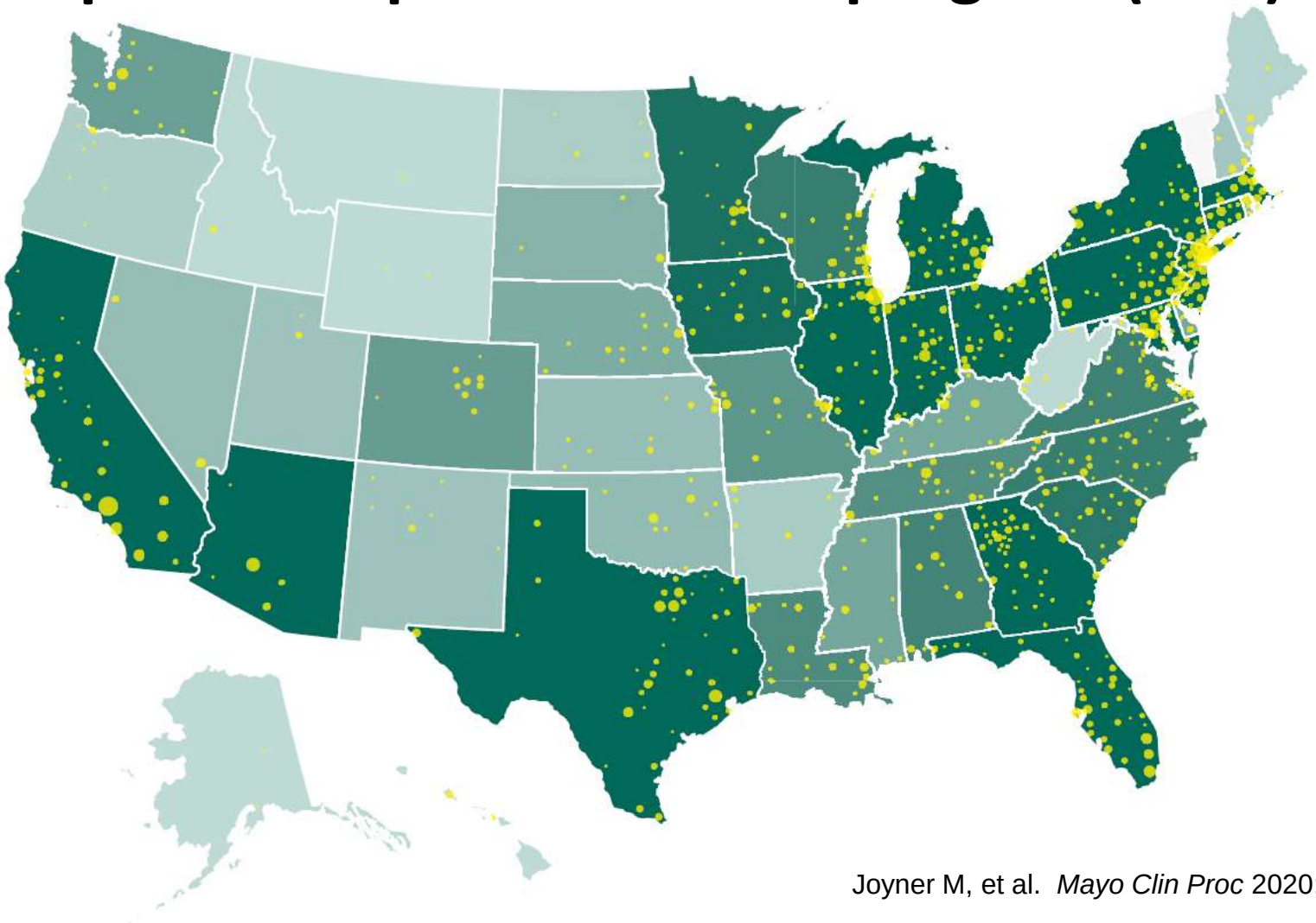
PNAS, first published April 6, 2020

National expanded access program (EAP)

- FDA-initiated, national, multicenter, open-label program to provide access to CCP
- Eligibility criteria:
  - Age ≥18 years
  - Hospitalized with a laboratory-confirmed SARS-CoV-2
  - Severe or life-threatening COVID-19 or judged by provider to be at high risk of progression
- Pre-specified plan to create control comparator group to evaluate efficacy

Joyner M, et al. *Mayo Clin Proc* 2020; 95:1888

Participation in the US COVID-19 convalescent plasma expanded access program (EAP)



Joyner M, et al. *Mayo Clin Proc* 2020; 95:1888

Daily CCP administrations under the national expanded access program (EAP)

Joyner M, et al. medRxiv preprint, posted Aug 12, 2020 https://doi.org/10.1101/2020.08.

Who has been receiving CCP in the U.S.?

Patient characteristics

- 60% ≥60 years old
- 61% male
- 20% Black, 5% Asian
- 35% Hispanic or Latino

	April	May	Total
Characteristic			
N	6214	13,786	20,000
Clinical status			
Current severe or life-threatening COVID-19	4963 (79.9)	9274 (67.3)	14,237 (71.2)
High risk of severe or life-threatening COVID-19	1251 (20.1)	4512 (32.7)	5763 (28.8)
Intensive care unit admission	4038 (65.0)	7522 (55.0)	11,560 (58.1)
Mechanical ventilation[c]	2709 (48.5)	4155 (30.4)	6864 (35.6)

Adapted from Joyner M, et al. *Mayo Clin Proc* 2020; 95:1888

Safety Indicators of COVID-19 Convalescent Plasma in 20,000 Patients

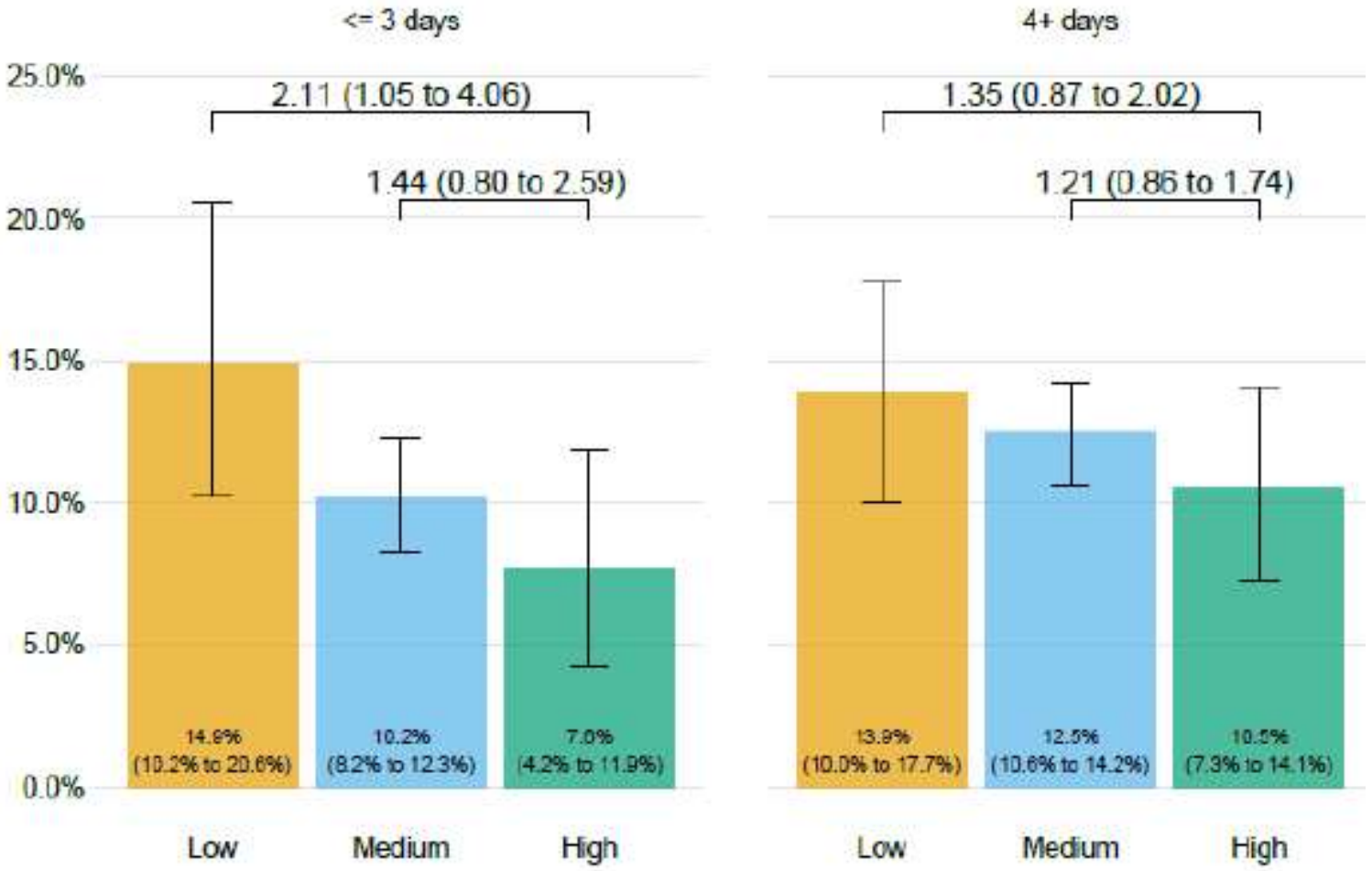
TABLE 2. SAE Characteristics in Patients Transfused With COVID-19 Convalescent Plasma (N=20,000)[a]

SAE: Transfusion reactions	Reported	Related	% Estimate[b] (95% CI)
Mortality within four hours of transfusion	63	10	0.05 (0.03-0.09)
TACO	36	36	0.18 (0.13-0.25)
TRALI	21	21	0.10 (0.07-0.16)
Severe allergic transfusion reaction	21	21	0.10 (0.07-0.16)
7-day SAE reports			
Thrombolic or thromboembolic complication	113	38	0.19 (0.14-0.26)
Sustained hypotension[c]	457	54	0.27 (0.21-0.35)
Cardiac events[d]	677	80	0.40 (0.32-0.50)

Joyner M, et al. *Mayo Clin Proc* 2020; 95:1888

Mortality after CCP infusion by antibody titer and time to infusion

7-day mortality



Joyner M, et al. medRxiv preprint, posted August 12th
https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1

JAMA | Original Investigation

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

Ling Li, MD, PhD; Wei Zhang, MD; Yu Hu, MD, PhD; Xunliang Tong, MD, PhD; Shangen Zheng, MD; Juntao Yang, PhD; Yujie Kong, MD; Lili Ren, PhD; Qing Wei, MD; Heng Mei, MD, PhD; Caiying Hu, MD; Cuihua Tao, MD; Ru Yang, MD; Jue Wang, MD; Yongpei Yu, PhD; Yong Guo, PhD; Xiaoxiong Wu, MD; Zhihua Xu, MD; Li Zeng, MD; Nian Xiong, MD; Lifeng Chen, MD; Juan Wang, MD; Ning Man, MD; Yu Liu, PhD; Haixia Xu, MD; E. Deng, MS; Xuejun Zhang, MS; Chenyue Li, MD; Conghui Wang, PhD; Shisheng Su, PhD; Linqi Zhang, PhD; Jianwei Wang, PhD; Yanyun Wu, MD, PhD; Zhong Liu, MD, PhD

- Open-label RCT at 7 hospitals in Wuhan, China
- Target enrollment of 200 patients with severe or life-threatening COVID-19
- Primary endpoint: clinical improvement at 28 days
- Study terminated after 103 patients enrolled

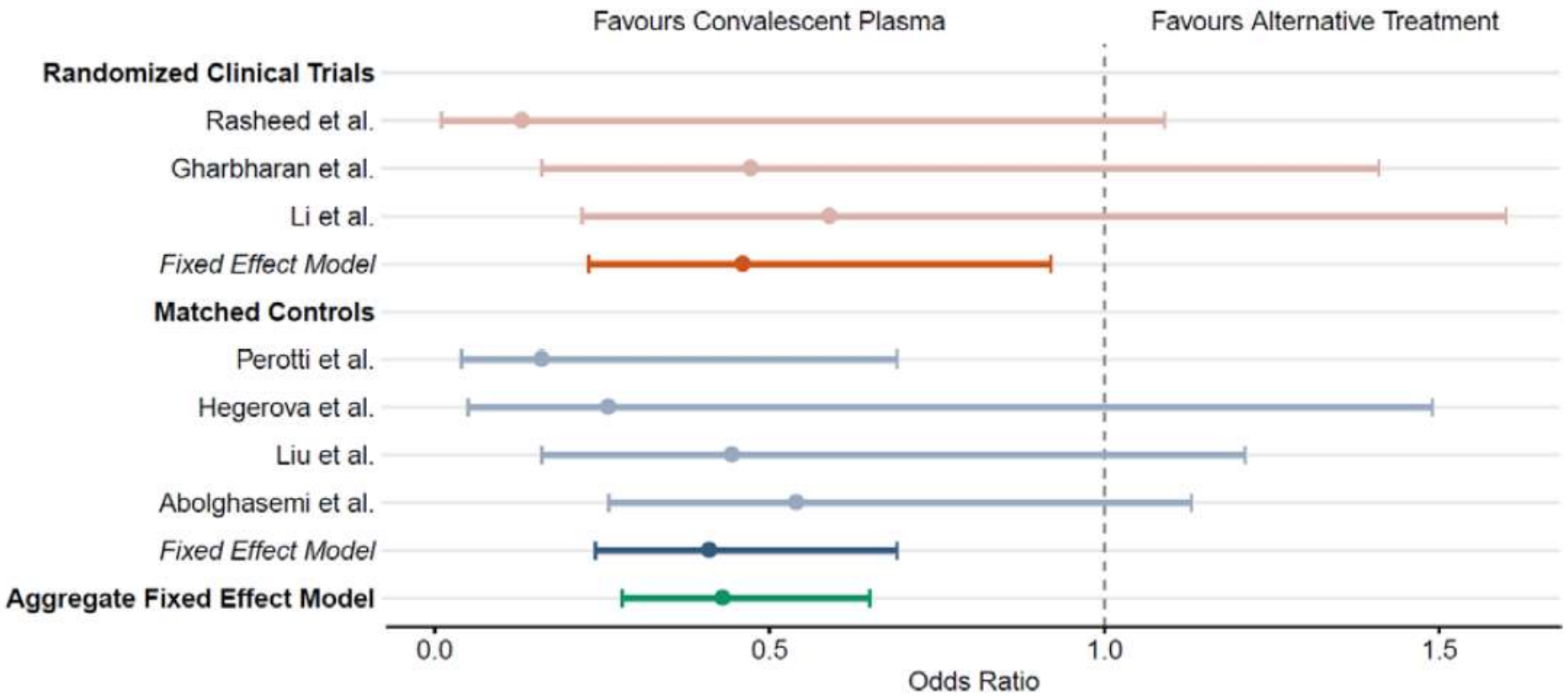
JAMA 2020; 324:460 (published online June 3rd)

Clinical outcomes

	Convalescent plasma (n = 52)	Control (n = 51)	*P*
Primary			
Clinical improvement (28 days)	51.9%	43.1%	.37
Secondary			
Discharge rate (28 days)	51%	36%	.13
Death (28 days)	15.7%	24%	.3
Time to viral clearance (3 days)	87.2%	37.5%	<.001

Adapted from Li et al. JAMA 2020; 324:460

Meta-analysis of the effect of CCP on mortality in COVID-19



Adapted from Joyner M et al. medRxiv preprint (published online July 30th)
https://doi.org/10.1101/2020.07.29.20162917

FDA Emergency Use Authorization
August 23, 2020

- Indication: hospitalized patients with COVID-19
- No specific clinical criteria put forth (intubated or non-intubated)
- High antibody titer CCP recommended
- Treat prior to intubation and within 3 days of diagnosis when possible
- Dose 1 unit (about 200mL), additional units based on provider judgment

Giving CCP under the FDA EUA[1]

1. Discuss investigational nature and potential risks, benefits, and alternatives with patient
2. FDA Fact Sheets available to patients and providers[2,3]
3. Document the consent process
4. Institutional consent for blood products
5. Report serious adverse events or deaths potentially attributable to CCP

1) https://www.fda.gov/media/141477/download
2) https://www.fda.gov/media/141479/download
3) https://www.fda.gov/media/141478/download

National guideline recommendations

Infectious Diseases Society of America[1]

"Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap)"

National Institutes of Health[2]

"There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19."

1) https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (last updated 9/4/2020)
2) https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/blood-derived-products/convalescent-plasma/ (last updated 7/17/20)

Unanswered questions

- Is it safe and does it improve outcomes in adequately powered randomized trials?
- What is the incremental benefit over corticosteroids and remdesivir, if any?
- In what patient populations should it be used?
- What is the optimal timing?
- What is the necessary antibody titer?
- What is the optimal volume?

Randomized trials in process

Passive Immunity Trial for Our Nation (PASSItOn)

- Setting: 51 U.S. hospitals
- Population: adults hospitalized with COVID-19
- Intervention: CCP vs. placebo
- Primary outcome: clinical status at day 15 by the COVID ordinal outcomes scale
- Sample size: 1000 patients
- Estimated completion: April 2021

Clinicaltrials.gov (accessed 9/19/20)

Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO)

- Setting: 50 hospital emergency departments
- Population:
  - adults presenting with mild, symptomatic COVID-19
  - risk for progression to severe disease
  - clinically stable for outpatient management
- Intervention: CCP vs. placebo
- Primary outcome: disease progression at 15 days
- Sample size: 600 patients
- Estimated completion: December 2022

Clinicaltrials.gov (accessed 9/19/20)

Summary

- Current clinical data are suggestive, but do not prove, that CCP is safe and may improve clinical outcomes
- Recently granted FDA emergency use approval
- Numerous unanswered questions require adequately powered randomized trials

Thank you

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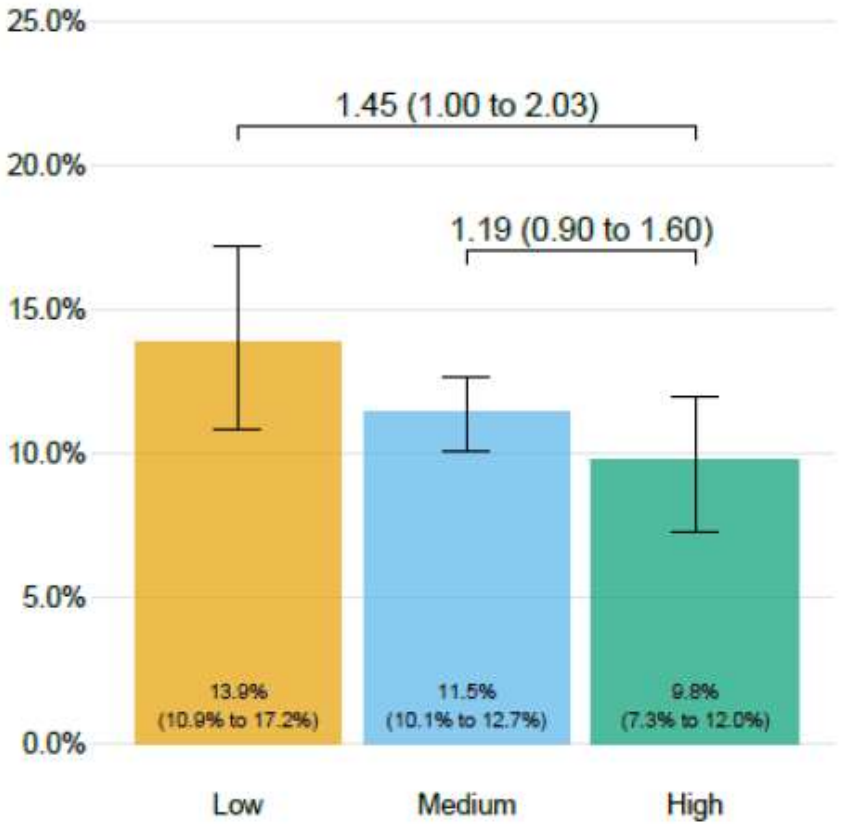
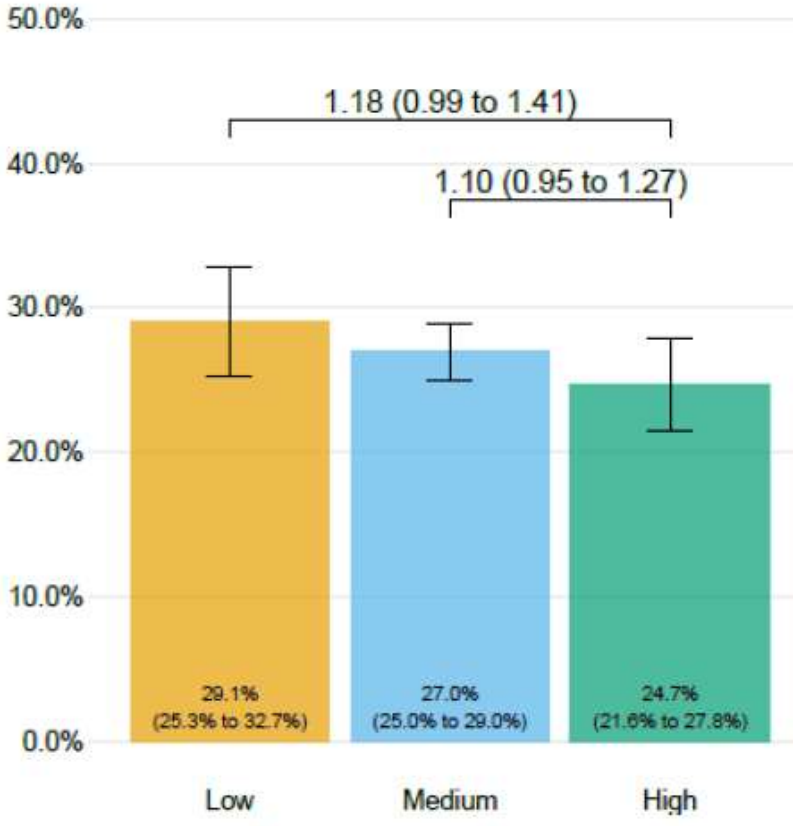
Mortality after CCP infusion by antibody levels

7-day mortality



30-day mortality



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https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1

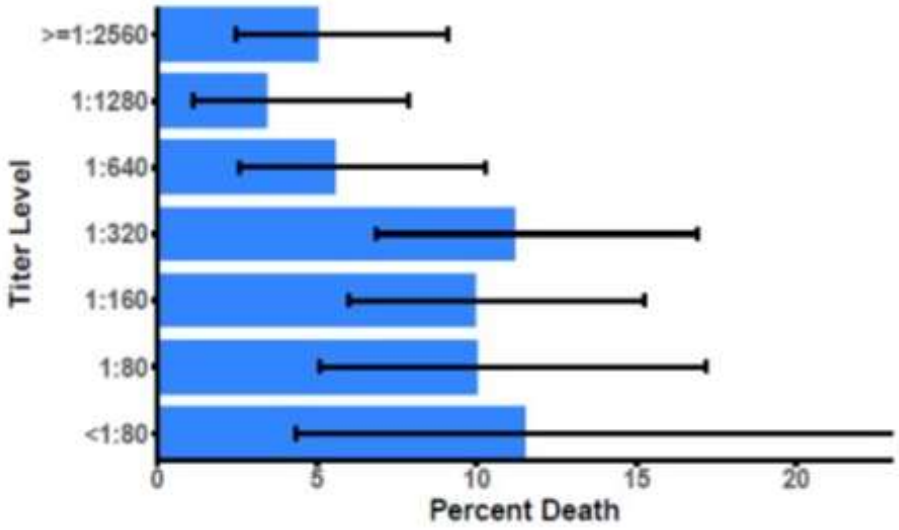
Meta-analysis of the effect of CCP on mortality in COVID-19

	# studies	# subjects	Convalescent plasma	Control	OR	*P*
Randomized trials	3	236	13%	26%	.46	.03
Matched control studies	4	494	12%	25%	.41	.001
Aggregate of controlled studies	**7**	**730**	**13%**	**25%**	**.43**	**<.001**

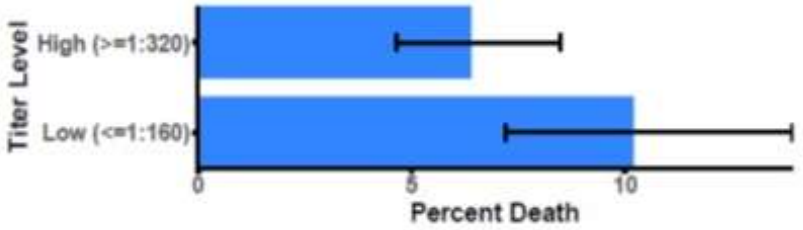
Adapted from Joyner M et al. medRxiv preprint, published online July 30th https://doi.org/10.1101/2020.07.29.20162917

COVID-19 Convalescent Plasma Reduction in Death at 7 Days

Non-intubated patients treated within 72 h age 80 or less (n=1018)



Statistically significant 37% reduction in mortality in those treated with high titer convalescent plasma (p=.03)



High titer corresponds approximately to Ortho VITROS S/C level ≥ 12

www.fda.gov

https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment#:~:text=Today%2C%20the%20U.S.%20Food%20and,efforts%20to%20fight%20COVID%2D19.