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Exciting biological insights and findings

COVID-19 Therapeutics in 2022

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Disclosures

- None

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Safe in 5,000: <1% transfusion-associated reactions

The Journal of Clinical Investigation CLINICAL MEDICINE

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

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Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients

Abstract

Objective: To provide an update on key safety metrics after transfusion of convalescent plasma in hospitalized coronavirus 2019 (COVID-19) patients, having previously demonstrated safety in 5000 hospitalized patients.

Patients and Methods: From April 3 to June 2, 2020, the US Food and Drug Administration Expanded Access Program for COVID-19 convalescent plasma transfused a convenience sample of 20,000 hospitalized patients with COVID-19 convalescent plasma.

Results: The incidence of all serious adverse events was low; these included transfusion reactions (n=78; <1%), thromboembolic or thrombotic events (n=113; <1%), and cardiac events (n=677, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=75) and cardiac events (n=597) were judged to be unrelated to the plasma transfusion per se. The 7-day mortality rate was 13.0% (12.5%, 13.4%), and was higher among more critically ill patients relative to less ill counterparts, including patients admitted to the intensive care unit versus those not admitted (15.6 vs 9.3%), mechanically ventilated versus not ventilated (18.3% vs 9.9%), and with septic shock or multiple organ dysfunction/failure versus those without dysfunction/failure (21.7% vs 11.5%).

Conclusion: These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

 ■ Mayo Clin Proc. 2020;95(9):1888-1897

Is CCP therapeutic?

And if so, by what mechanism?

CCP = 1,000+ proteins

CCP

- SARS-CoV-2 nAb
- Ab
- Cytokines
- Sugars/glycans
- EVs
  - -microRNAs (miRs)
  - -other??

viruses

Viruses 2021, 13, 1594 MDPI

Review

COVID-19 Convalescent Plasma Is More Than Neutralizing Antibodies: A Narrative Review of Potential Beneficial and Detrimental Co-Factors

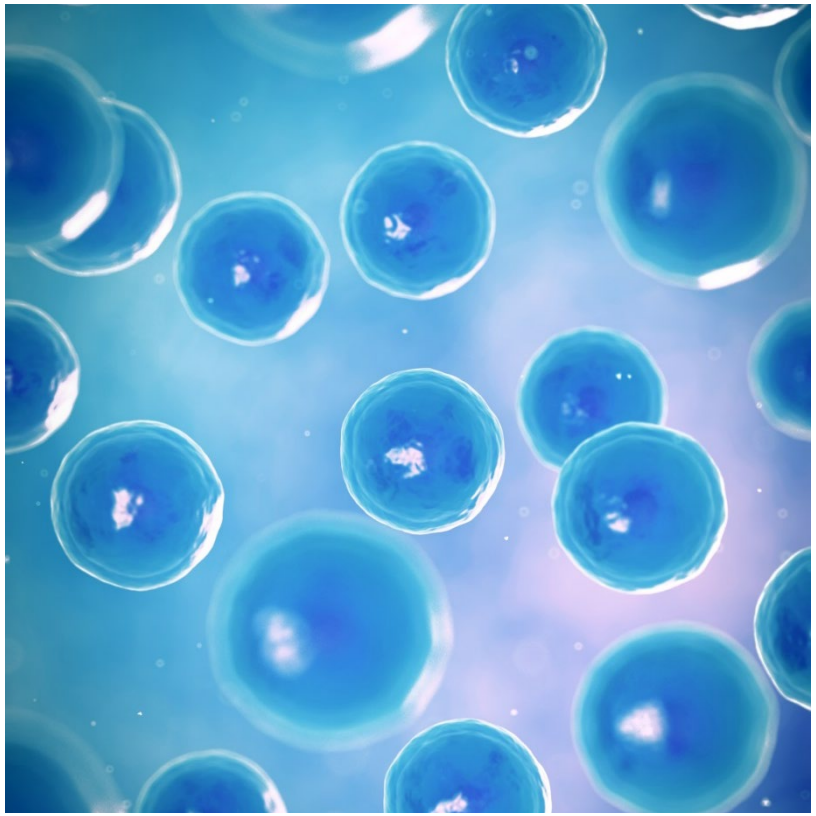
Daniele Focosi [1,*], Massimo Franchini [2], Liise-anne Pirofski [3], Thierry Burnouf [4], DeLisa Fairweather [5], Michael J. Joyner [6] and Arturo Casadevall [7]

Protective effects of CCP

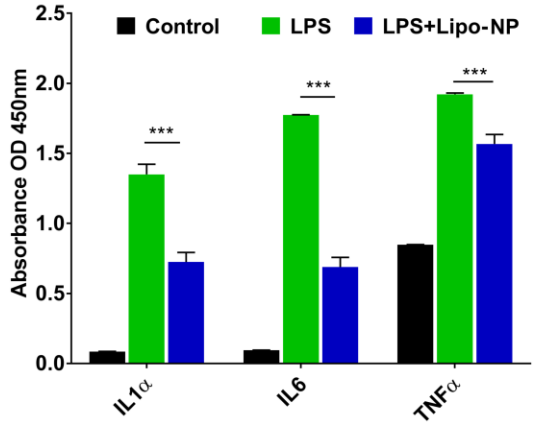
- Anti-viral
- Anti-thrombotic
- Anti-inflammatory

Detrimental effects of CCP

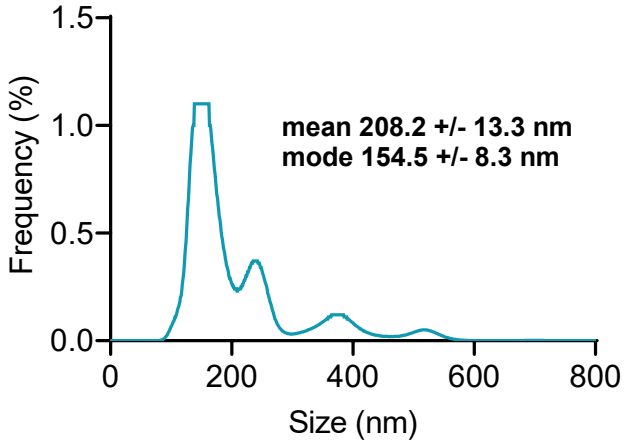
- Pro-viral
- Pro-thrombotic
- Pro-inflammatory

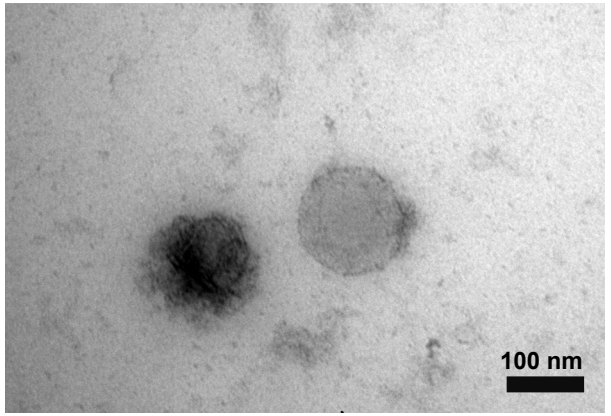


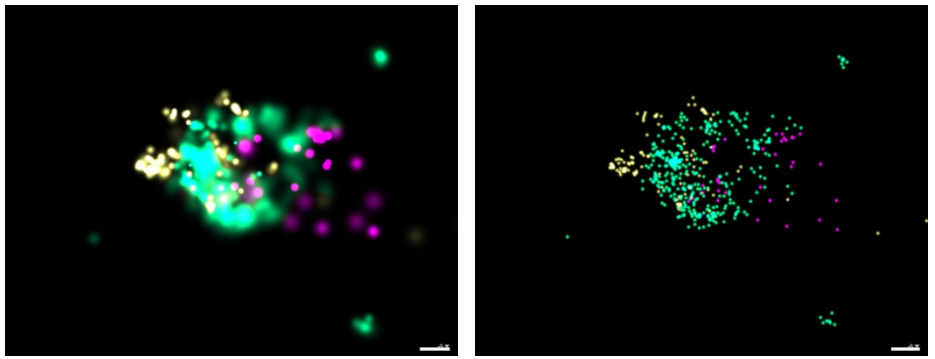
Protective effects of Extracellular Vesicles



- EVs composed of lipid bilayer with internal core
- Contain wide variety of lipids, carbohydrates, proteins, nucleic acids
- Exosomes 30-100 nm vs. microvesicles bud from cell 50-1K nm
- EVs shown in culture (RAW mac) and animal studies to suppress inflammation, oxidative and apoptotic pathways via microRNAs (miRs)







CD9 (yellow), CD81 (teal), CD63 (purple)

Anti-viral factors in CCP

- **Anti-viral**
  - Neutralizing Ab
    - From previous COVID infection
    - From COVID vaccine
    - From a different infection
    - From a different vaccine
  - ACE2+ EVs- act as decoy receptors
  - Factor Xa (FXa)- blood clotting cascade

ORIGINAL ARTICLE

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

M.J. Joyner, R.E. Carter, J.W. Senefeld, S.A. Klassen, J.R. Mills, P.W. Johnson, E.S. Theel, C.C. Wiggins, K.A. Bruno, A.M. Klompas, E.R. Lesser, K.L. Kunze, M.A. Sexton, J.C. Diaz Soto, S.E. Baker, J.R.A. Shepherd, N. van Helmond, N.C. Verdun, P. Marks, C.M. van Buskirk, J.L. Winters, J.R. Stubbs, R.F. Rea, D.O. Hodge, V. Herasevich, E.R. Whelan, A.J. Clayburn, K.F. Larson, J.G. Ripoll, K.J. Andersen, M.R. Buras, M.N.P. Vogt, J.J. Dennis, R.J. Regimbal, P.R. Bauer, J.E. Blair, N.S. Paneth, D.L. Fairweather, R.S. Wright, and A. Casadevall

ABSTRACT

BACKGROUND

Convalescent plasma has been widely used to treat coronavirus disease 2019 (Covid-19) under the presumption that such plasma contains potentially therapeutic antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can be passively transferred to the plasma recipient. Whether convalescent plasma with high antibody levels rather than low antibody levels is associated with a lower risk of death is unknown.

METHODS

In a retrospective study based on a U.S. national registry, we determined the anti–SARS-CoV-2 IgG antibody levels in convalescent plasma used to treat hospitalized adults with Covid-19. The primary outcome was death within 30 days after plasma transfusion. Patients who were enrolled through July 4, 2020, and for whom data on anti–SARS-CoV-2 antibody levels in plasma transfusions and on 30-day mortality were available were included in the analysis.

RESULTS

Of the 3082 patients included in this analysis, death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. The association of anti–SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32).

CONCLUSIONS

Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Joyner at the Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at joyner.michael@mayo.edu.

Drs. Joyner, Carter, and Senefeld and Drs. Paneth, Fairweather, Wright, and Casadevall contributed equally to this article.

This article was published on January 13, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2031893

Higher Ab levels reduce mortality

Table 3. Summary of Models Exploring the Association Between Anti-SARS-CoV-2 Antibody Levels and Mortality.

	Quasi-likelihood (Relative Risk)	
	Estimate (95% CI)	P value
ENTIRE COHORT		
Base Model (n = 3,082)		
Low	Ref	
Medium	0.92 (0.80, 1.07)	0.30
High	0.75 (0.61, 0.93)	**0.007**
Model 2 (n = 3,021)		
Low	Ref	
Medium	0.89 (0.77, 1.02)	0.10
High	0.79 (0.65, 0.96)	**0.020**
Model 3 (n = 2,858)		
Low	Ref	
Medium	0.90 (0.78, 1.05)	0.18
High	0.82 (0.67, 1.00)	0.051

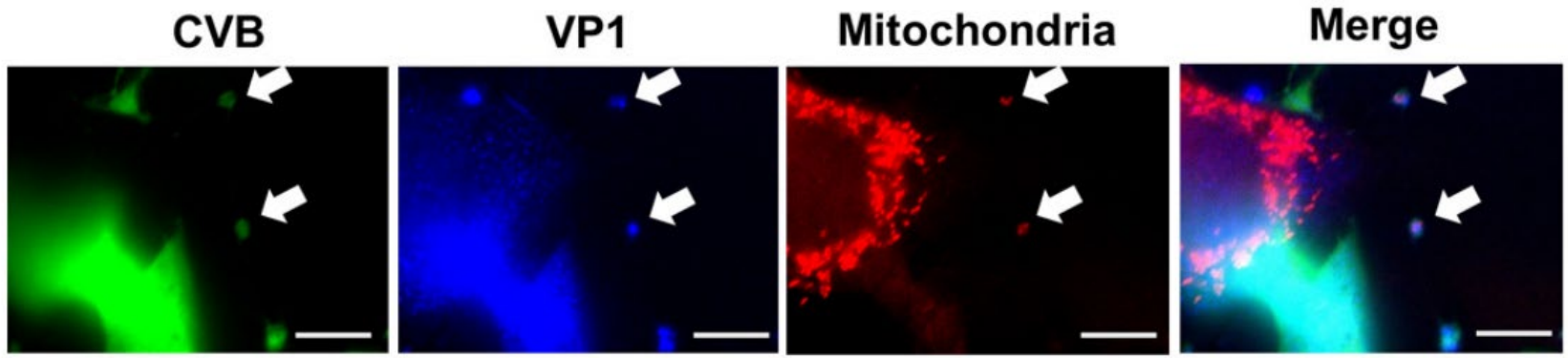
High antibody level only protects if not ventilated

NON-MECHANICALLY VENTILATED PATIENTS		
Base Model (n = 2,014)		
Low	Ref	
Medium	0.87 (0.70, 1.09)	0.23
High	0.64 (0.46, 0.88)	**0.006**
Model 2 (n = 2,014)		
Low	Ref	
Medium	0.86 (0.69, 1.06)	0.16
High	0.67 (0.49, 0.91)	**0.012**
Model 3 (n = 1,936)		
Low	Ref	
Medium	0.87 (0.71, 1.08)	0.22
High	0.66 (0.48, 0.91)	**0.011**
MECHANICALLY VENTILATED PATIENTS		
Base Model (n = 1,007)		
Low	Ref	
Medium	0.95 (0.79, 1.15)	0.60
High	0.93 (0.72, 1.19)	0.55
Model 2 (n = 1,007)		
Low	Ref	
Medium	0.94 (0.78, 1.13)	0.49
High	0.93 (0.73, 1.19)	0.58
Model 3 (n = 922)		
Low	Ref	
Medium	0.99 (0.81, 1.21)	0.94
High	1.02 (0.78, 1.32)	0.90

Joyner et al.
2021 NEJM
384:1015-1027

Pro-viral factors in CCP

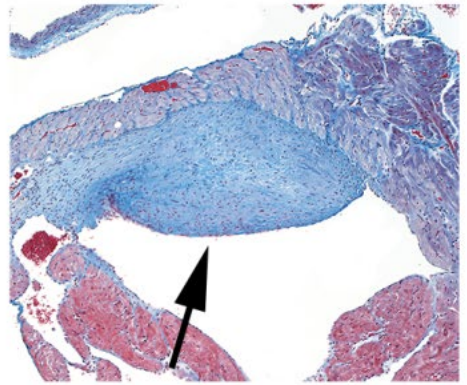
- **Pro-viral**
  - EVs expressing infectious virus or viral antigens
    - Virus-infected cells release exosomes that are implicated in infection through *transferring viral components* such as viral-derived miRNAs and proteins. As well, exosomes contain *receptors for viruses (i.e., ACE2, CD9)* that make recipient cells susceptible to virus entry.
  - EVs expressing tissue factor (TF)
  - Autoantibodies i.e., ADAMTS13, aPL, β_2G1, LAC, Annexin A2
  - Anti-plasmin (α_2AP)- serine protease inhibitor, fibrin clots
  - Soluble urokase plasminogen activator receptor (sUPAR)

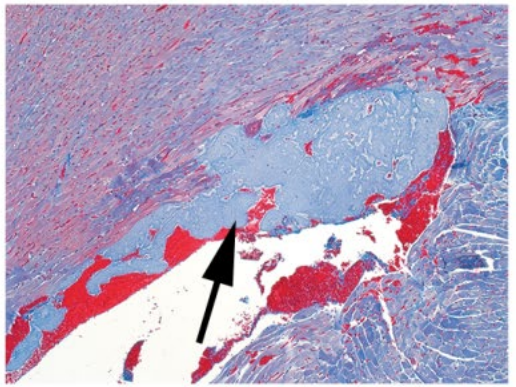


Sin J et al. J Virol 2017; 91(24): e01347-17

Pro- vs. anti-thrombotic factors in CCP

- **Anti-thrombotic**
  - Anti-thrombin III (ATIII)- decreases thrombosis
  - Albumin- decreases hyper-coagulability
  - Autoantibodies against Annexin A2- induces systemic thrombosis
- **Pro-thrombotic**
  - EVs expressing tissue factor (TF)
  - AutoAbs i.e., ADAMTS13, aPL, β2G1, LAC, Annexin A2
  - Phosphatidylserine/prothrombin (aPS/PT) autoAbs associated with higher prevalence of thrombotic events
  - Anti-plasmin (α2AP)- serine protease inhibitor, fibrin clots
  - Soluble urokase plasminogen activator receptor (sUPAR)- measured at admission predicts risk of future complications and mortality in adults with COVID-19

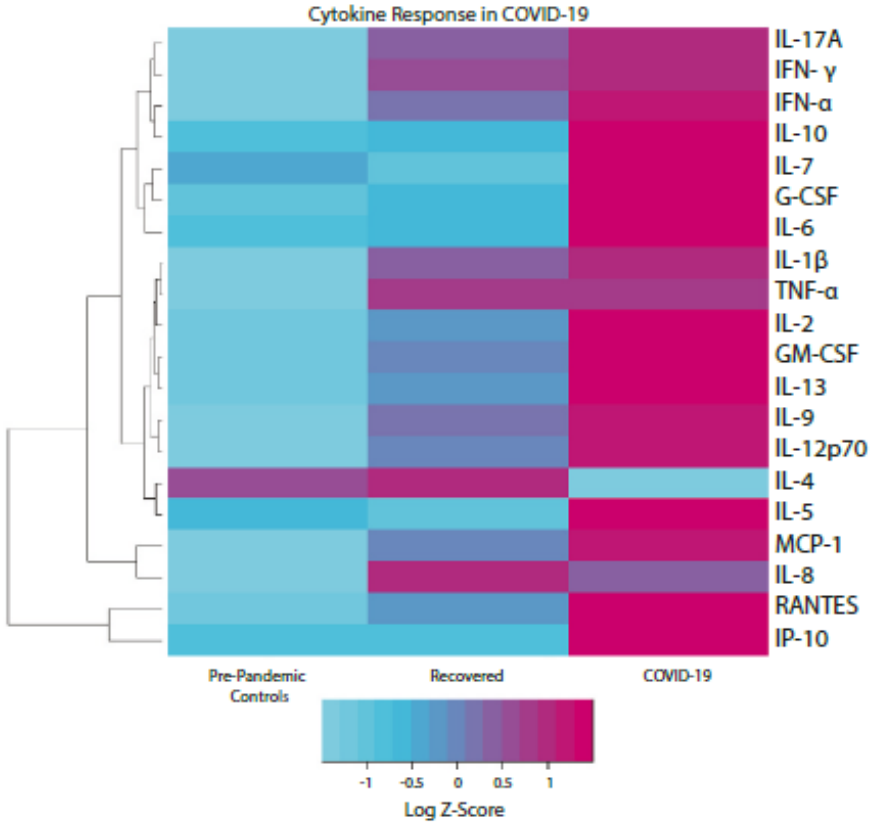


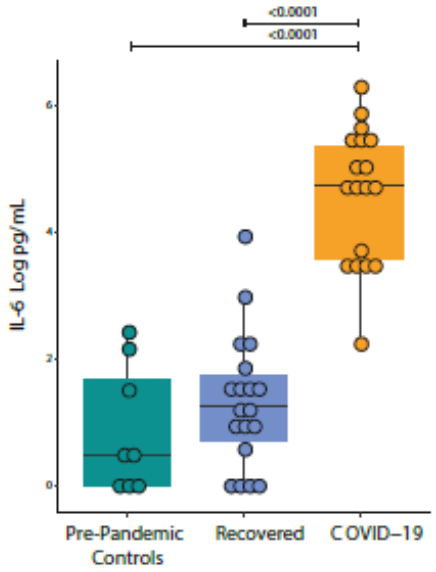


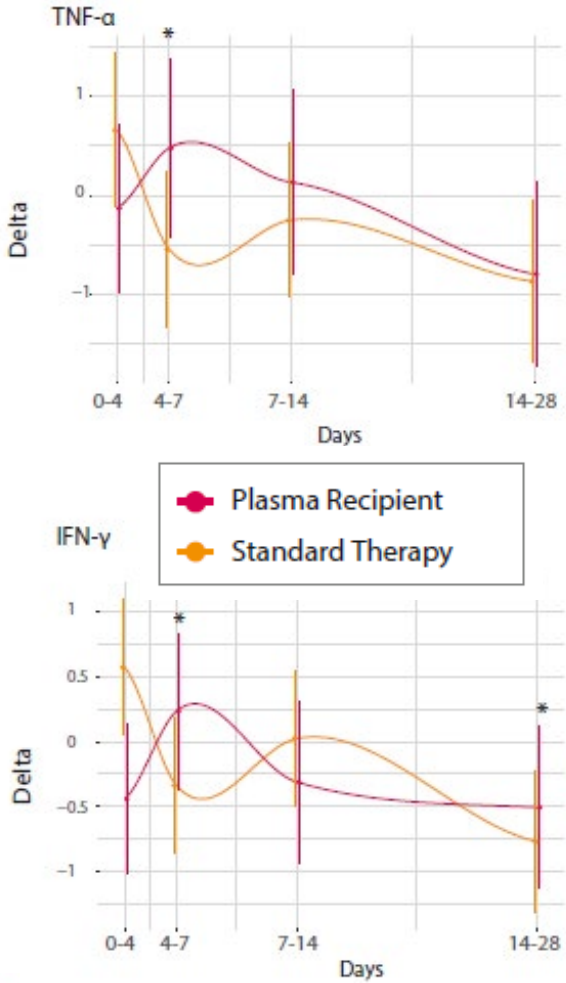
Pro- vs. anti-inflammatory factors in CCP

- **Anti-inflammatory**
  - Dilution of proinflammatory cytokines
  - Anti-inflammatory cytokines (i.e., IL-10, TGFβ)
  - Non-specific Ig (IL-21 promotes B cells)
  - Alpha1-anti-trypsin (α1AT)- inhibits neutrophil elastase/NETS
  - Anti-inflammatory EVs (i.e., anti-inflammatory miRs that inhibit TLRs &/or reduce cytokines such as TNF, IL-1β and IL-6)
- **Pro-inflammatory**
  - Increased proinflammatory cytokines (i.e., IFNs, IL-6, TNF- either protect against infection or amplify hyperimmune response)
  - Autoantibodies i.e., anti-ADAMTS13, aPL, β2G1, LAC, Annexin A2 (induce systemic thrombosis)
  - Antiplasmin (α2AP)- serine protease inhibitor, fibrin clots
  - Soluble urokase plasminogen activator receptor (sUPAR)
  - Proinflammatory EVs (i.e., proinflammatory miRs)

Cytokines elevated with COVID, elevated by CCP







Journal of Autoimmunity 118 (2021) 102598

Open Forum Infectious Diseases

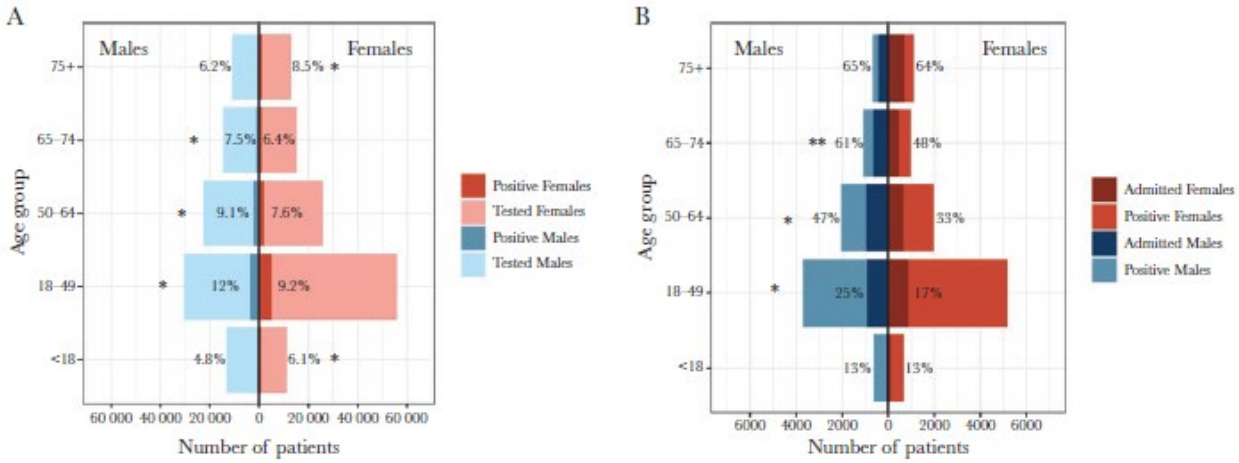
MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

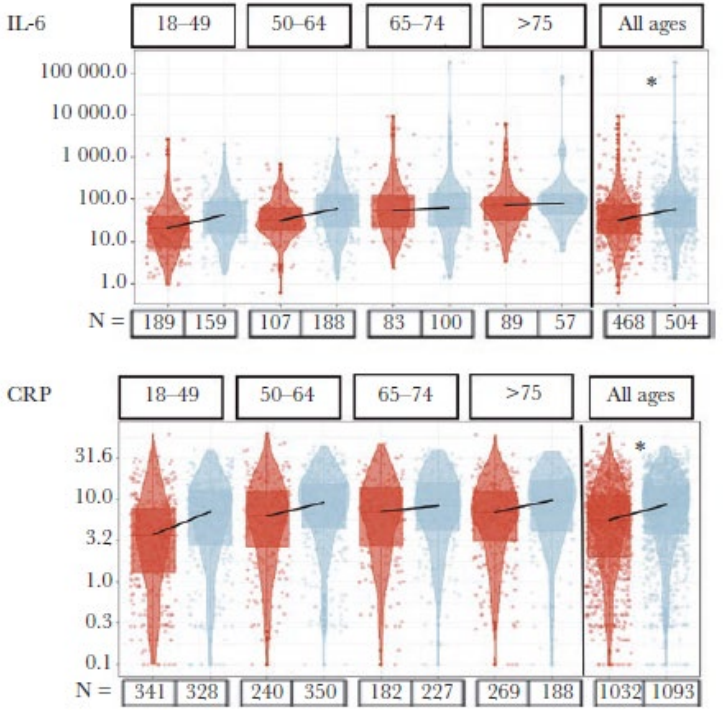
Sex Differences in COVID-19 Outcomes • OFID •

Sex and Gender Differences in Testing, Hospital Admission, Clinical Presentation, and Drivers of Severe Outcomes From COVID-19

Eileen P. Scully,[1,a] Grant Schumock,[2] Martina Fu,[2] Guido Massaccesi,[1] John Muschelli,[2] Joshua Betz,[2] Eili Y. Klein,[3] Natalie E. West,[4] Matthew Robinson,[1] Brian T. Garibaldi,[4] Karen Bandeen-Roche,[2] Scott Zeger,[2] Sabra L. Klein,[5,6,a] and Amita Gupta[1,7,a]; for the JH-CROWN registry team



Males > +ve tested & admitted with elevated sera IL-6 & CRP levels



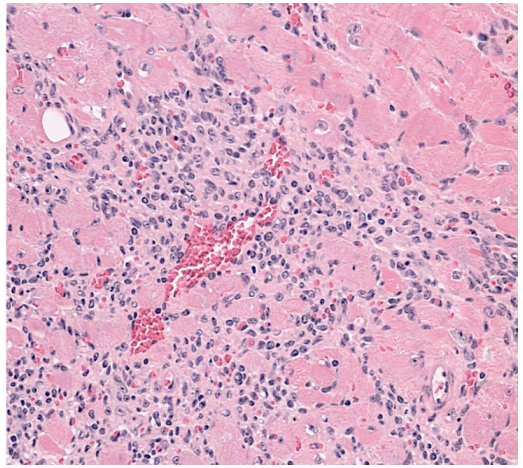
Location, Location, Location!

- Plasma factors and EVs are communicating, but what are they saying?
- Interpreting immune response and gene signatures is all about ‘context’
- Increased TNF and IL-6 early during infection by CCP may amplify protection, especially if other therapies inhibit this early protective response
- Or, elevated levels could contribute to the ‘cytokine storm’ of uncontrolled immune response that leads to COVID symptoms and *secondary comorbidities* of autoimmune diseases like myocarditis, antiphospholipid syndrome, and others…

SARS-CoV-2:COVID-19 and autoimmune disease

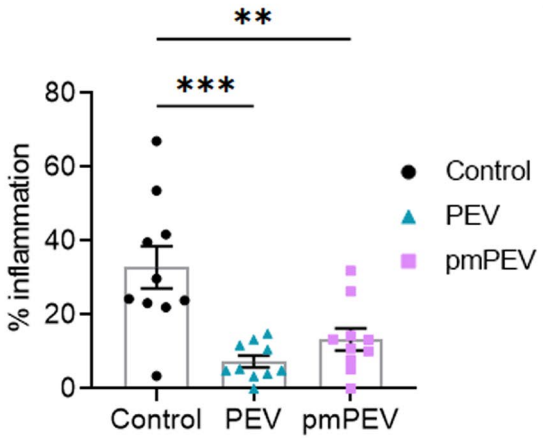
- autoAbs:
  - anti-cardiolipin (aCL)
  - lupus anti-coagulant (LAC)
  - beta2 glycoprotein I (β2GPI)
  - anti-phosphatidylserine/prothrombin (aPS/PT)- thrombi
  - neutralizing autoAbs against type I interferons (IFNα/β)- severe pneumonia
  - antinuclear antibodies (ANA) to β2GPI, aCL, p-ANCA, c-ANCA - vasculitis

- Autoimmune Diseases:
  - Myocarditis
  - Antiphospholipid syndrome
  - Guillain-Barré syndrome
  - Kawasaki disease
  - Vasculitis



Plasma EVs decrease viral myocarditis

a



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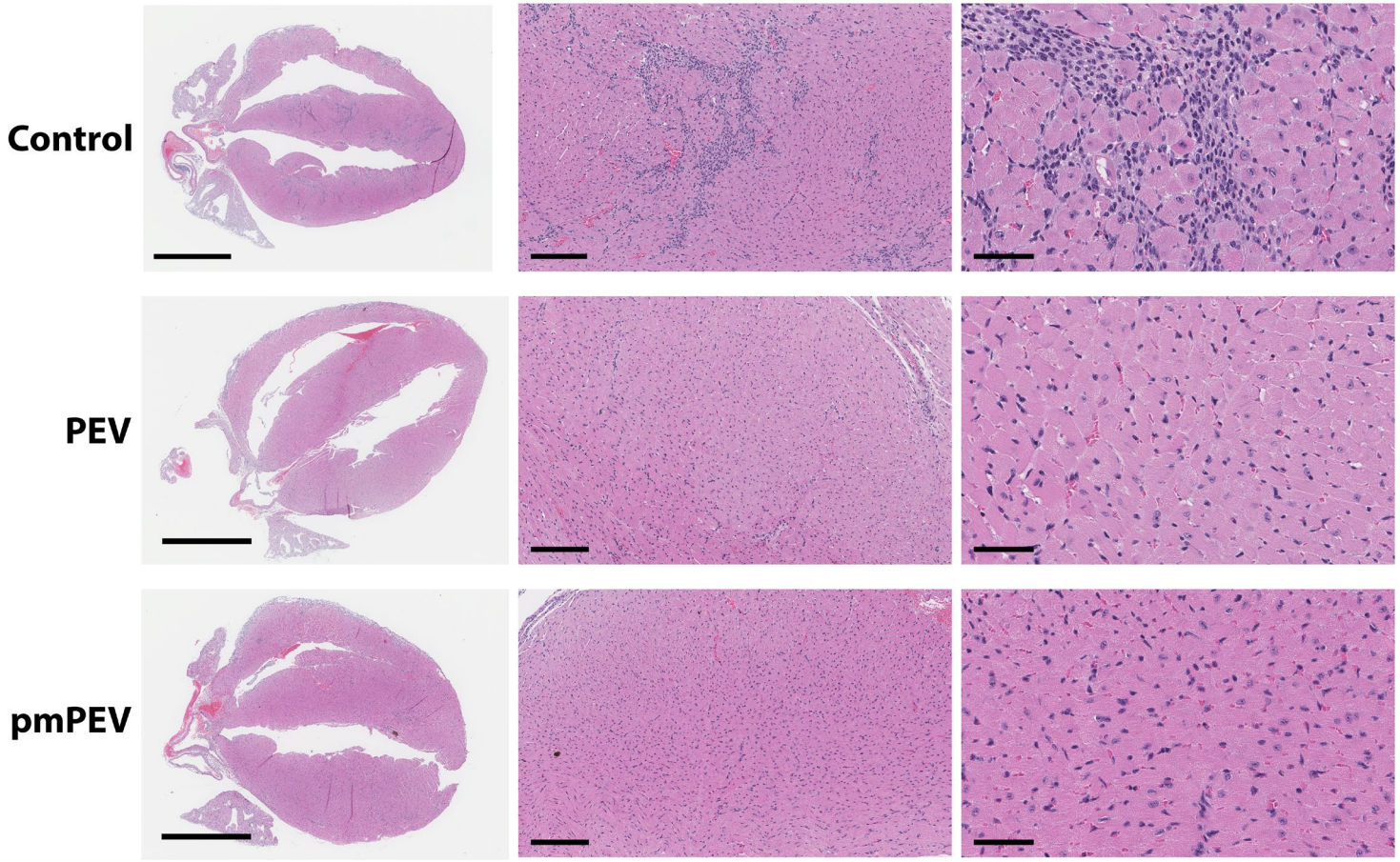
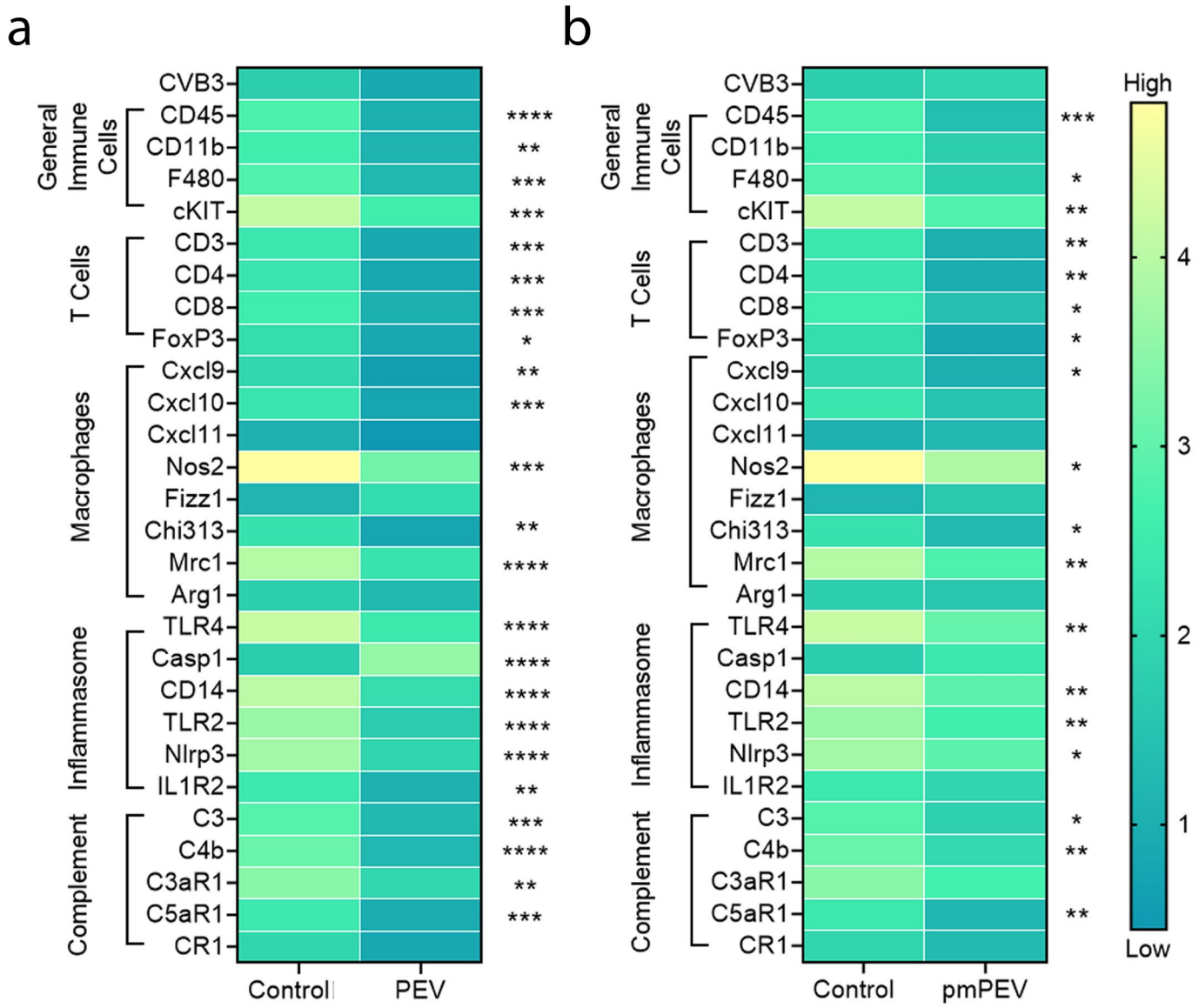


Bruno, Beetler, Fairweather, unpublished



Global downregulation (qRT-PCR) of proinflammatory pathways by plasma EVs

Bruno, Beetler, Fairweather, unpublished

Summary

- Proteins and other factors in CCP can be therapeutic or promote inflammation, viral infection and comorbidities like thrombosis and autoimmune diseases
- Transfusion of CCP is safe with less than 1% transfusion-associated reactions
- A major factor mediating anti-viral protection in CCP early during disease is neutralizing Ab against SARS-CoV-2
- Research suggests other factors in plasma may exert significant effects on the immune response like EVs that contain miRs, many are anti-inflammatory but they can also promote inflammation
- EVs have been demonstrated in culture, preclinical animal models and in patients to reduce inflammation and activate the body's natural reparative mechanisms
- A better understanding of the components and how they interact/communicate is needed in order to identify key signaling pathways that mediate the best protection

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THANK YOU

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