Clinical experience and rationale for use of convalescent plasma and specific immunoglobulin in COVID-19 patients

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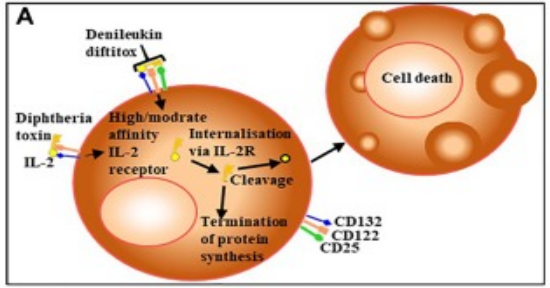
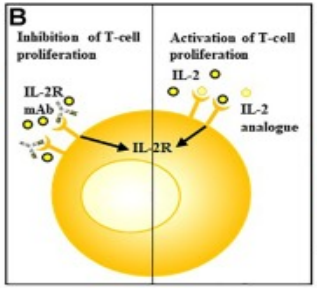
Department of Infectious Diseases
Medical University of Lublinie

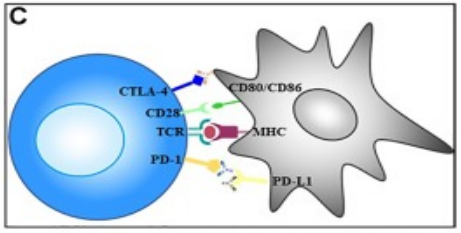
Therapeutic strategies based on T-cells



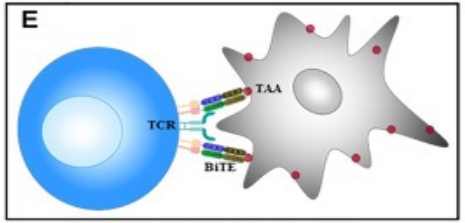
Depletion of T-reg



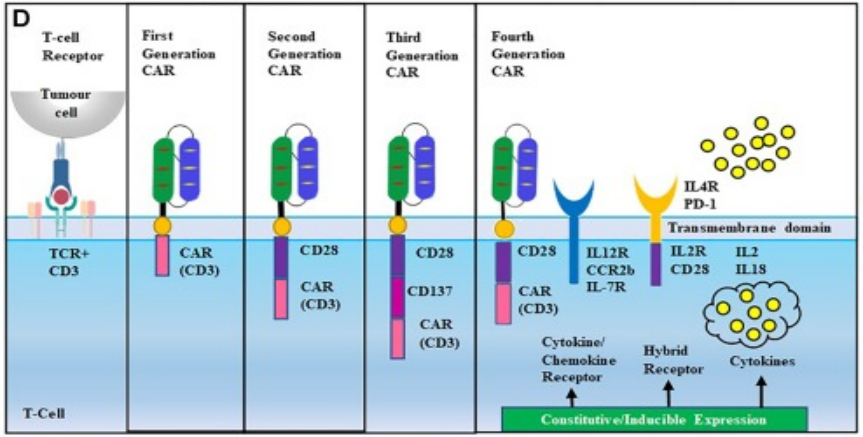
Cytokine Immunotherapy



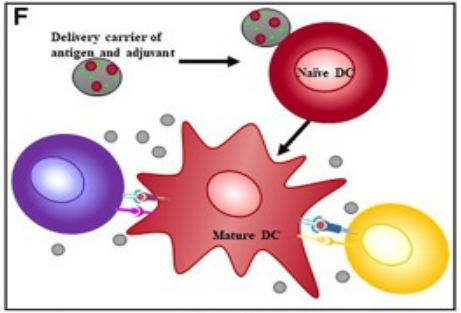
Immune Checkpoint Inhibitors



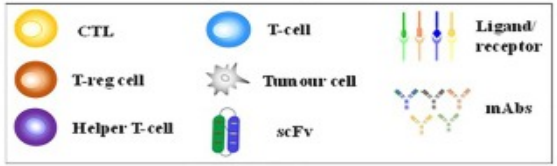
Bispecific Antibodies



Chimeric Antigen Receptor (CAR) T-cells

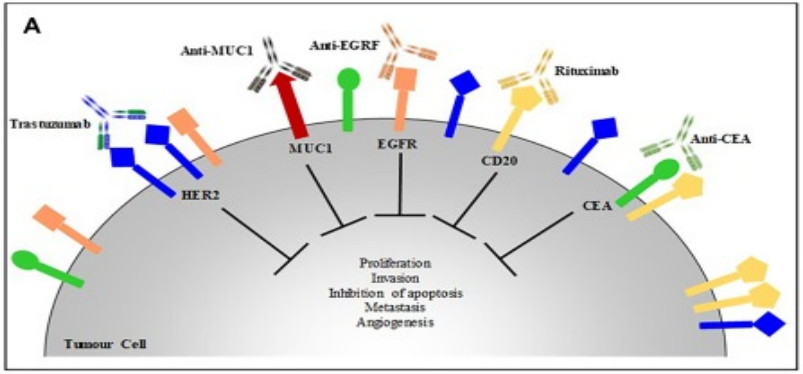


Vaccines

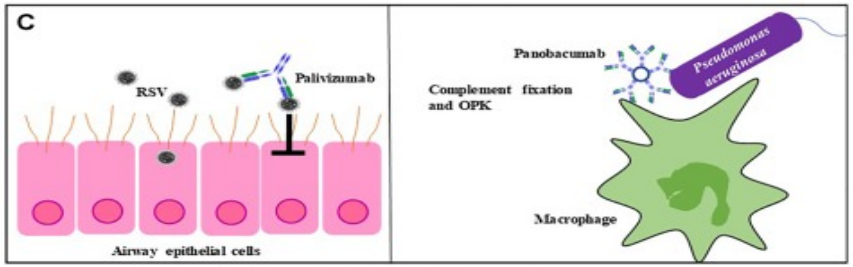


Naran K, et al. Front Microbiol 2018

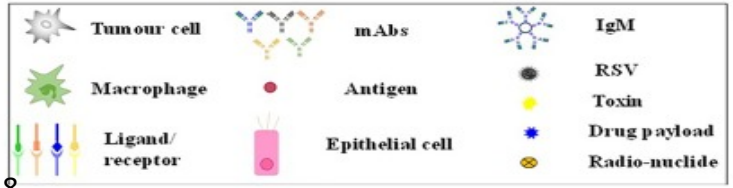
Therapeutic strategies based on antibodies

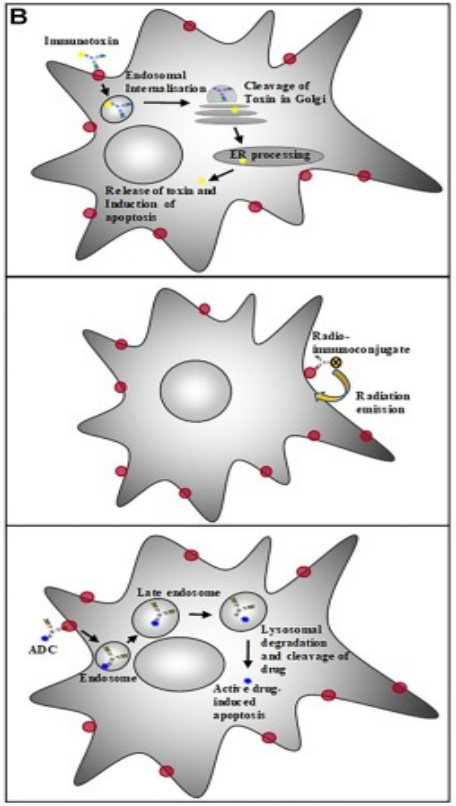


Anticancer Antibodies



Antibodies for infectious diseases

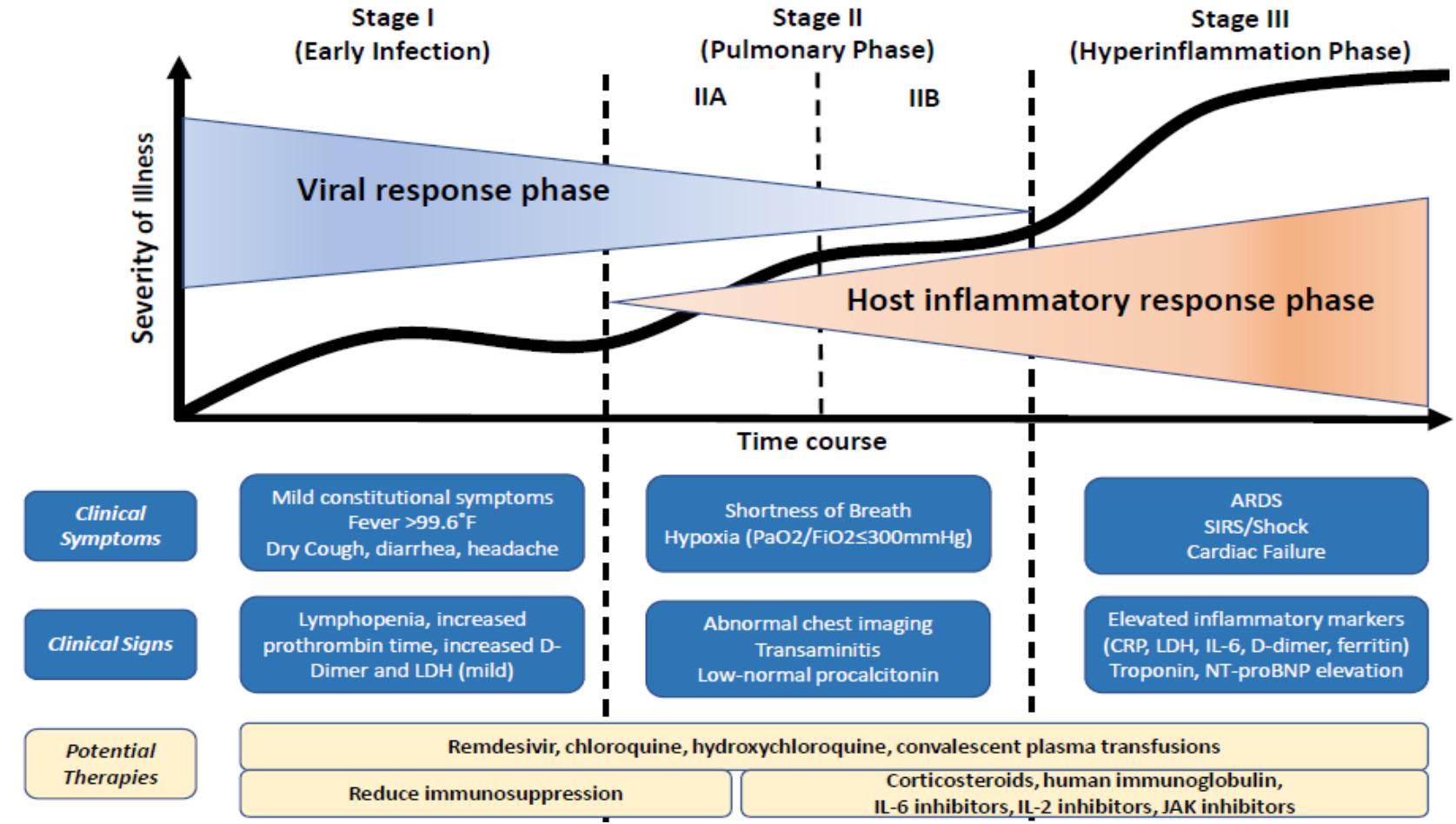




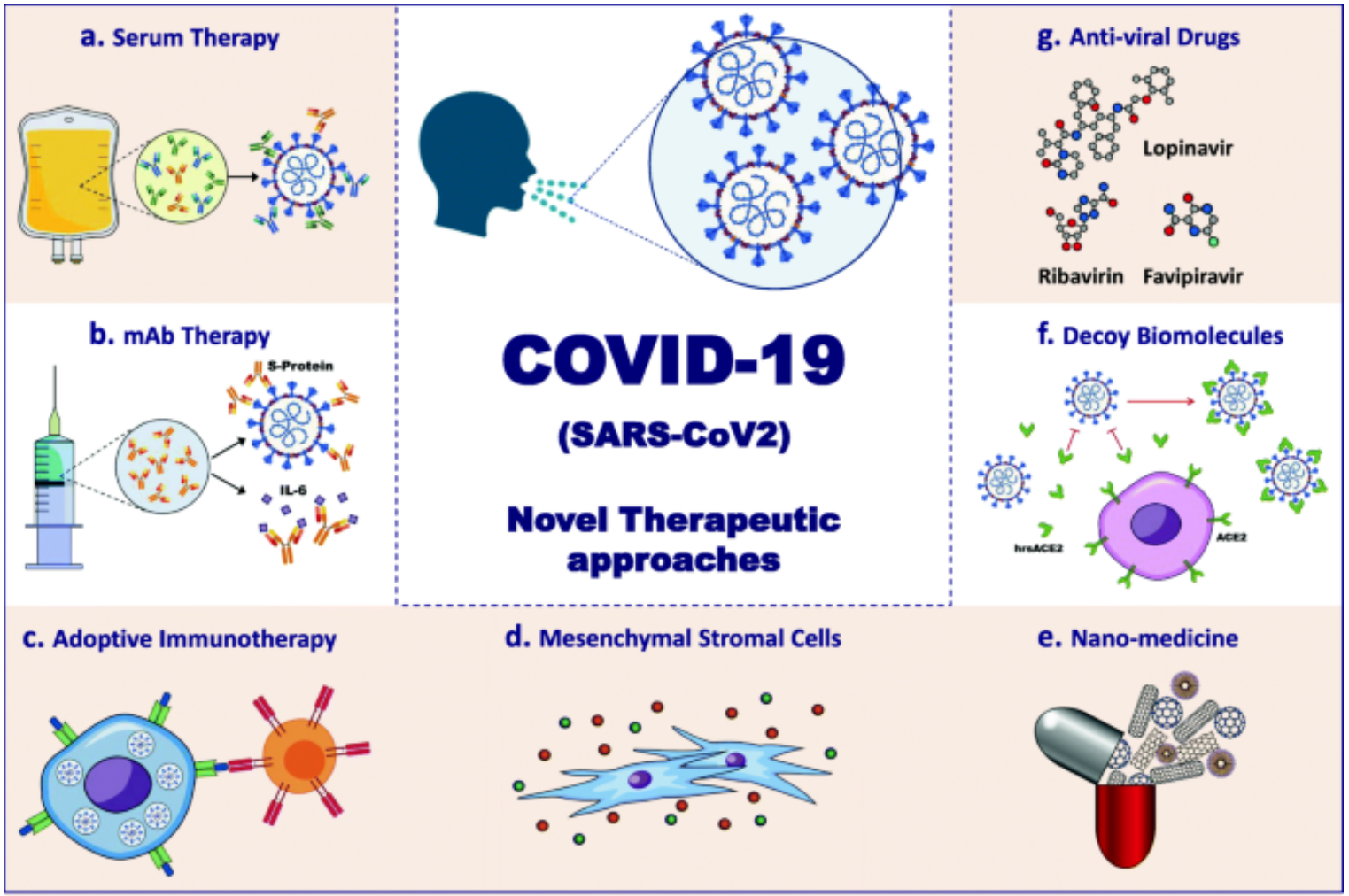
Antibody Conjugates

Naran K, et al. Front Microbiol 2018

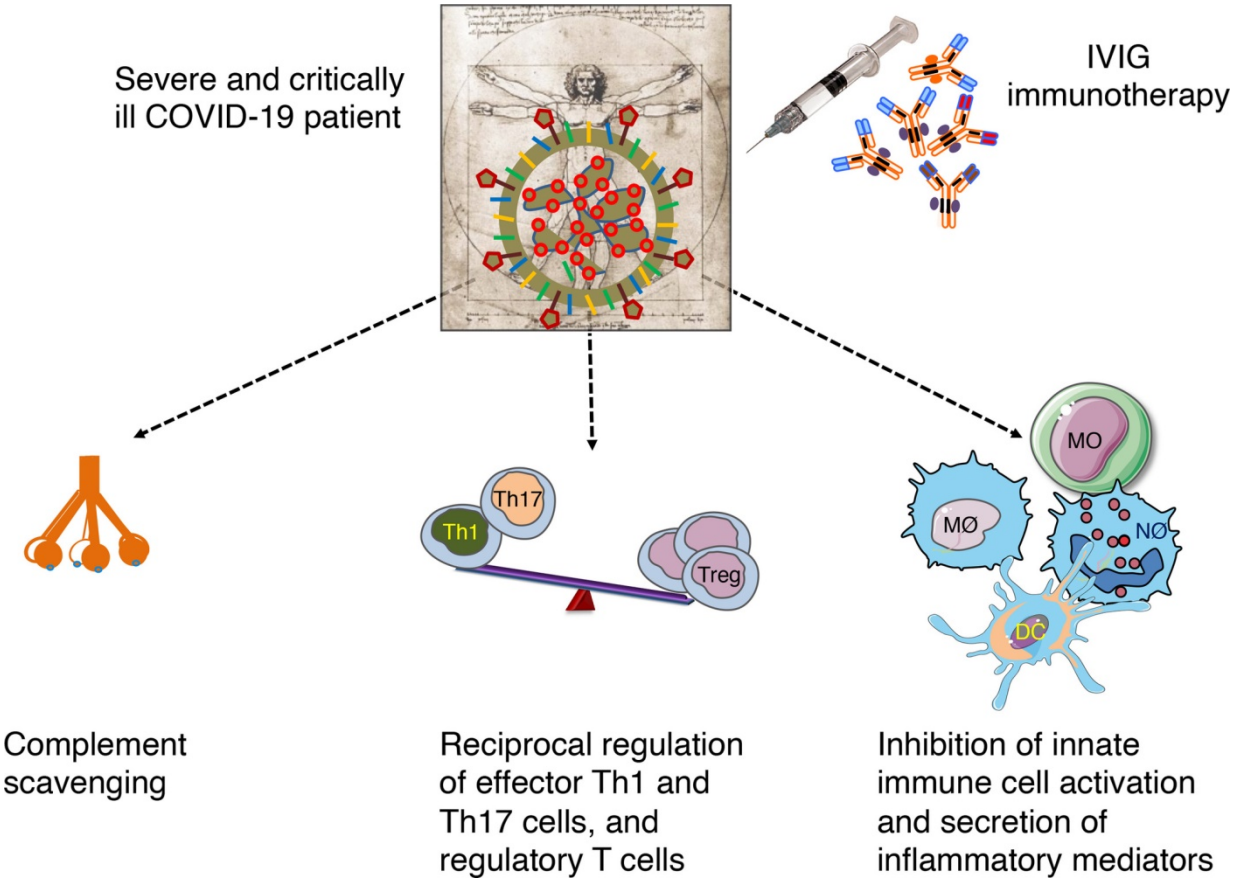
Eg: Palivizumab anti-RSV



Siddiqi HK, et al. J Heart Lung Transplant 2020

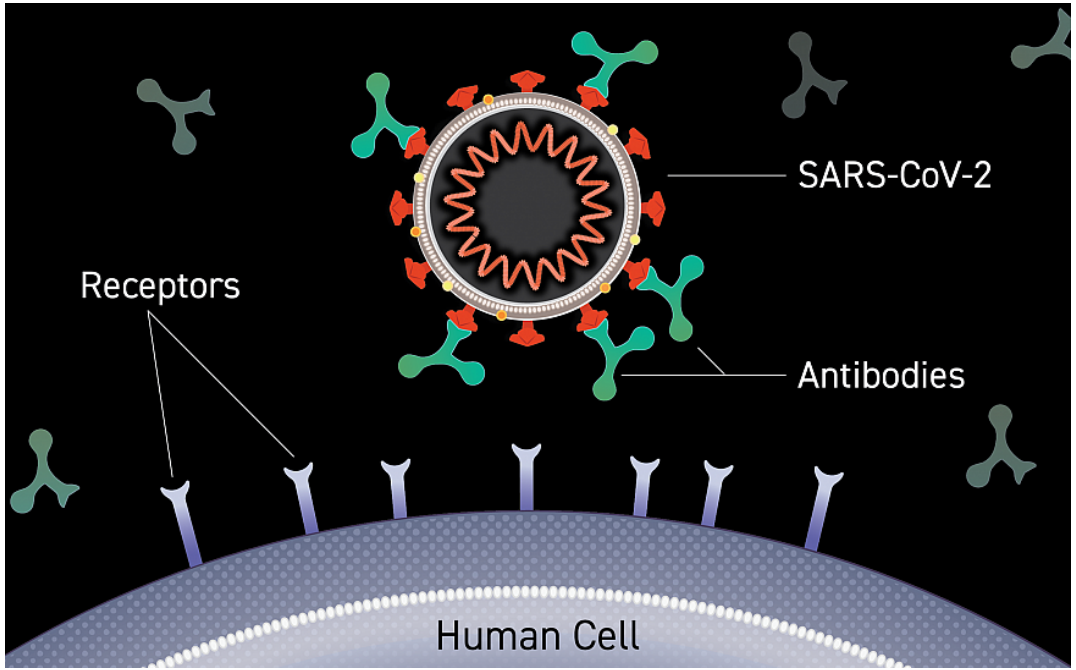


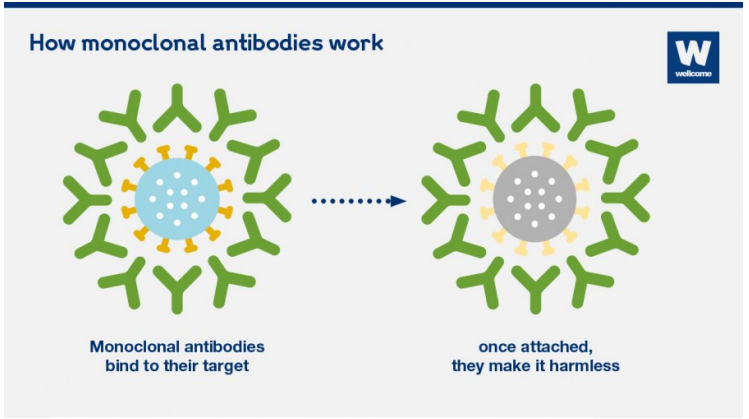
Galleotti C, et al. Clinical & Translational Immunology 2020



Galleotti C, et al. Clinical & Translational Immunology 2020

Monoclonal antibodies anti-SARS-CoV-2

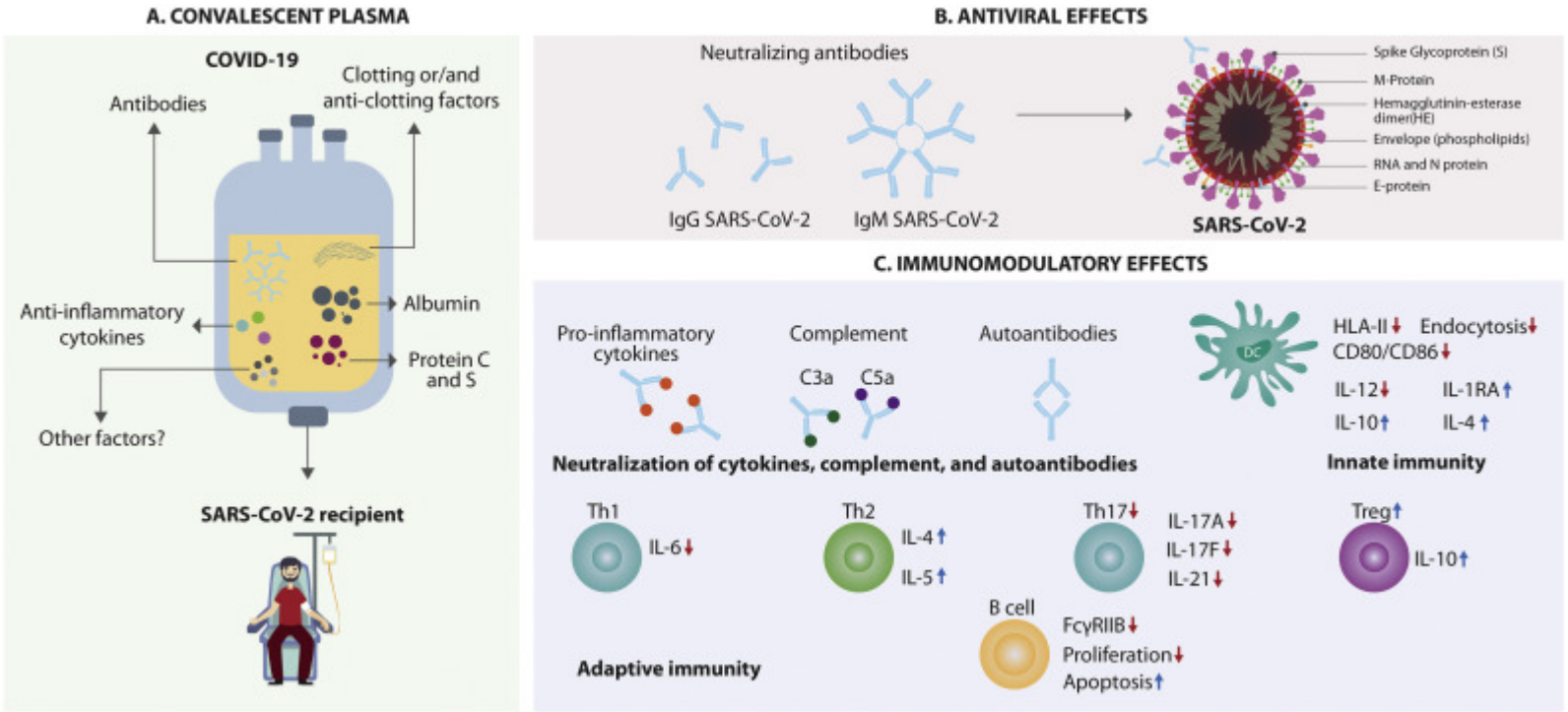




https://www.nih.gov

Monoclonal antibody stopped in ACTIV-3 study: bamlanivimab shows lack of benefit in people hospitalised with COVID-19

Convalescent plasma treatment - „New” old method of IDs therapy – including COVID-19



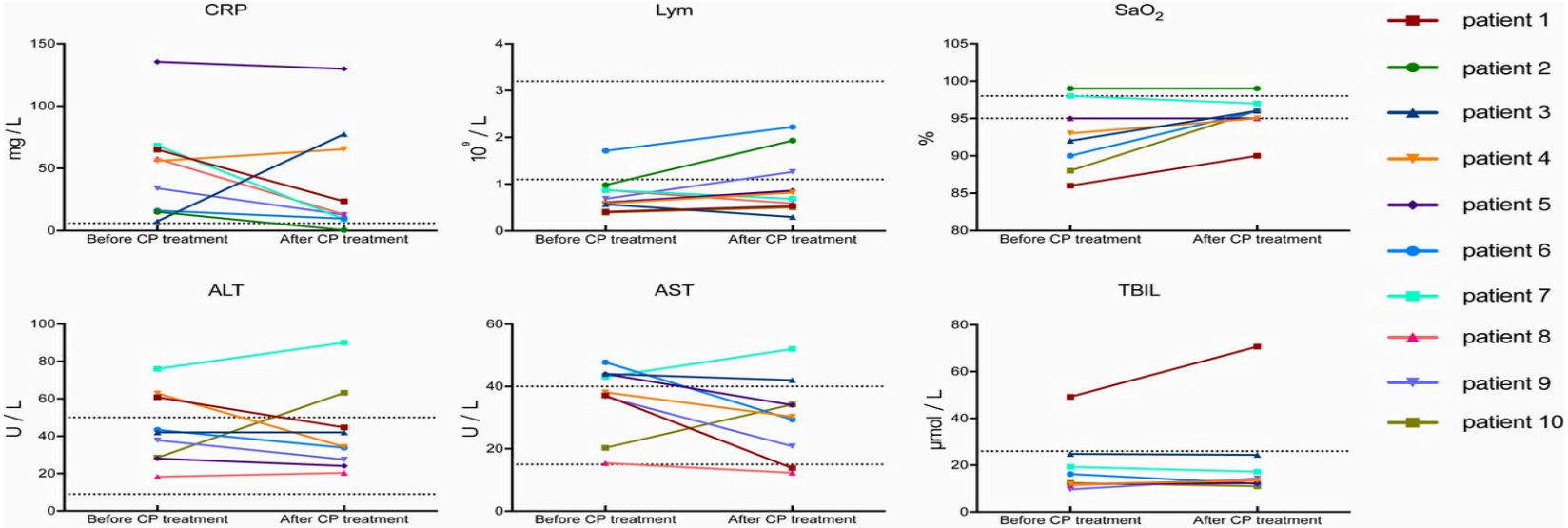
Rojas M, et al. Autoimmun Rev 2020 Jul;19(7):102554

Adverse effects of FFP

- 1. Allergy resulting in urticaria has been reported in 1–3% of transfusion, whil anaphylaxis is rare.
- 2.Transfusion-related acute lung injury:
  - 0.02% of transfusion.
  - Severe respiratory distress, with hypoxia, pulmonary edema, infiltrates or ‘white-out’ on chest X-ray, and sometimes fever and hypotension.
  - Usually develops within 4 h of transfusion.
  - It cannot be distinguished clinically from ARDS.

British Journal of Haematology 2004; 126:11

Dynamic changes of laboratory parameters in all patients.



Kai Duan et al. PNAS 2020;117:17:9490-9496

- ***Recommendation:***

There are insufficient data to recommend either for or against the use of **COVID-19 convalescent plasma** or **SARS-CoV-2 immune globulins** for the treatment of COVID-19 **(AIII)**.

NIH Recommendation **May 2020**

Tuesday, March 2, 2021

NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms

Study shows the treatment is safe, but provides no significant benefit in this group.

An independent data and safety monitoring board (DSMB) met on Feb. 25, 2021 for the second planned interim analysis of the trial data and determined that while the convalescent plasma intervention caused no harm, it was unlikely to benefit this group of patients.

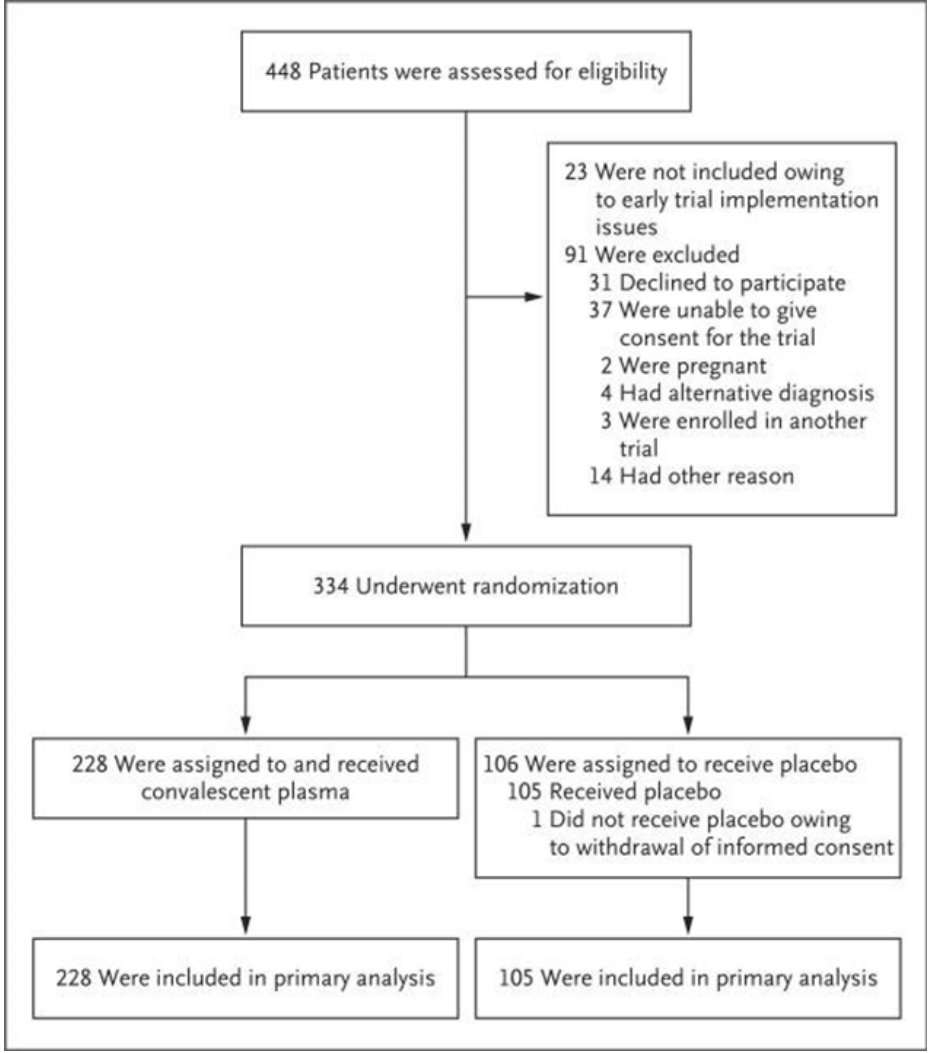
This trial was highly unlikely to demonstrate that COVID-19 convalescent plasma prevents progression from mild to severe illness in at-risk emergency department non-hospitalized participants.

After the meeting, the DSMB recommended that the National Heart, Lung, and Blood Institute (NHLBI), part of NIH, stop enrolling new patients into the study. NHLBI did so immediately.

Negative observations

PlasmAr - a double-blind, placebo-controlled, multicenter trial conducted at 12 clinical sites in Argentina and coordinated by Hospital Italiano de Buenos Aires.

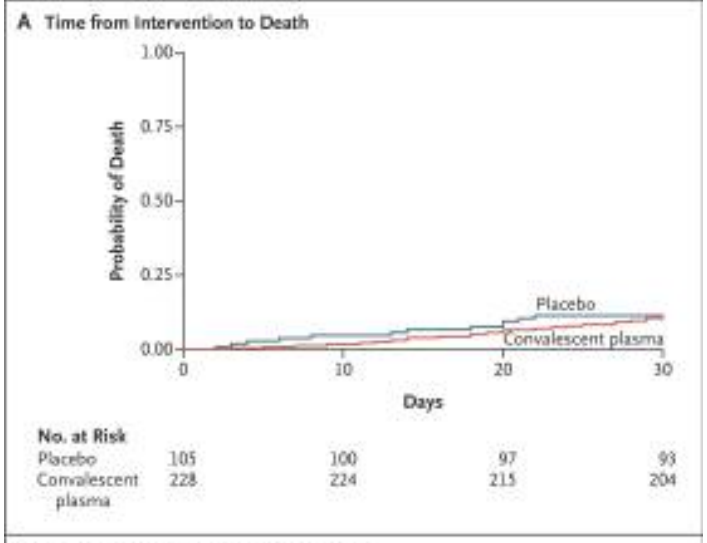
Simonovich VA, et al. N Engl J Med. 2020 Nov 24 : NEJMoa2031304

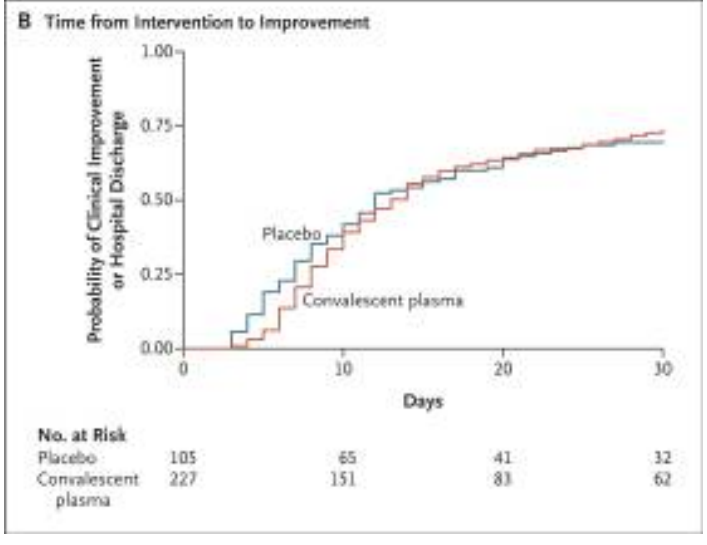


Simonovich VA, et al.
N Engl J Med. 2020 Nov 24 : NEJMoa2031304

Conclusions

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo.





Simonovich VA, et al.
N Engl J Med. 2020 Nov 24 : NEJMoa2031304

Positive observations

The NEW ENGLAND JOURNAL of MEDICINE

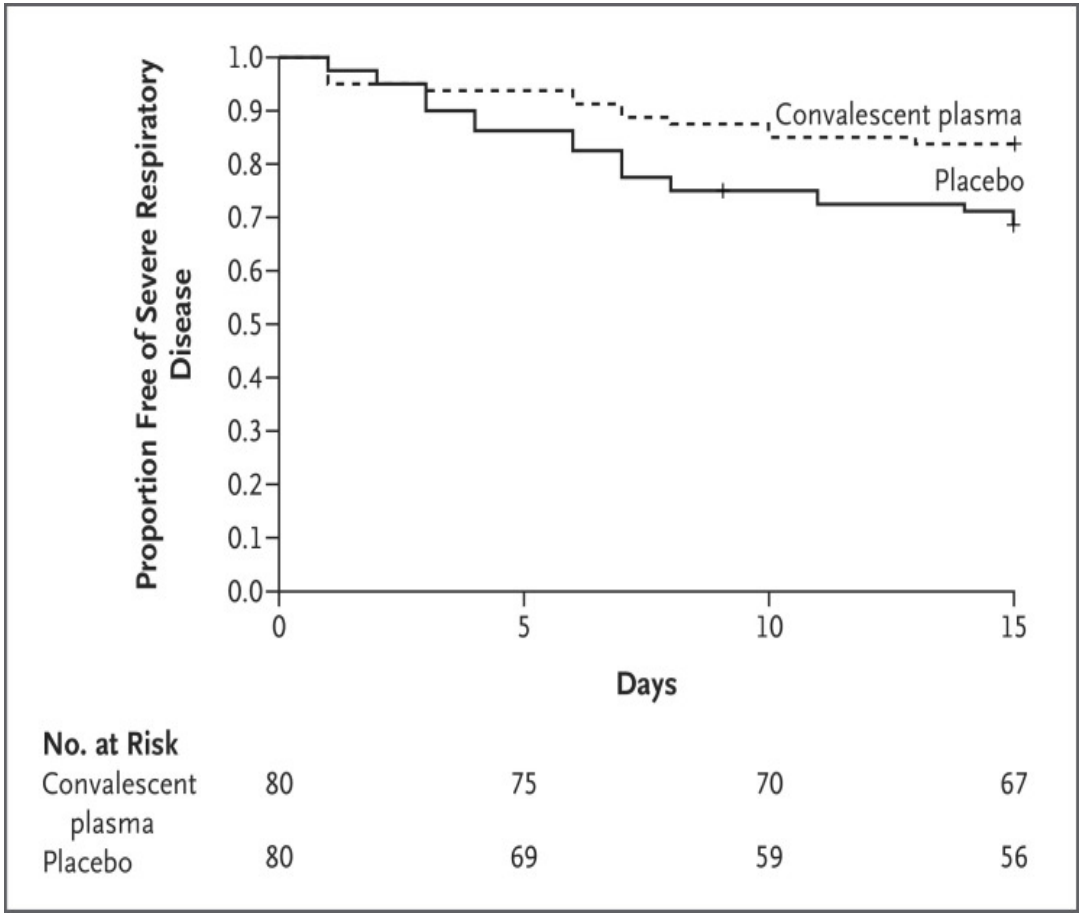
ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem, I. Esteban, M.T. Caballero, C. Wood, M. Berrueta, A. Rondan, G. Lescano, P. Cruz, Y. Ritou, V. Fernández Viña, D. Álvarez Paggi, S. Esperante, A. Ferreti, G. Ofman, Á. Ciganda, R. Rodriguez, J. Lantos, R. Valentini, N. Itcovici, A. Hintze, M.L. Oyarvide, C. Etchegaray, A. Neira, I. Name, J. Alfonso, R. López Castelo, G. Caruso, S. Rapelius, F. Alvez, F. Etchenique, F. Dimase, D. Alvarez, S.S. Aranda, C. Sánchez Yanotti, J. De Luca, S. Jares Baglivo, S. Laudanno, F. Nowogrodzki, R. Larrea, M. Silveyra, G. Leberzstein, A. Debonis, J. Molinos, M. González, E. Perez, N. Kreplak, S. Pastor Argüello, L. Gibbons, F. Althabe, E. Bergel, and F.P. Polack, for the Fundación INFANT–COVID-19 Group*

A randomized, double-blind, placebo-controlled trial of convalescent plasma with **high IgG titers** against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adult patients **within 72 hours after the onset of mild Covid-19 symptoms**.

Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19.



Libster R, et al.
N Engl J Med. 2021 Jan 6 : NEJMoa2033700.

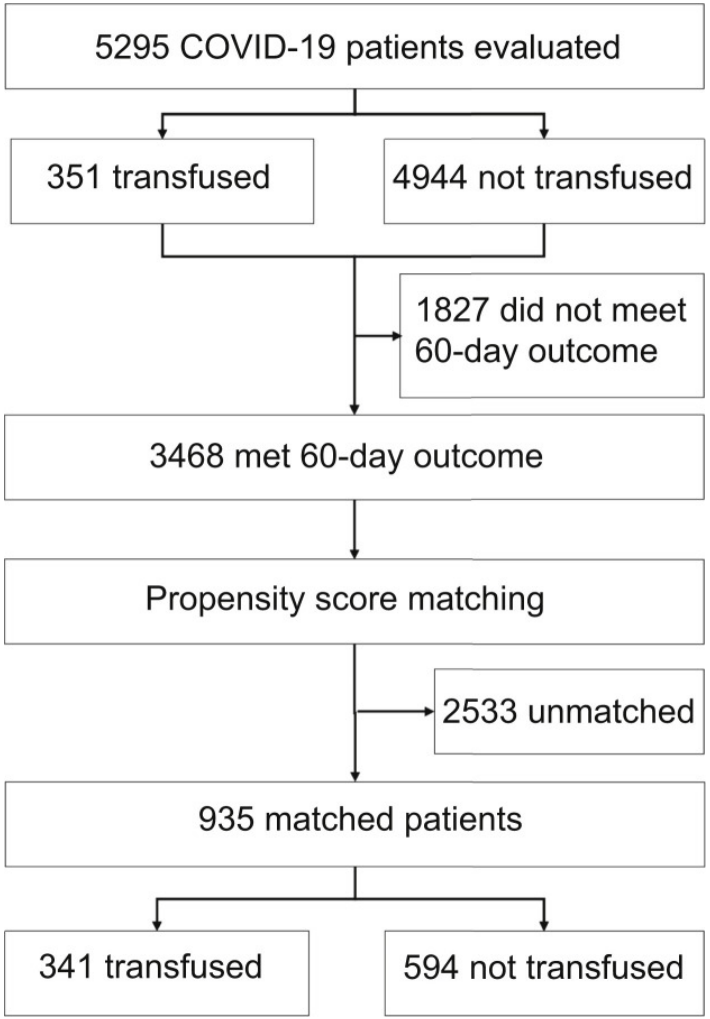
The American Journal of Pathology, Vol. 191, No. 1, January 2021

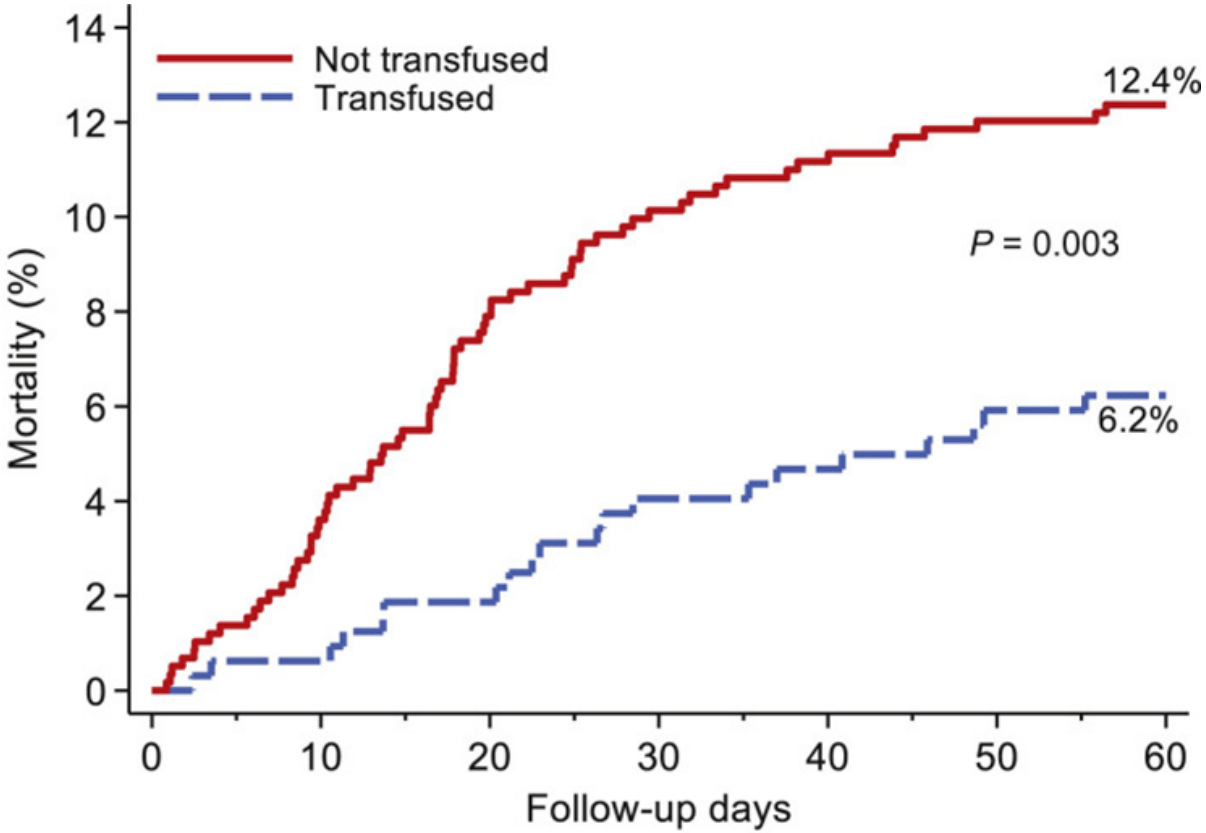
The American Journal of
PATHOLOGY
ajp.amjpathol.org

IMMUNOPATHOLOGY AND INFECTIOUS DISEASES

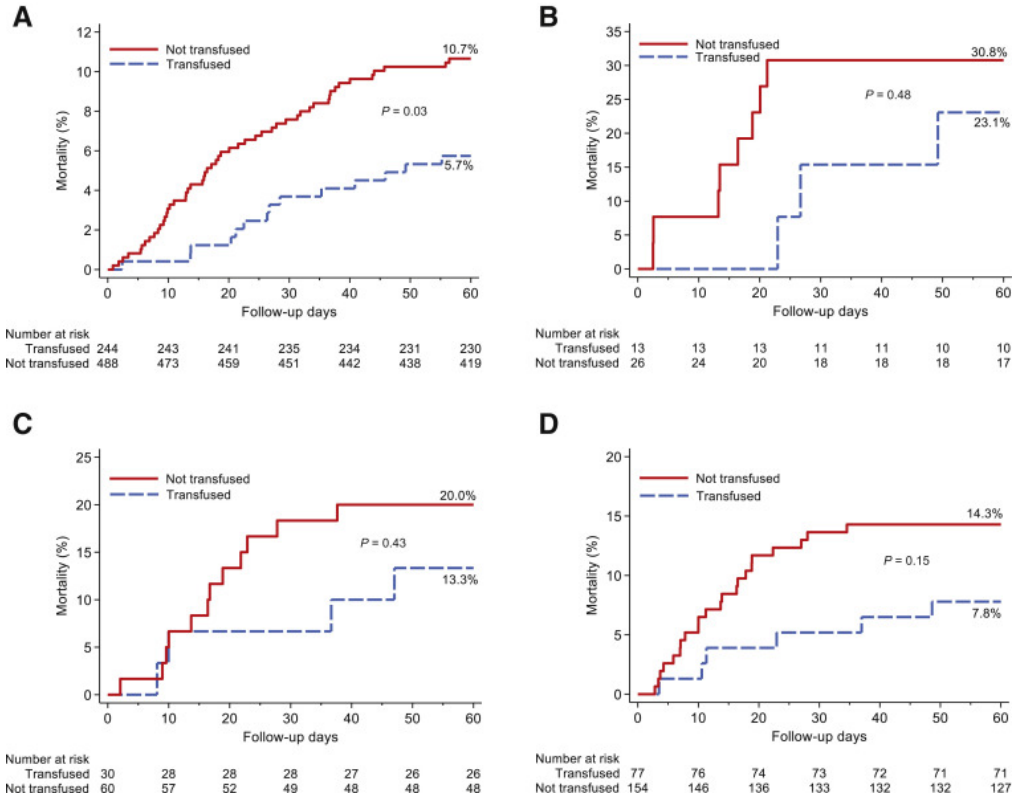
Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti—Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG

Eric Salazar,*† Paul A. Christensen,* Edward A. Graviss,*‡ Duc T. Nguyen,‡ Brian Castillo,* Jian Chen,* Bevin V. Lopez,§ Todd N. Eagar,*† Xin Yi,*† Picheng Zhao,* John Rogers,* Ahmed Shehabeldin,* David Joseph,* Faisal Masud,¶ Christopher Leveque,* Randall J. Olsen,*†‡ David W. Bernard,*† Jimmy Gollihar,‖ and James M. Musser*†‡


5295 COVID-19 patients evaluated
351 transfused
4944 not transfused
1827 did not meet 60-day outcome
3468 met 60-day outcome
Propensity score matching
2533 unmatched
935 matched patients
341 transfused
594 not transfused



Number at risk							
Transfused	321	319	315	308	306	302	301
Not transfused	582	561	536	523	517	512	487



A: Patients transfused with plasma with IgG titer ≥1:1350 and transfused within 72 hours of admission

B: Patients transfused with plasma with IgG titer ≥1:1350 and intubated at day 0.

C: Patients transfused with plasma with IgG titer <1:1350

D: Patients transfused with plasma with IgG titer ≥1:1350 and transfused >72 hours after admission

Journal of
Clinical Medicine

MDPI

Article

Convalescent Plasma Transfusion for the Treatment of COVID-19—Experience from Poland: A Multicenter Study

Anna Moniuszko-Malinowska [1,*,†], Piotr Czupryna [1,†], Dorota Zarębska-Michaluk [2], Krzysztof Tomasiewicz [3], Sławomir Pancewicz [1], Marta Rorat [4,5], Anna Dworzańska [3], Katarzyna Sikorska [6], Beata Bolewska [7], Beata Lorenc [8], Andrzej Chciałowski [9], Dorota Kozielewicz [10], Barbara Oczko-Grzesik [11], Anna Szymanek-Pasternak [12], Bartosz Szetela [13], Magdalena Figlerowicz [14], Magdalena Rogalska [15], Izabela Zaleska [16] and Robert Flisiak [15]

J. Clin. Med. **2021**, 10, 28. https://dx.doi.org/10.3390/jcm10010028

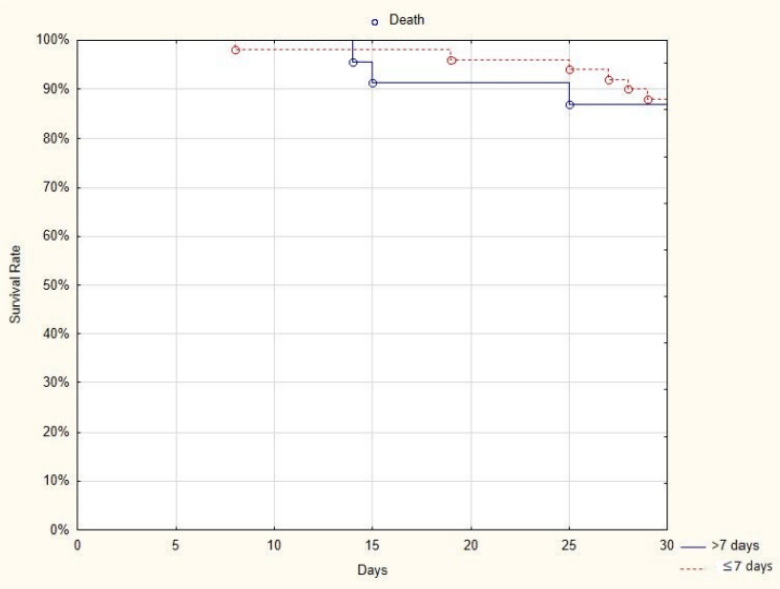


Figure 2. Kaplan-Meier curve presenting the 30-day survival rate of patients who received plasma in the first seven days after the onset of the disease and those who received plasma more than seven days after the onset of the disease.

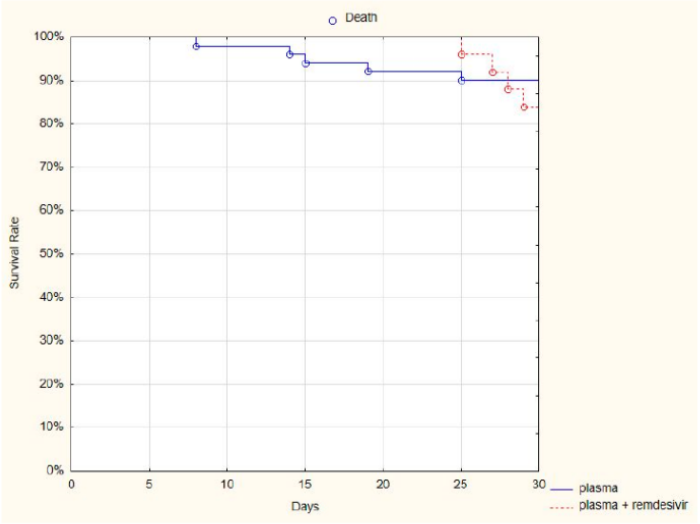
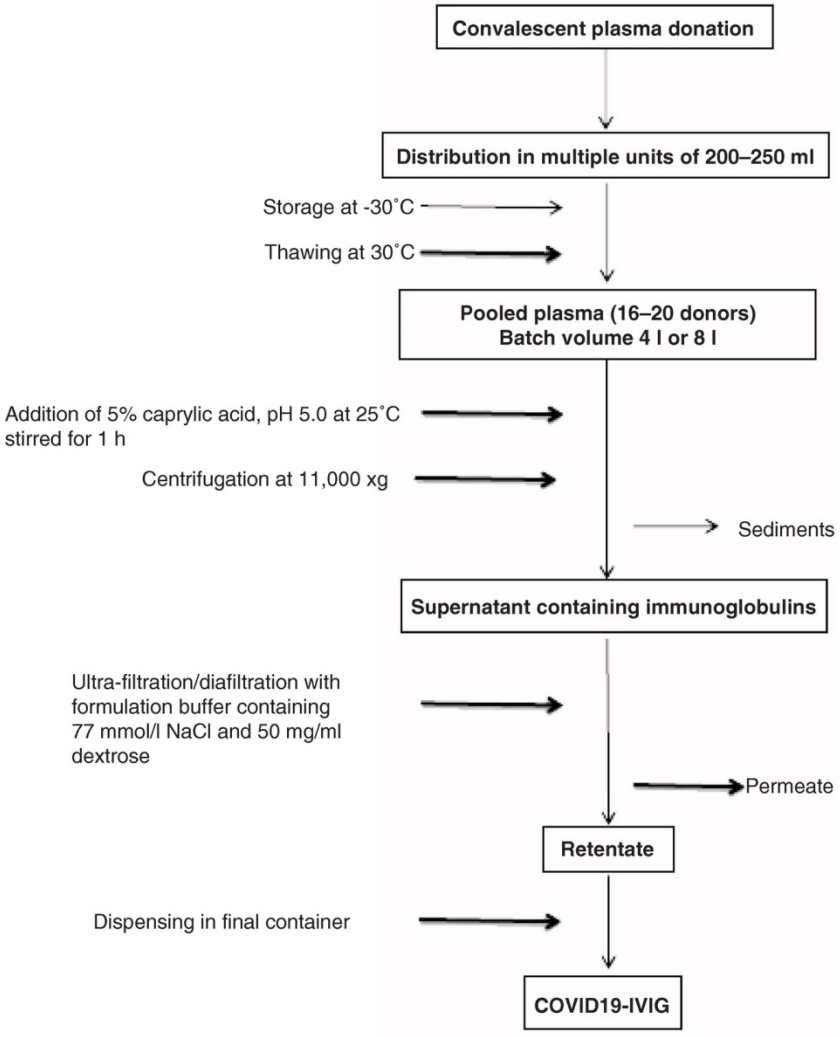


Figure 3. Kaplan-Meier curve presenting the 30-day survival rate of patients treated with convalescent plasma and remdesivir, and only plasma.



Ali et al. Immunotherapy(2021) 13(5), 397–40

Specific immunoglobulin (plasma-derived)

The project includes:

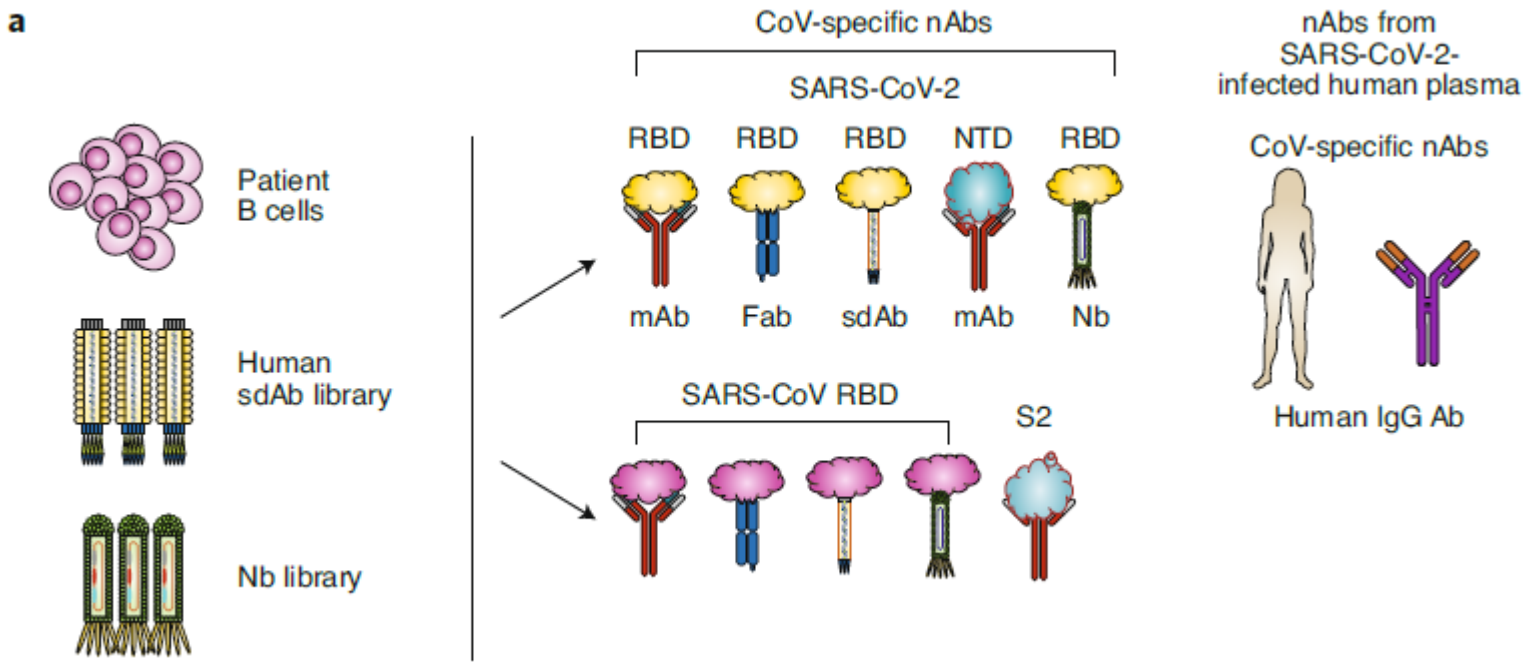
1. studies related to the process of receiving anti-SARS-CoV-2 immunoglobulin and

2. clinical studies regarding its use in patients with COVID-19

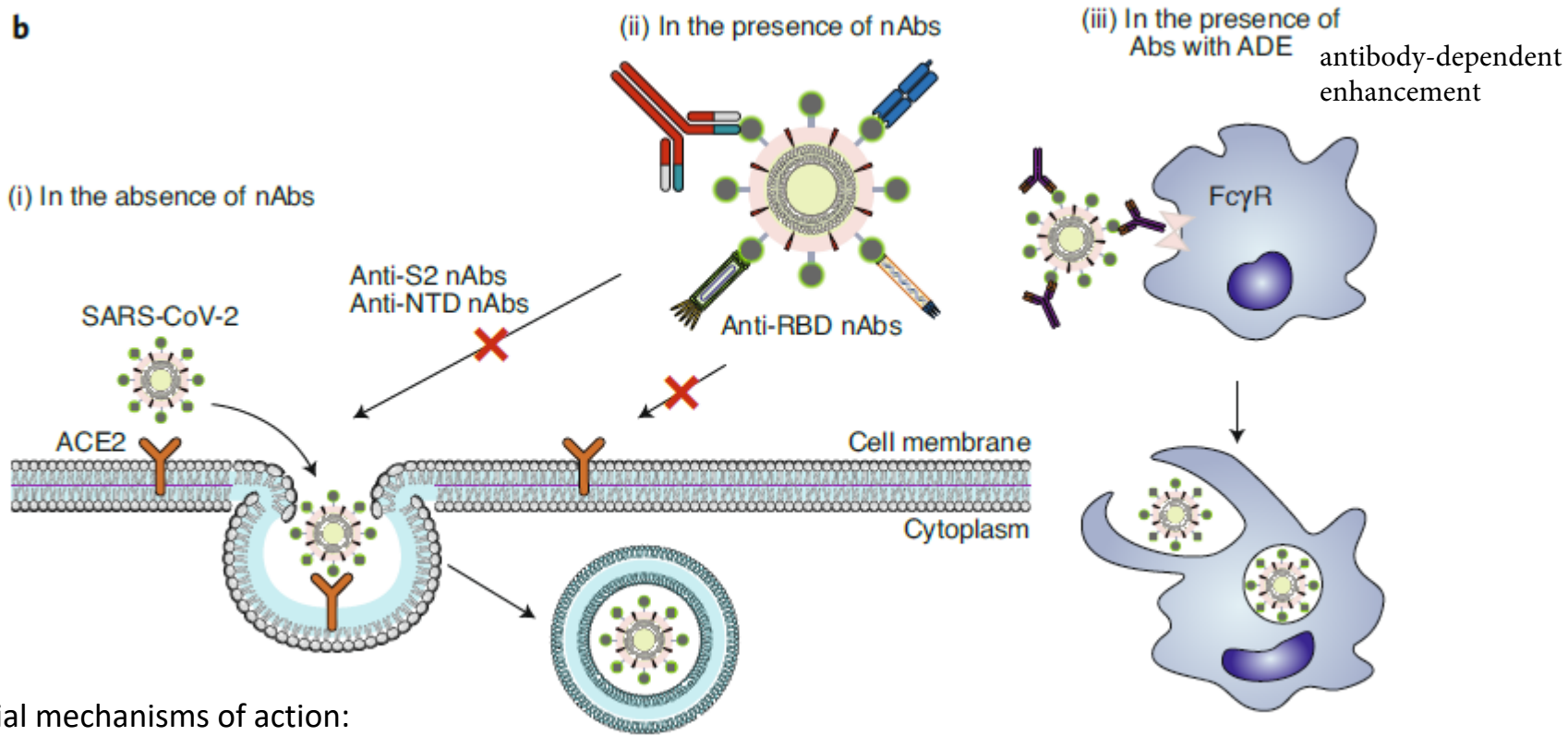
Specific immunoglobulin

- Convalescent plasma from COVID-19 patients was collected through plasmapheresis, then pooled and fractionated
- The C-IVIG preparation is a liquid formulation that can be administered intramuscularly into COVID-19 patients in early stages to neutralize SARS-CoV-2.
- The product has been registered for clinical trials to evaluate its safety and efficacy in patients with SARS-CoV-2 infection.

Specific immunoglobulin



Jiang S, et al. Nature Biomedical Engineering . Dec 2020; 4: 1134–1139



Potential mechanisms of action:

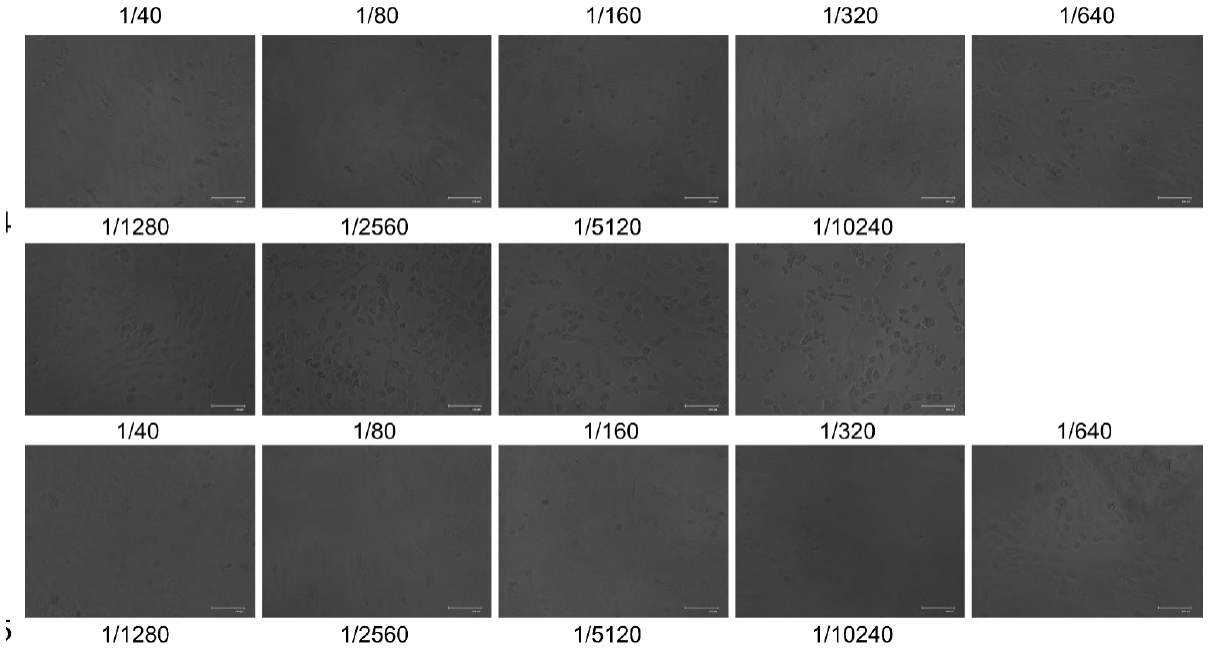
(ii) In the presence of RBD-specific nAbs, the antibodies bind to the RBD and inhibit RBD binding to ACE2, resulting in the inhibition of membrane fusion and the entry of the virus into the host cell.

(iii) In the presence of nAbs with suboptimal or negligible neutralizing activity, the antibody-bound virions may enter cells (such as monocytes or macrophages) through the FcγR, leading to enhanced viral entry, viral replication or inflammation

Jiang S, et al. Nature Biomedical Engineering . Dec 2020; 4: 1134–1139

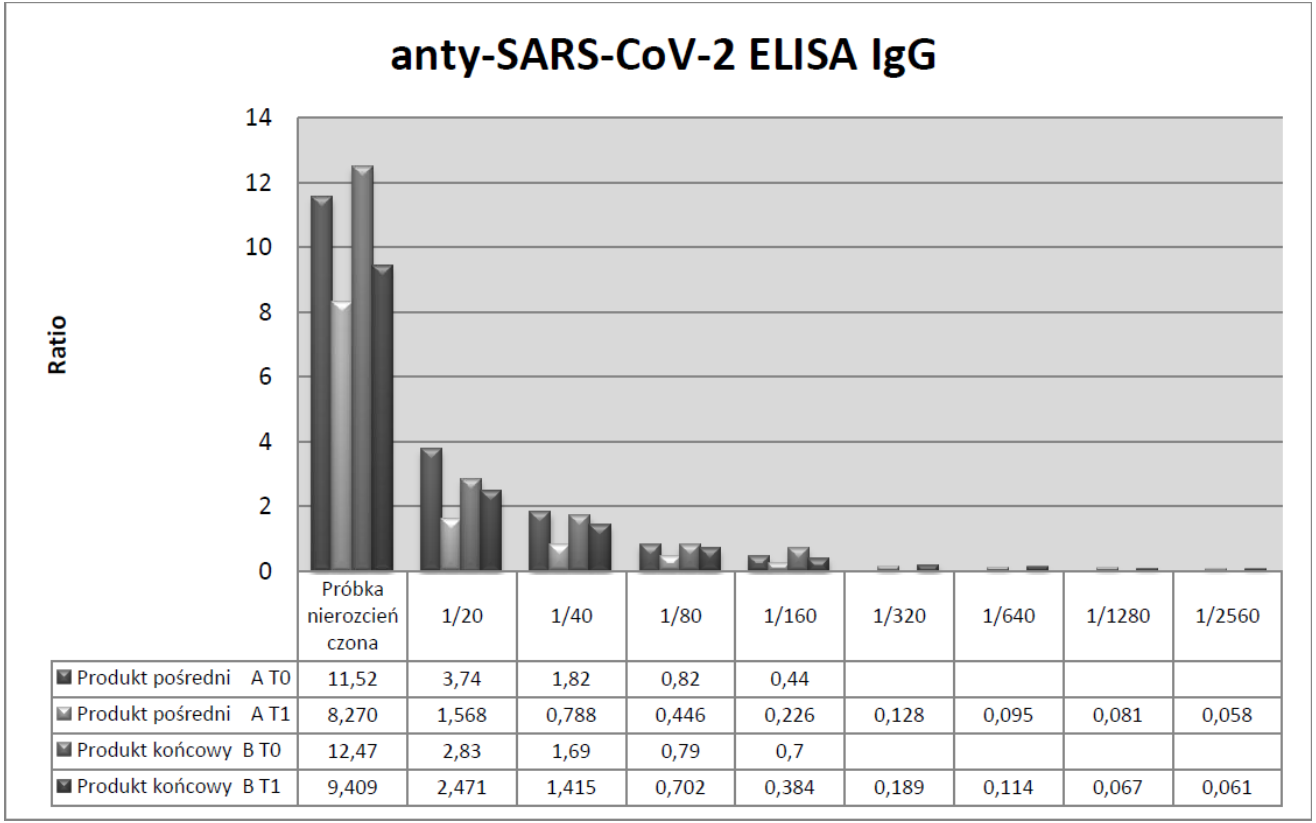
Neutralizing antibodies in specific immunoglobulin anti-SARS-CoV-2

Cell line: Verob.SARS-CoV-2(Munchen-1.2 2020/984)



	1/40	1/80	1/160	1/320	1/640	1/1280	1/2560	1/5120	1/10240
174	+++	+++	+++	++	++	+	-	-	-
185	+++	+++	+++	+++	++	++	+	-	-
186	+++	+++	+++	++	++	-	-	-	-

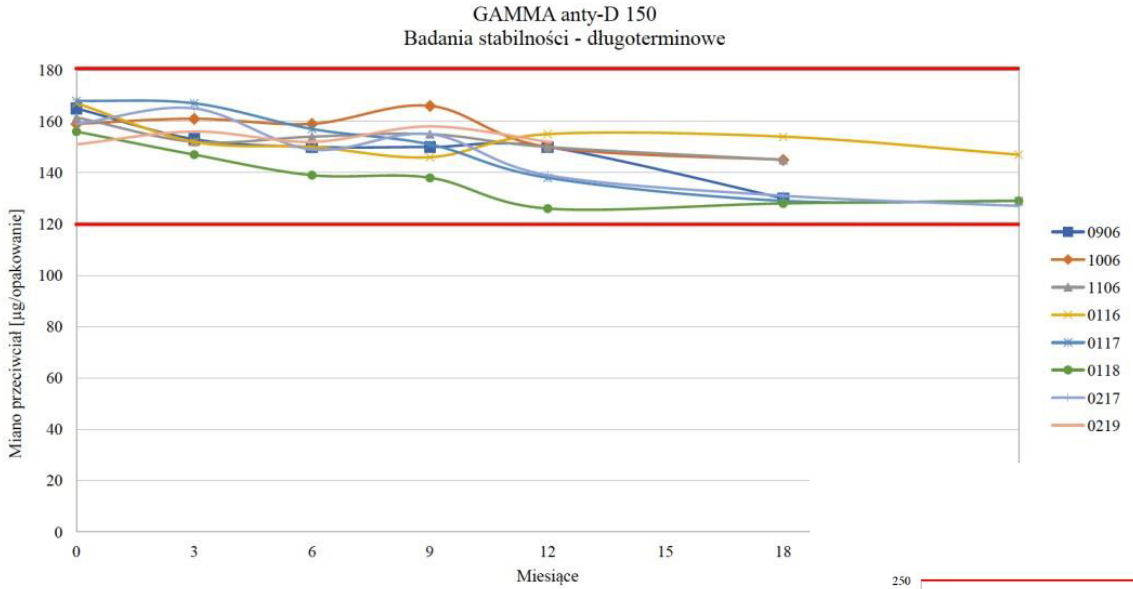
- no inhibition of CPE
+ weak inhibition of CPE
++ moderate inhibition of CPE
+++ strong inhibition of CPE

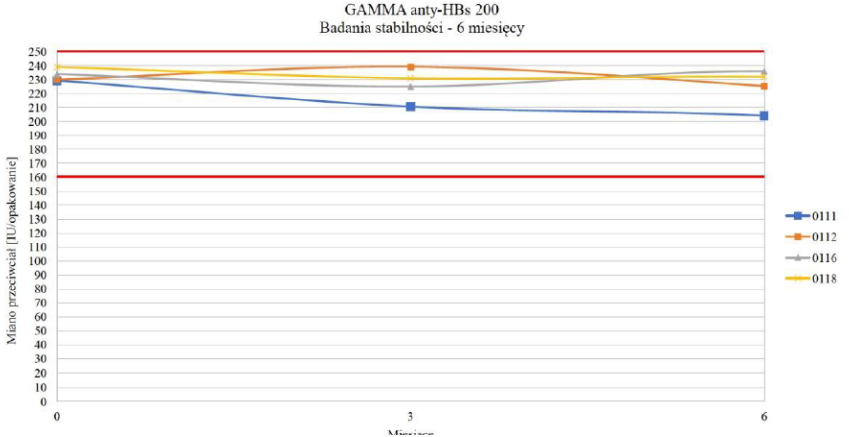


	Próbka nierozcieńczona	1/20	1/40	1/80	1/160	1/320	1/640	1/1280	1/2560
Produkt pośredni A T0	11,52	3,74	1,82	0,82	0,44				
Produkt pośredni A T1	8,270	1,568	0,788	0,446	0,226	0,128	0,095	0,081	0,058
Produkt końcowy B T0	12,47	2,83	1,69	0,79	0,7				
Produkt końcowy B T1	9,409	2,471	1,415	0,702	0,384	0,189	0,114	0,067	0,061

(A T1) 71,8% IgG anty-SARS-CoV-2 – after 1 month,
(B T1) 75,4 % IgG anty-SARS-CoV-2 – after 1 month

Stability


GAMMA anty-D 150
Badania stabilności - długoterminowe
Miano przeciwciał [µg/opakowanie]
Miesiące
0906
1006
1106
0116
0117
0118
0217
0219


GAMMA anty-HBs 200
Badania stabilności - 6 miesięcy
Miano przeciwciał [IU/opakowanie]
0111
0112
0116
0118

Take home messages

- Controversial results of studies with convalescent plasma use in COVID-19 patients, but personal experience and results of many trials are optimistic
- There is no excessive risk of such form of treatment
- Speciffic immunoglobulin – different technology od forms of medication (IV, IM); clinical trials are ongoing, we have to wait…
- Own experience from clincal trial in Poland – stable form of medication, rich in neutralizing Abs and safe procedure, with a number of advantages when compared to plasma