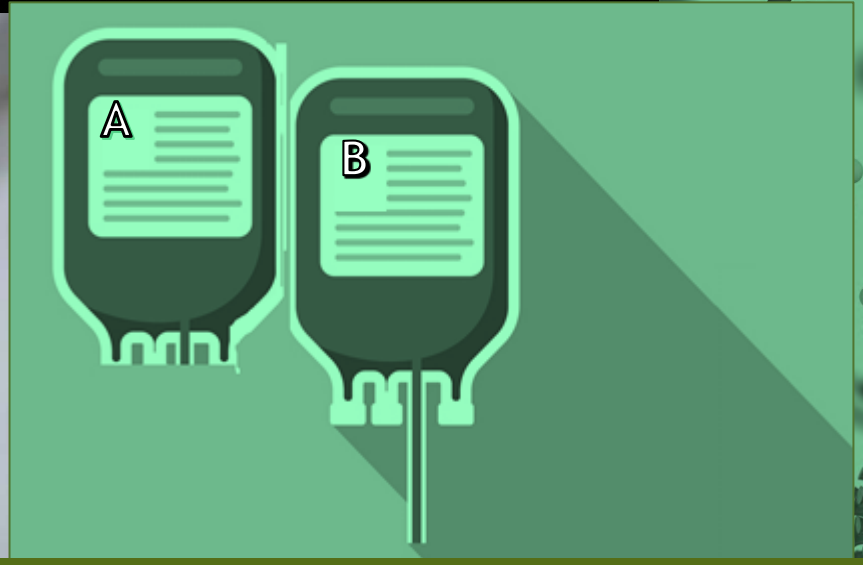
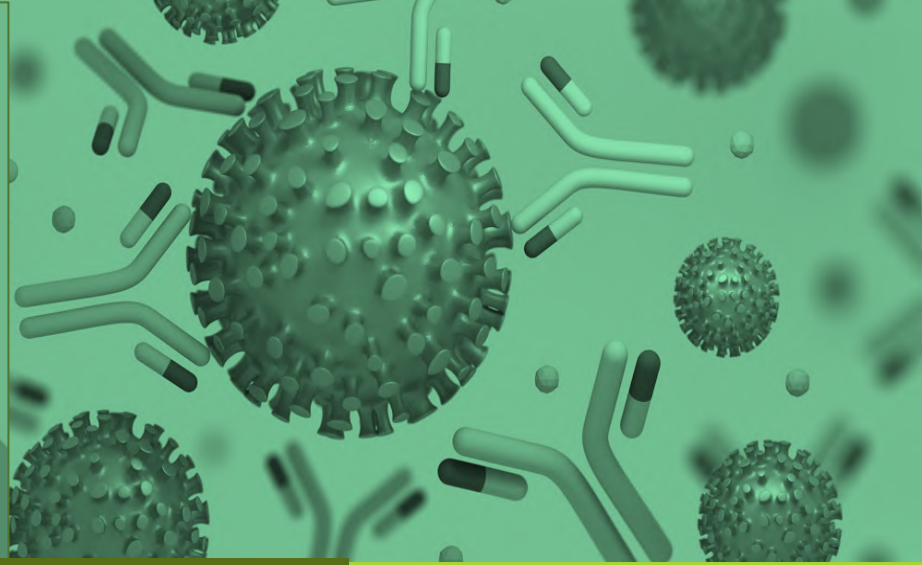




CONVALESCENT PLASMA THERAPY FOR COVID-19:

The right donor and the right patient

David Handojo Muljono

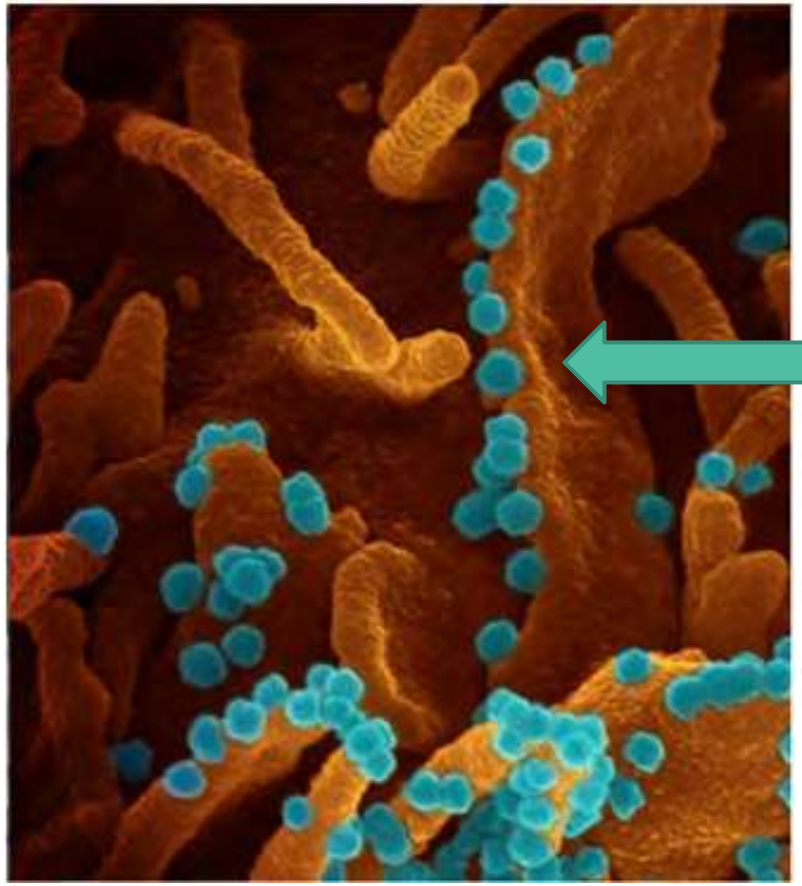
Eijkman Institute for Molecular Biology

Webinar **HOPE FOR CONVALESCENT PLASMA THERAPY**
Jakarta, 23 January 2021

Outline

- **Pathogenesis of Covid-19**

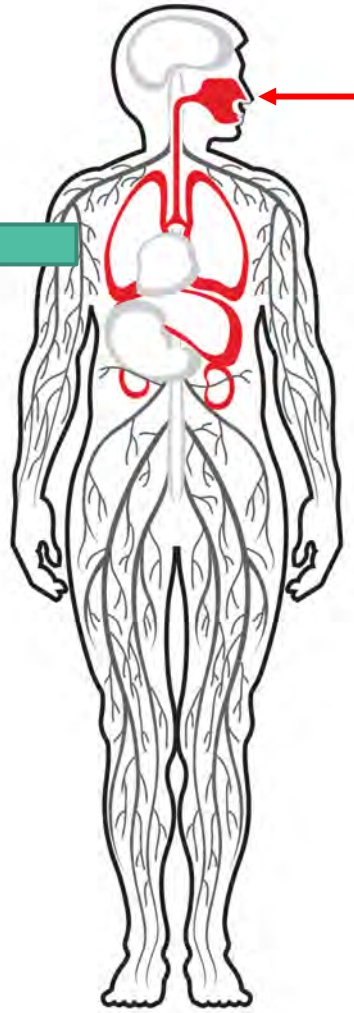
Reseptor ACE-2
banyak terdapat
di paru hati ginjal

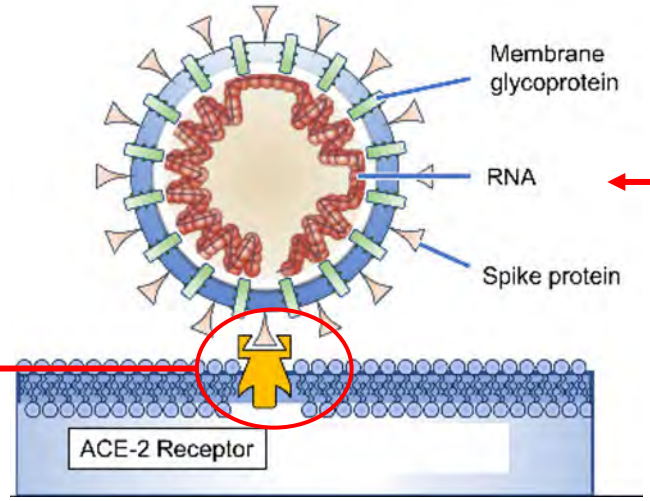


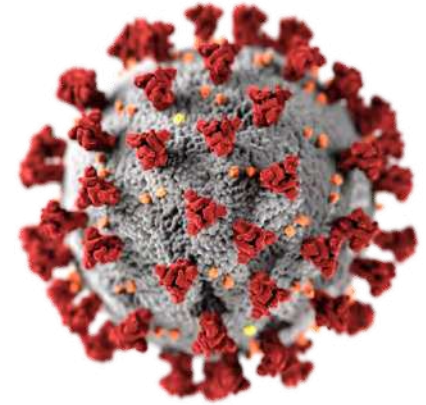
Capturing Viral Shedding in Action

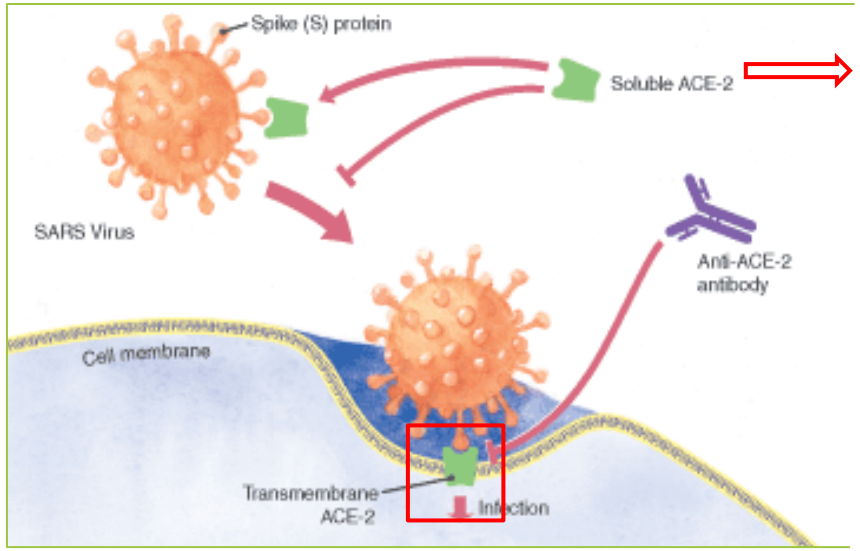
Posted by Dr. Francis Collins

Credit: Rocky Mountain Laboratories,
National Institute of Allergy and Infectious Diseases, Hamilton, MT

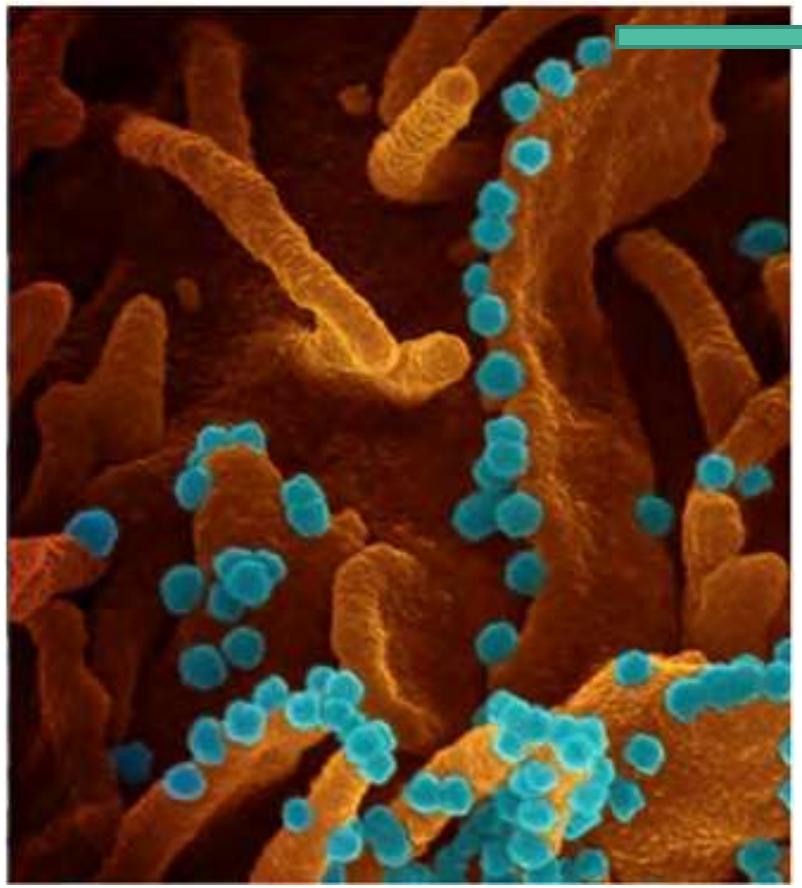








Reseptor ACE-2
juga terdapat di
dalam sirkulasi (larut
dalam darah)



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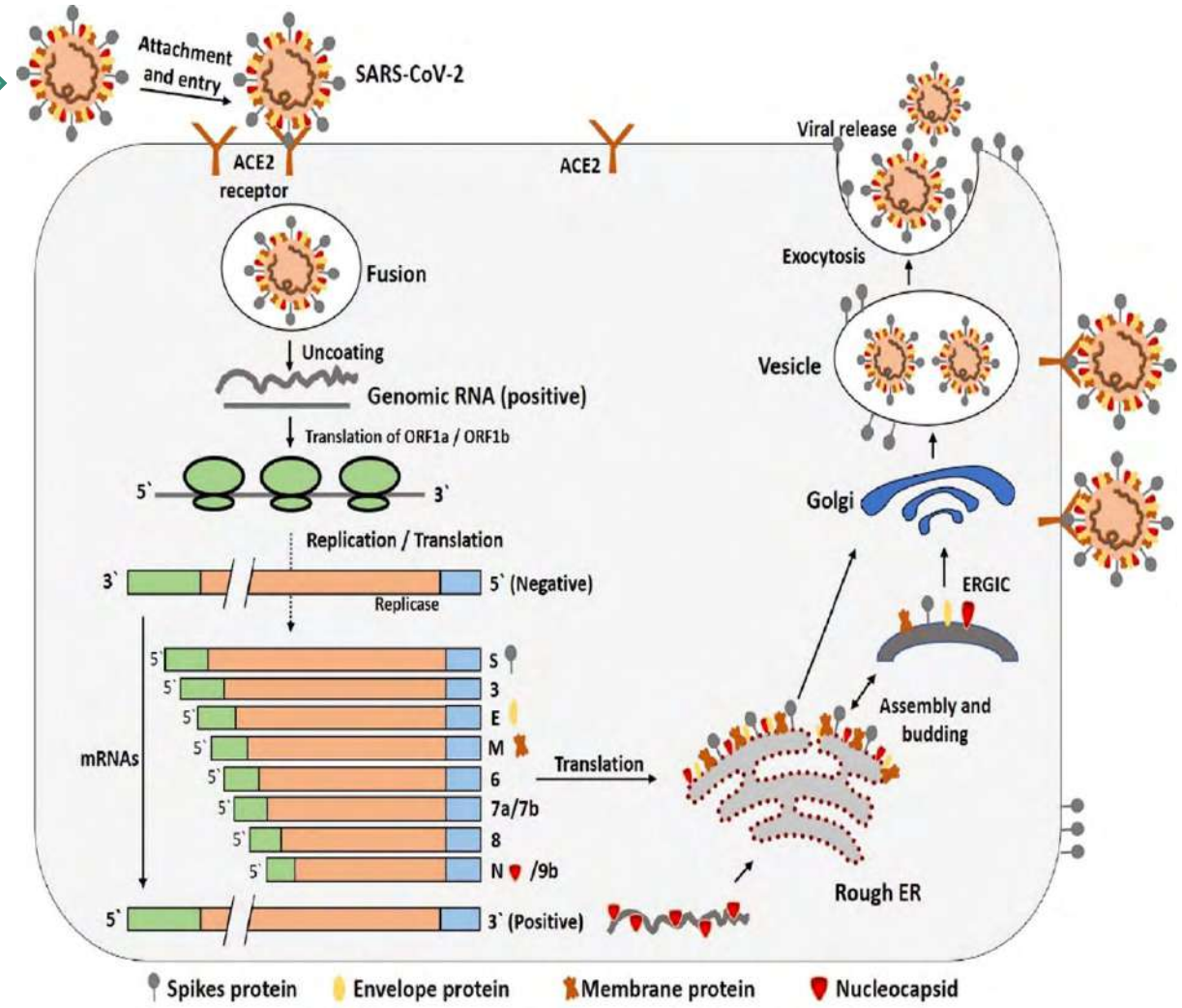
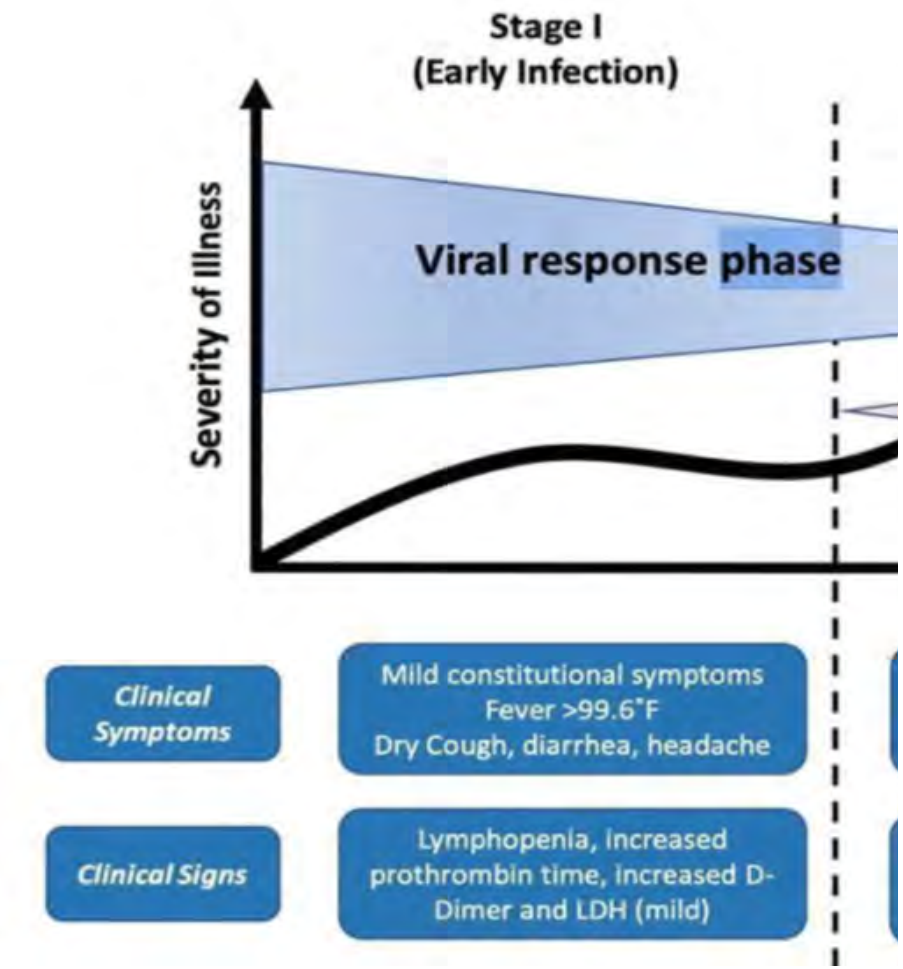


Viremia

1. Fase awal (viremia)



Berlangsung 5-7hari

Gejala tidak spesifik:

– **demam**

– sakit kepala

– **batuk** (dengan/**tanpa** produksi sputum)

– anoreksia

– *malaise*

– nyeri otot

– sakit tenggorokan

– sesak

– kongesti hidung

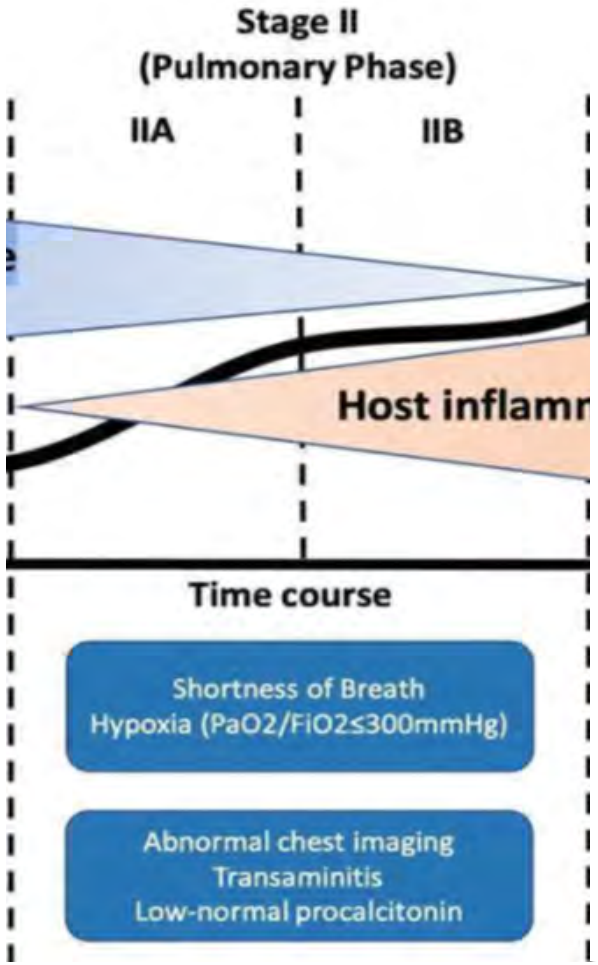
– diare mual atau muntah (< SARS-CoV)

Hasan K. Siddiqi MD MSCR Mandeep R. Mehra MD MSc COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal Journal of Heart and Lung Transplantation(2020) doi: https://doi.org/10.1016/j.healun.2020.03.012

2. Fase Sedang

Dua hal pokok:

1. Peran virus berkurang
2. Radang meningkat



Dua kemungkinan (*persimpangan jalan*):

- Berhasil → **perbaikan**
- **Tidak berhasil** → radang semakin aktif

Rasio Neutrofil/Limfosit (NLR) ↗
C-Reactive protein ↗

Hiperinflamasi

Hasan K. Siddiqi MD MSCR Mandeep R. Mehra MD MSc COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal Journal of Heart and Lung Transplantation(2020) doi: https://doi.org/10.1016/j.healun.2020.03.012

3. Fase Hiperinflamasi

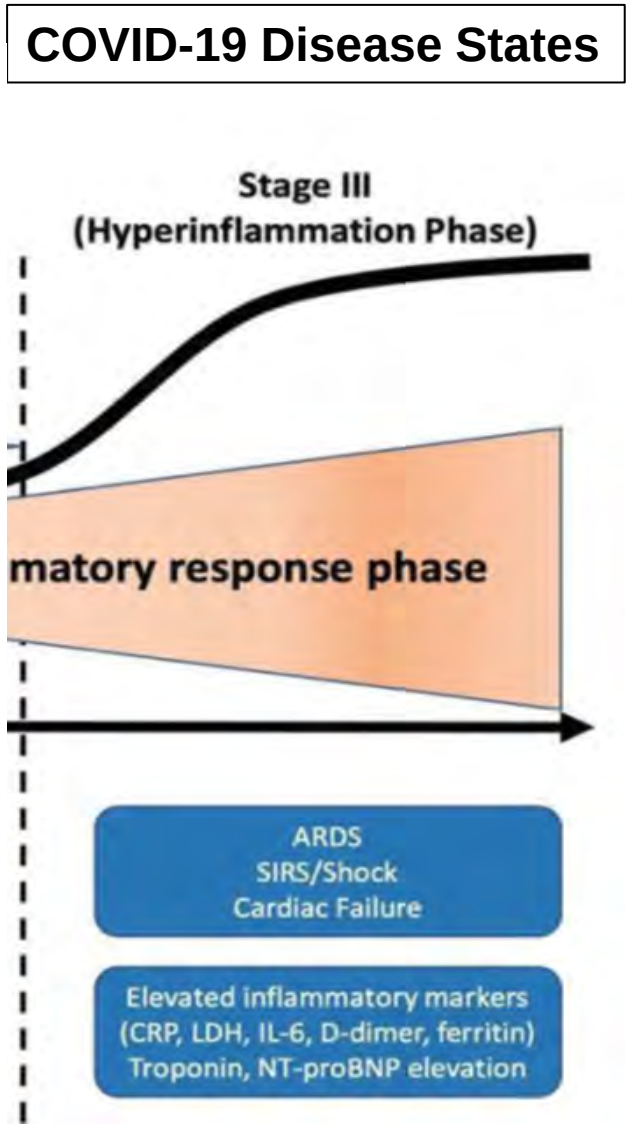
Fase Berat

- Hiperinflamasi → cytokine storm
  - CRP, D-Dimer, Pro-calcitonin meningkat tinggi

- Terjadi Pneumonia, disertai :
  - Frekuensi napas ≥ 30x/menit
  - Distress pernapasan berat
  - Saturasi O2 <93%

Fase kritis (ARDS)

- Baru terjadi atau perburukan dalam 1 minggu
- Ringan (PaO2/FiO2: 200 - ≤300 mmHg)
- Sedang (PaO2/FiO2: 100 - ≤200 mmHg)
- Berat (PaO2/FiO2: ≤100 mmHg)

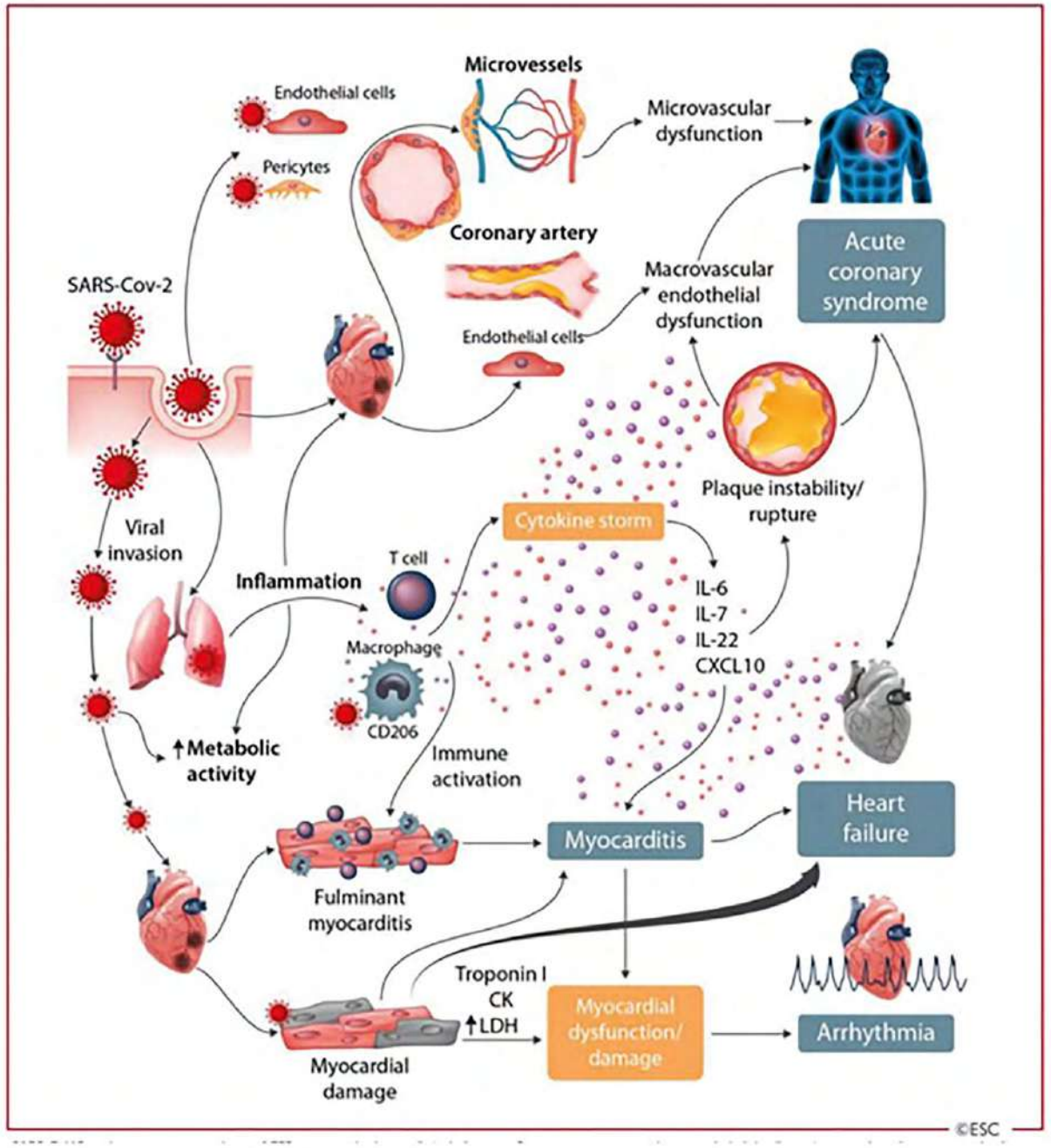


Hasan K. Siddiqi MD MSCR Mandeep R. Mehra MD MSc COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal Journal of Heart and Lung Transplantation(2020) doi: https://doi.org/10.1016/j.healun.2020.03.012

3. Fase Hiperinflamasi

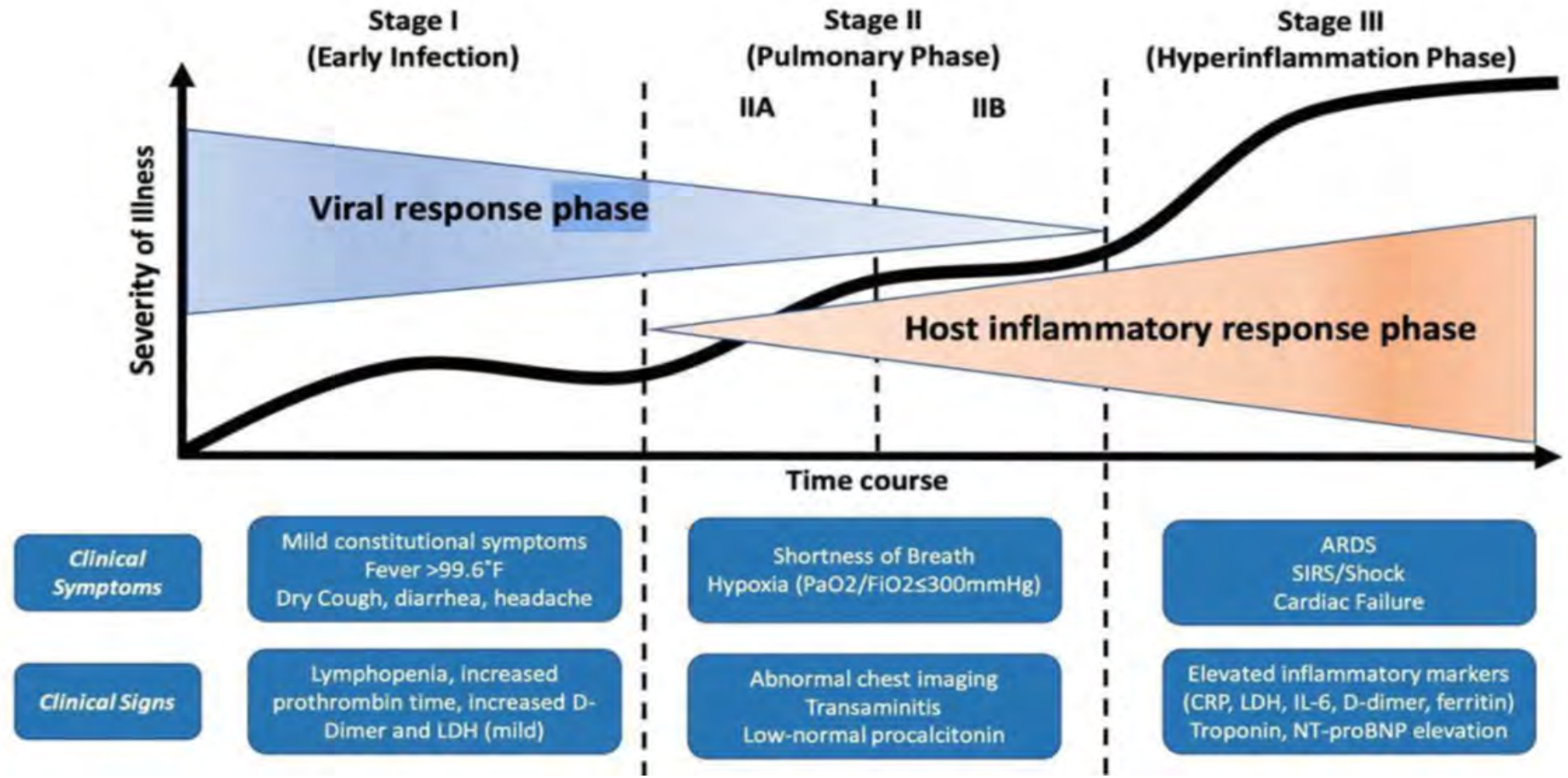
- Radang sistemik (seluruh tubuh) (Increased Pro-calcitonin, C-Reactive protein, IL-6, etc.)
  → kegagalan fungsi berbagai organ

- Gangguan pembekuan:
  (kenaikan D-Dimer; Prothrombin time, etc.)
  → Penyumbatan atau perdarahan



Ref: Consensus of Cardiology Association in the Management of COVID-19 (2020)

DISEASE MANIFESTATION



Hasan K. Siddiqi MD MSCR Mandeep R. Mehra MD MSc COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal Journal of Heart and Lung Transplantation(2020) doi: https://doi.org/10.1016/j.healun.2020.03.012

Outline

- Pathogenesis of Covid-19
- **Therapy of COVID-19: Convalescent plasma is an option**

Plasma Konvalesen

- Dalam ketiadaan pengobatan COVID-19 yang baku, terapi Plasma konvalesen merupakan opsi panjang (***long option***) bagi negara berkembang (Low- and middle economy country/LMIC), termasuk Indonesia,
  - Teknologi yang “tidak sebanding” dengan negara yang memiliki infrastruktur riset yang mapan dan ditunjang kesiapan industri farmasi
  - Ketidak pastian akses untuk memanfaatkan hasil riset dan obat baru (bila ada)
- Indonesia memiliki ‘populasi’ Penyintas COVID-19 yang dapat menjadi donor:
  - Data 22 januari 2021:
    - 965.283 positif (ranking 19),
    - 27.453 meninggal (ranking 17),
    - Sembuh **781.147 (80.9%)**

Plasma Konvalesen

- **Opsi** pengobatan
- Riwayat: telah digunakan (***dicoba***) untuk penganganan Spanish Flu (1908), SARS, MERS, EBOLA, H5N1 influenza
- **Studi/Pengobatan Pendahuluan pada COVID-19:**
  - cukup '*aman*' (tak ada efek samping nyata)
  - Namun dilakukan dalam skala kecil, sporadik, tanpa indikasi yang jelas, tanpa protokol (jadwal, dosis, dll)

FDA dan Otoritas Regulasi diberbagai negara:

- PK belum menjadi 'standar pengobatan (Standard of Care)
- Memperbolehkan dalam bentuk **clinical trial (Uji Klinik)**

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

Effectiveness of convalescent plasma therapy in severe COVID-19 patients

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

[Novel Reports]

CHEST

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

Mengapa Perlu Uji Klinik?

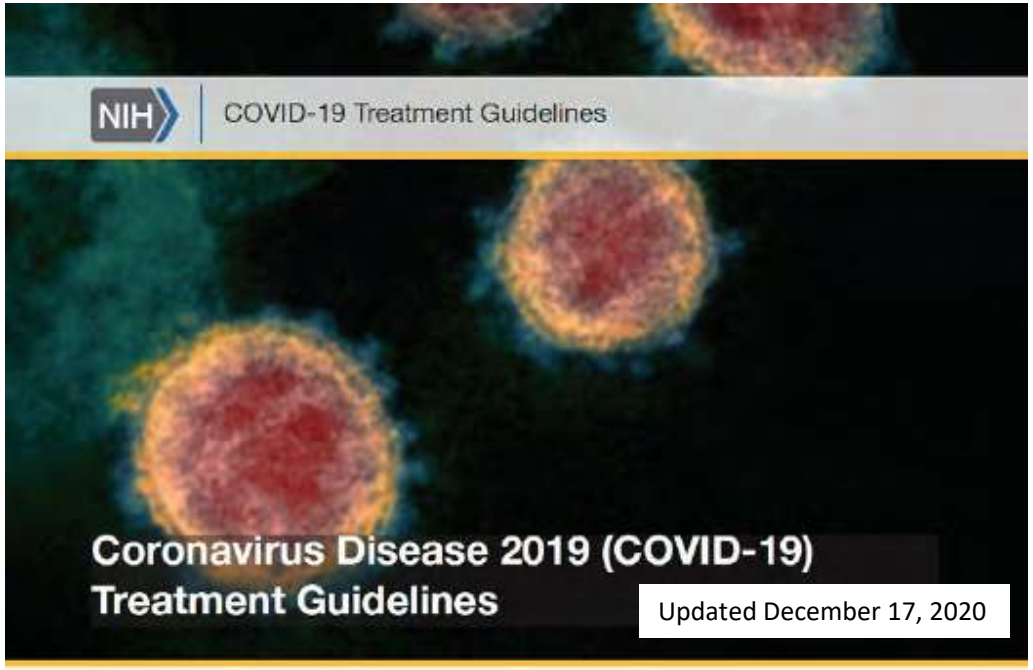
WORLD MEDICAL ASSOCIATION

WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

64th WMA General Assembly, Fortaleza, Brazil, October 2013

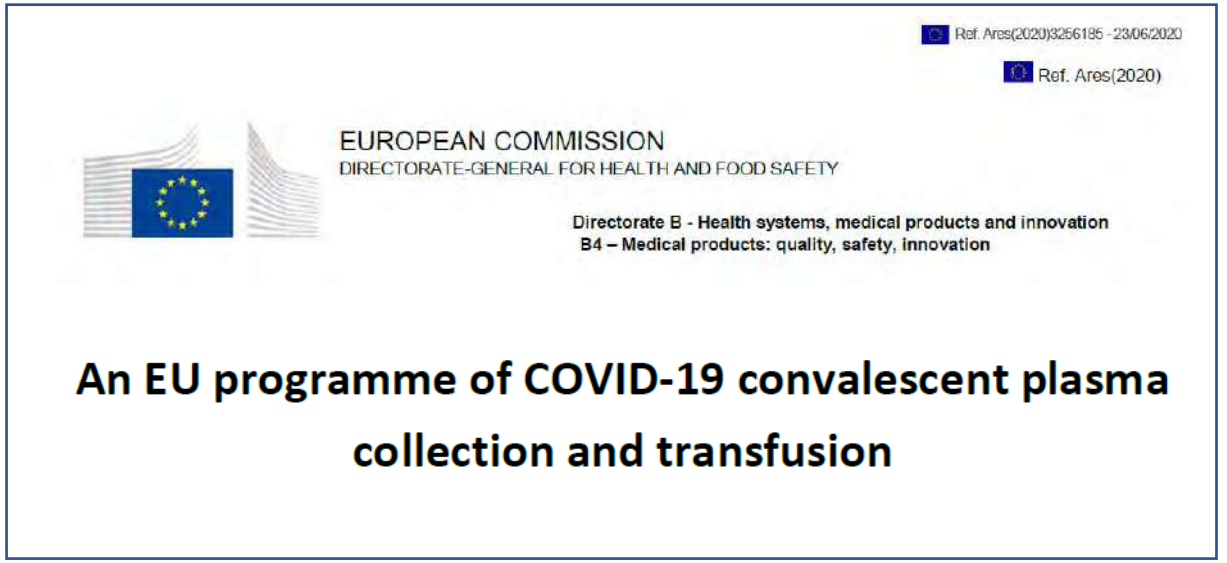
Unproven Interventions in Clinical Practice

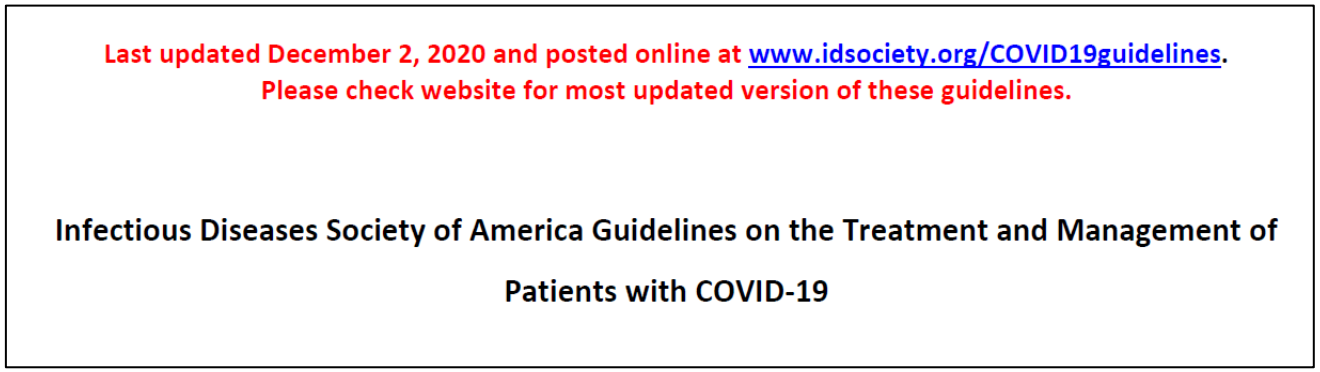
37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

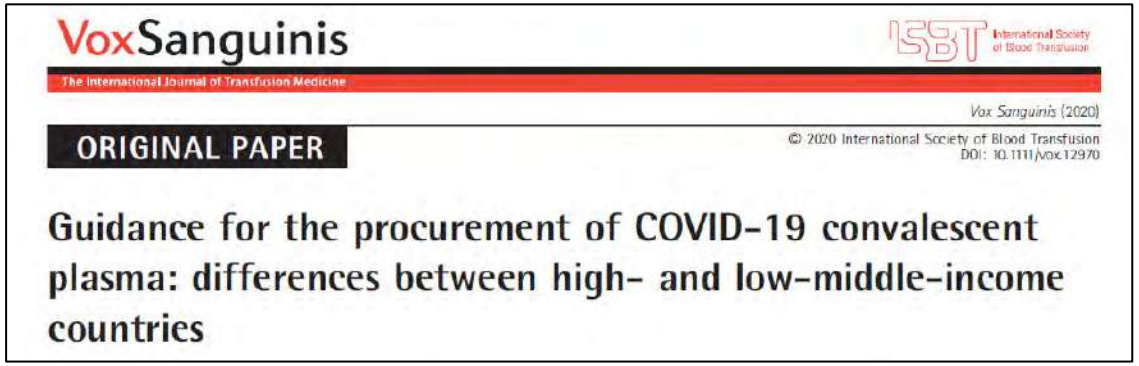


Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.
- Results of powered, randomized clinical trials are needed
- Points to consider:
  - Donor prequalification
  - Timing and Schedule of treamtnet
  - Type of patients







MENTERI KESEHATAN
REPUBLIK INDONESIA

KEPUTUSAN MENTERI KESEHATAN REPUBLIK INDONESIA
NOMOR HK.01.07/MENKES/346/2020
TENTANG
TIM PENELITIAN UJI KLINIS PEMBERIAN PLASMA KONVALESEN
SEBAGAI TERAPI TAMBAHAN *CORONA VIRUS DISEASE* 2019 (COVID-19)

DENGAN RAHMAT TUHAN YANG MAHA ESA

MENTERI KESEHATAN REPUBLIK INDONESIA,

Menimbang : a. bahwa untuk upaya percepatan penanganan *Corona Virus Disease* 2019 (Covid-19), perlu dilakukan terapi tambahan dalam pengobatan penderita Covid-19;

b. bahwa kekebalan imunitas pasif melalui pemberian *immunoglobulin* dengan plasma konvalesen dipandang tepat dilakukan sebagai terapi tambahan pengobatan pasien Covid-19;

c. bahwa untuk mengevaluasi keamanan dan efek plasma konvalesen sebagai terapi tambahan pengobatan standar pada penderita Covid-19, perlu dilakukan uji klinis yang dilakukan oleh tim penelitian;

SUSUNAN ORGANISASI
TIM PENELITIAN UJI KLINIS PEMBERIAN PLASMA KONVALESEN
SEBAGAI TERAPI TAMBAHAN COVID-19

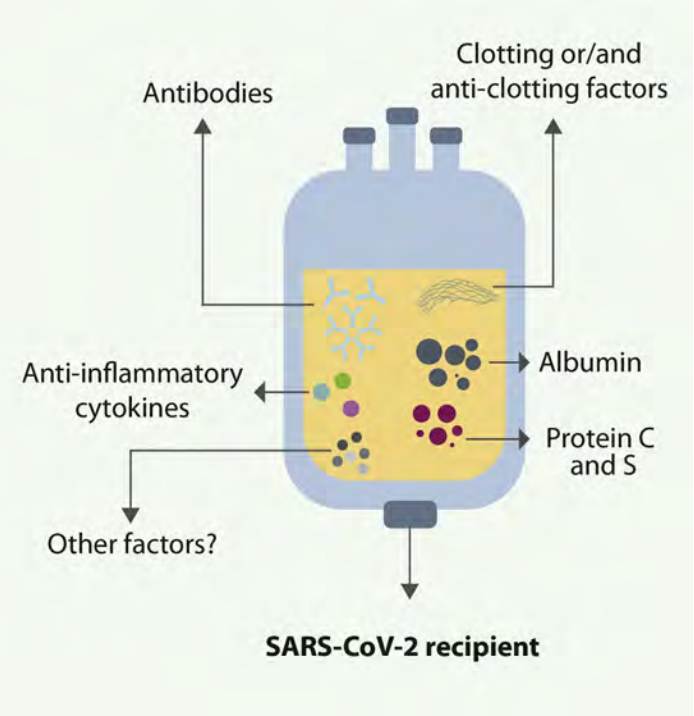
I. Pembina :
1. Menteri Kesehatan
2. Menteri Riset dan Teknologi / Kepala Badan Riset dan Inovasi Nasional (BRIN)

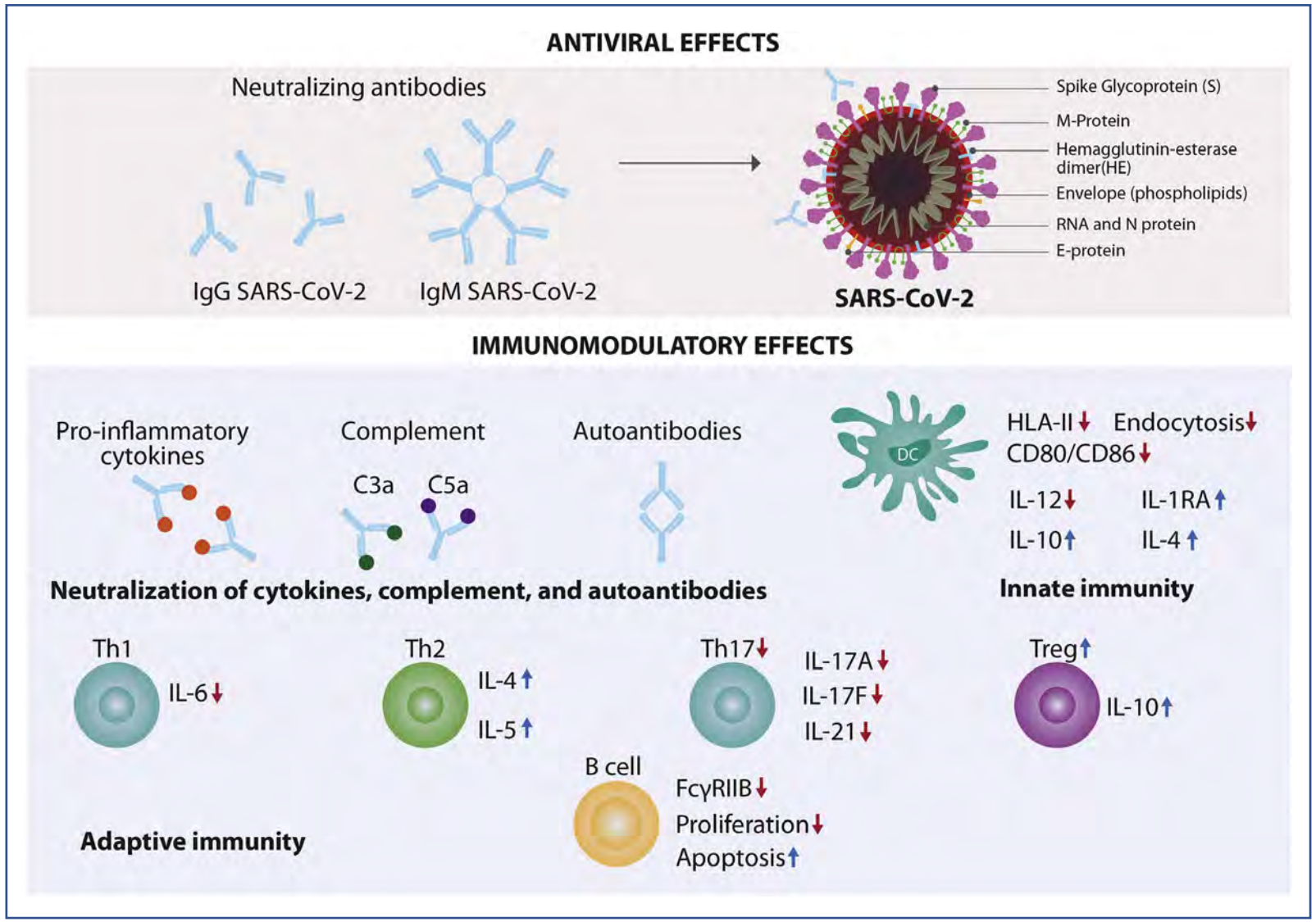
II. Penanggung Jawab : Kepala Badan Penelitian dan Pengembangan Kesehatan

III. Tim Penasihat :
1. Prof. dr. Abdul Kadir, PhD, Sp.THT-KL(K), MARS
2. Prof. dr. R. Sjamsuhidajat, Sp.B(KBD)
3. Prof. dr. Ali Ghufron Mukti, MSc, PhD
4. Prof. dr. Amin Soebandrio, Sp.MK (K), PhD
5. Prof. dr. Menaldi Rasmin, Sp.P (K)
6. Prof. Dr. dr. Agus Purwadianto, DFM., SH, M.Si, Sp.F(K)
7. Prof. Dr. dr. Tubagus Djumhana Atmakusuma, Sp.PD-KHOM
8. dr. Siswanto, MHP, DTM
9. dr. R. Triono Soendoro, PhD
10. dr. Albertus Budi Sulistiya Sp.THT-KL(K)
11. dr. Alex Ginting S, Sp.P(K)
12. Dr. dr. Fathema Djan Rachmat, Sp.B, Sp.BTKV (K), MPH
13. Dra. Rita Endang, Apt, M.Kes
14. Dr. M. Rahman Roestan, Apt, MM
15. dr. Linda Lukitari Waseso
16. Dr. dr. Agus Dwi Susanto, Sp.P (K), FISR, FAPSR
17. dr. Rita Rogayah, Sp.P(K), MARS
18. dr. I Wayan Agus Putra, Sp.P
19. Dr. dr. Erlina Burhan, Sp.P(K), M.Sc

Peran Plasma konvalesen bagi pengobatan COVID-19

- ✓ **Antibodi spesifik**
- ✓ **Imunomodulator**





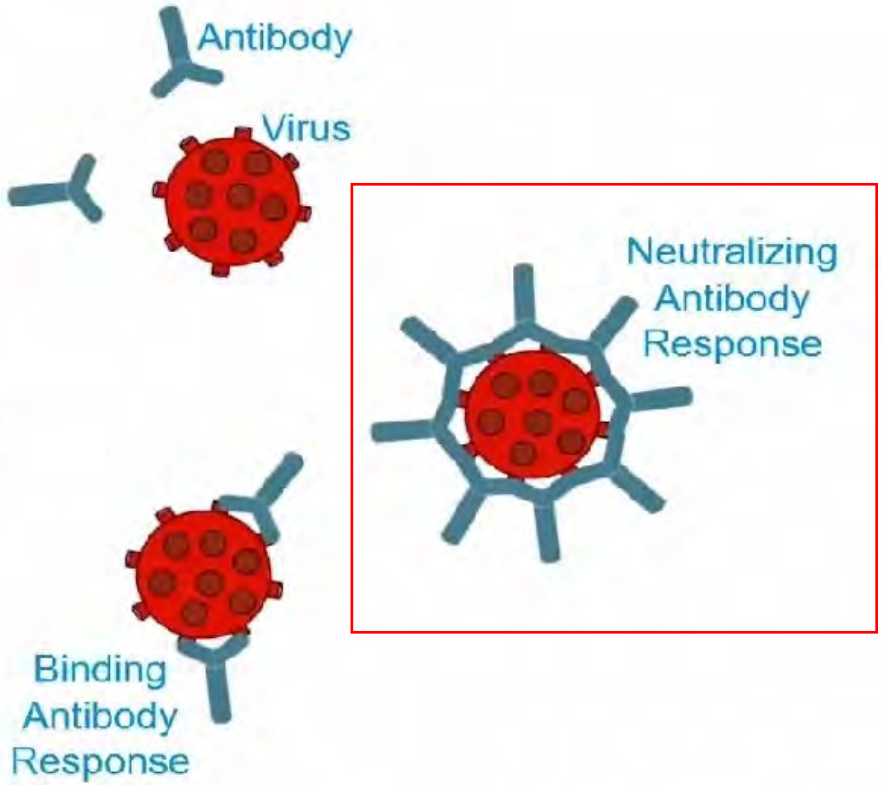
Rojas et al. Convalescent plasma in Covid-19: Possible mechanisms of action Autoimmune reviews 2020. doi.org/ 10.1016 / j.autrev.2020.

Outline

- **Pathogenesis of Covid-19**
- Therapy of COVID-19: Convalescent plasma is an option
- **Convalescent plasma – donor's side**

Types of Protective Immune Responses

- Neutralizing antibodies
  - Antibodies bind and inactivate virus
  - Prevent viral entry into cells
  - Promote viral clearance
- Binding antibodies
- Non-neutralizing antibodies with other effector functions
- Cellular immune responses



AASLD

What do we know about immunity to COVID-19?

- Protective immunity may be transient after infection
- Neutralizing antibodies likely contribute to protection
- Presence of antibodies does not guarantee protection
  - Quantity and quality of antibodies not measured by routine assays
  - Some antibodies can be harmful ('Antibody-Dependent Enhancement'); the 'right' antibodies are needed

UCSF
University of California

Kemampuan Plasma Konvalesen?

Saat ini belum ada Teknologi yang tersedia **mendeteksi dan mengukur** Antibodi Netrakisasi yang spesifik
(*Gold standard: PRNT*)
• Belum tahu:
o Apakah mengandung antibodi spesifik/non spesifik?
o Berapa titernya?

nature reviews immunology

Published: 21 April 2020

The potential danger of suboptimal antibody responses in COVID-19

Akiko Iwasaki ✉ & Yexin Yang

Nature Reviews Immunology **20**, 339–341(2020)

106k Accesses | **10** Citations | **1562** Altmetric | Metrics

There is a desperate need for effective therapies and vaccines for SARS-CoV-2 to mitigate the growing economic crisis that has ensued from societal lockdown. Vaccines are being developed at an unprecedented speed and are already in clinical trials, without preclinical testing for safety and efficacy. Yet, safety evaluation of candidate vaccines must not be overlooked.

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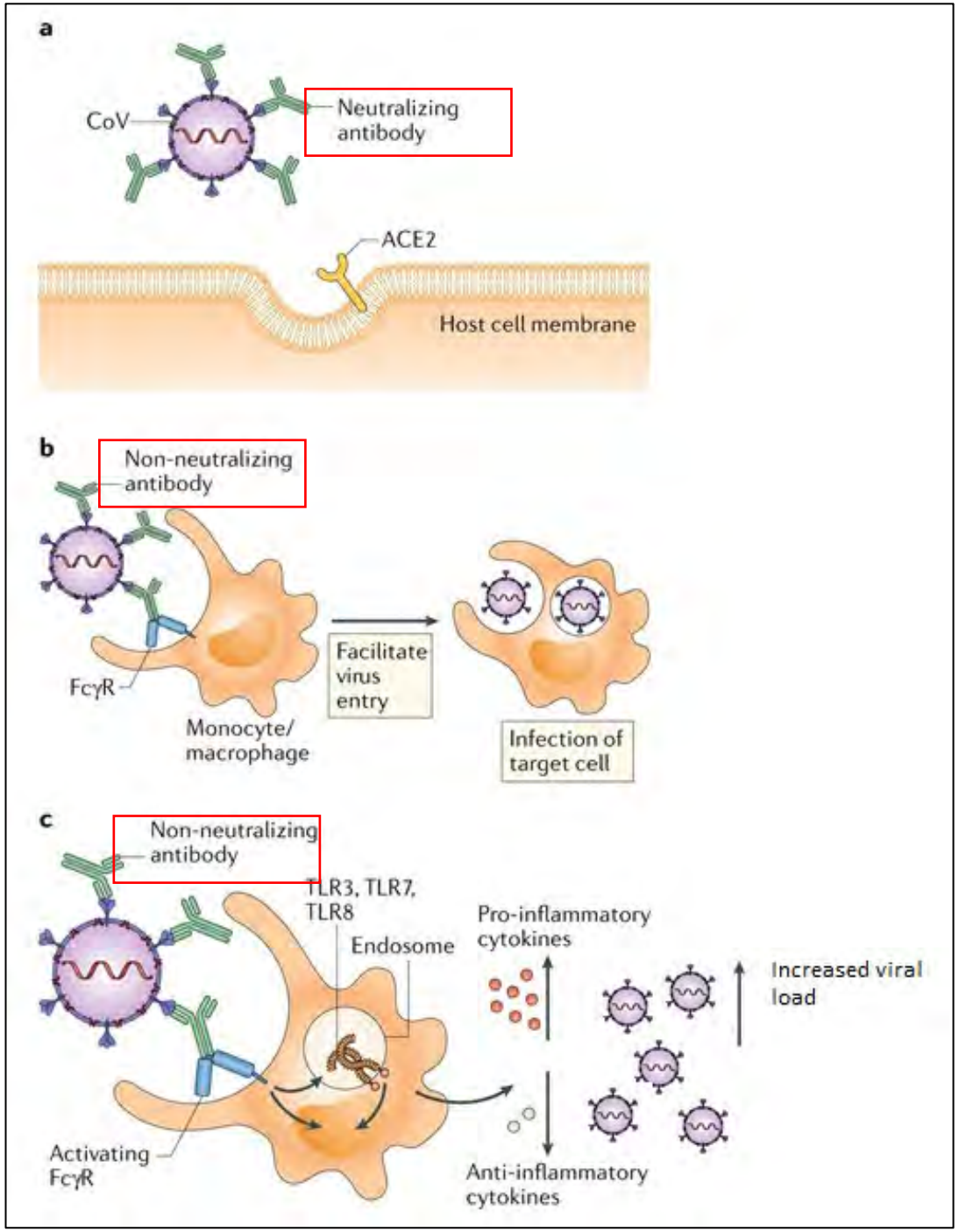


Donor

nature medicine

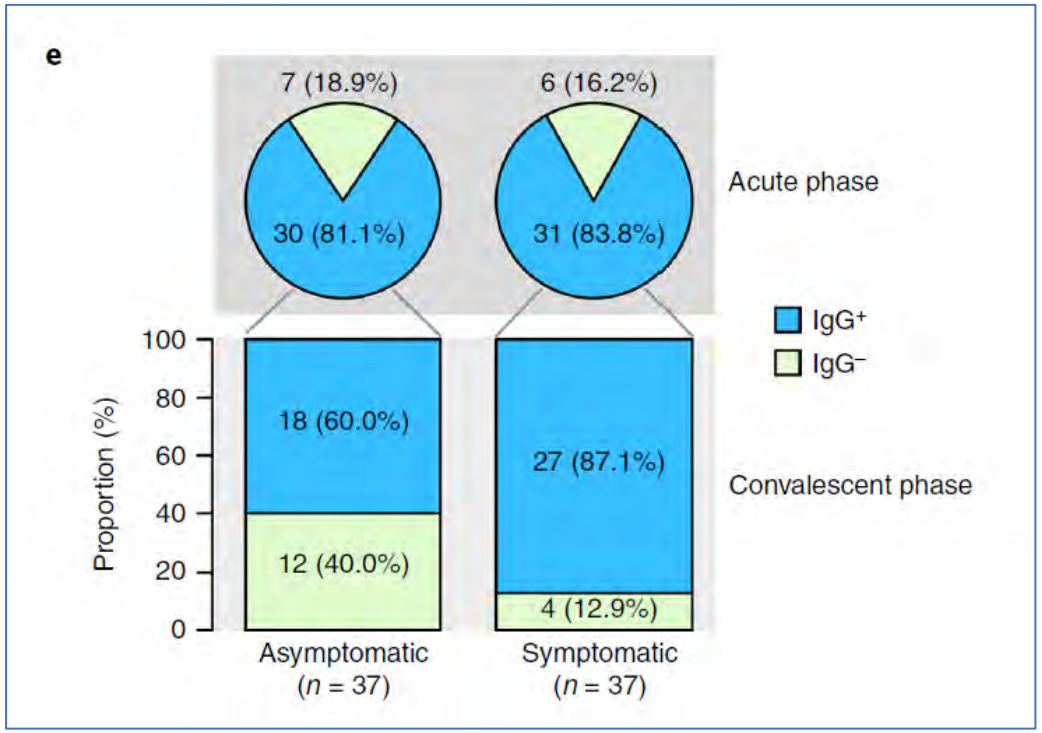
LETTERS

https://doi.org/10.1038/s41591-020-0965-6

Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections

Quan-Xin Long[1,8], Xiao-Jun Tang[2,8], Qiu-Lin Shi[2,8], Qin Li[3,8], Hai-Jun Deng[1,8], Jun Yuan[1], Jie-Li Hu[1], Wei Xu[2], Yong Zhang[2], Fa-Jin Lv[4], Kun Su[3], Fan Zhang[5], Jiang Gong[5], Bo Wu[6], Xia-Mao Liu[7], Jin-Jing Li[7], Jing-Fu Qiu[2✉], Juan Chen[1✉] and Ai-Long Huang[1✉]

- Plasma from asymptomatic individuals had **lower** IgG that symptomatic group
- Asymptomatic individuals became seronegative **faster** in the early convalescent phase



Convalescent plasma in the management of moderate COVID-19 in India: An open-label parallel-arm phase II multicentre randomized controlled trial - PLACID Trial

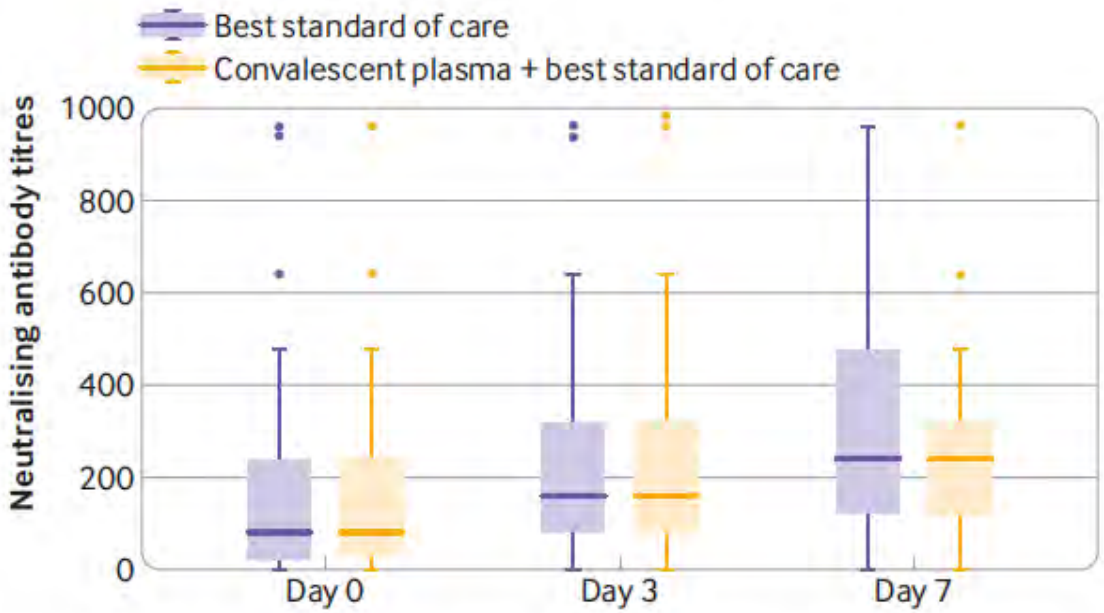


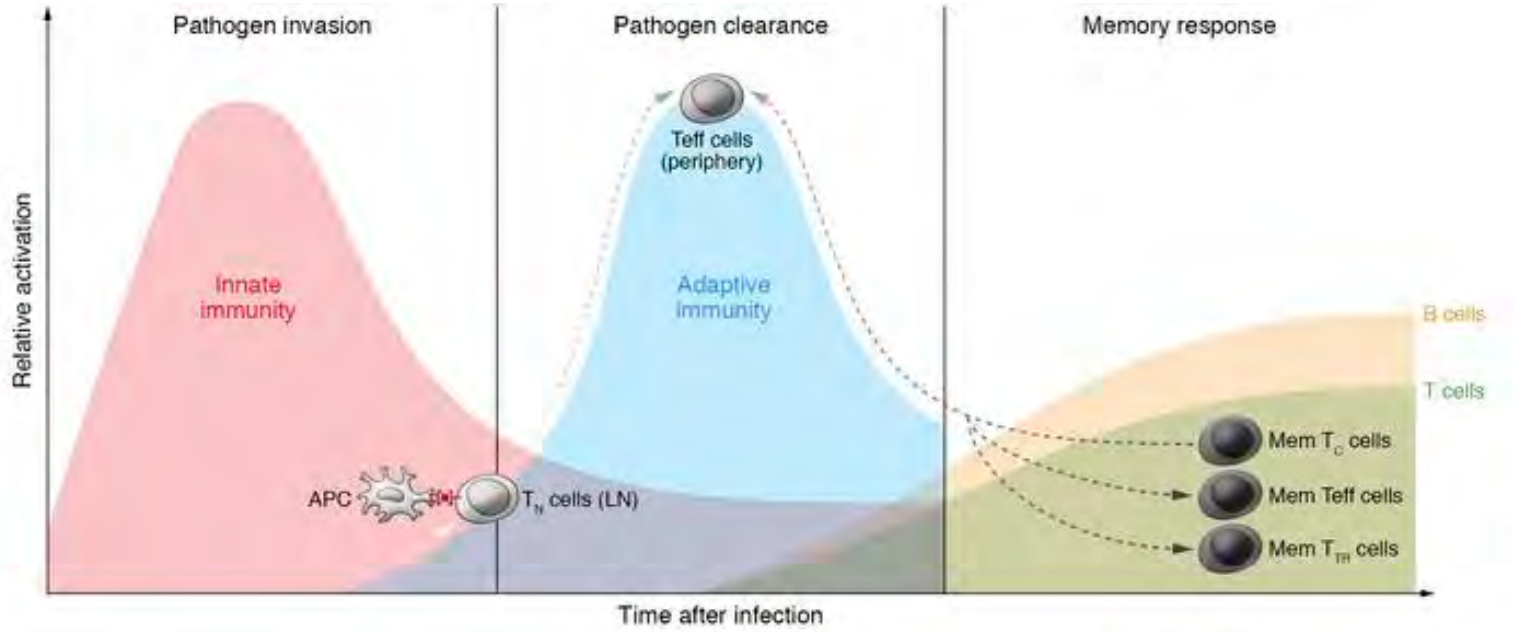
Fig 3 | Comparison of neutralising antibody titres between intervention (convalescent plasma therapy and best standard of care and control (best standard of care) arms, by days 0, 3, and 7 post-enrolment

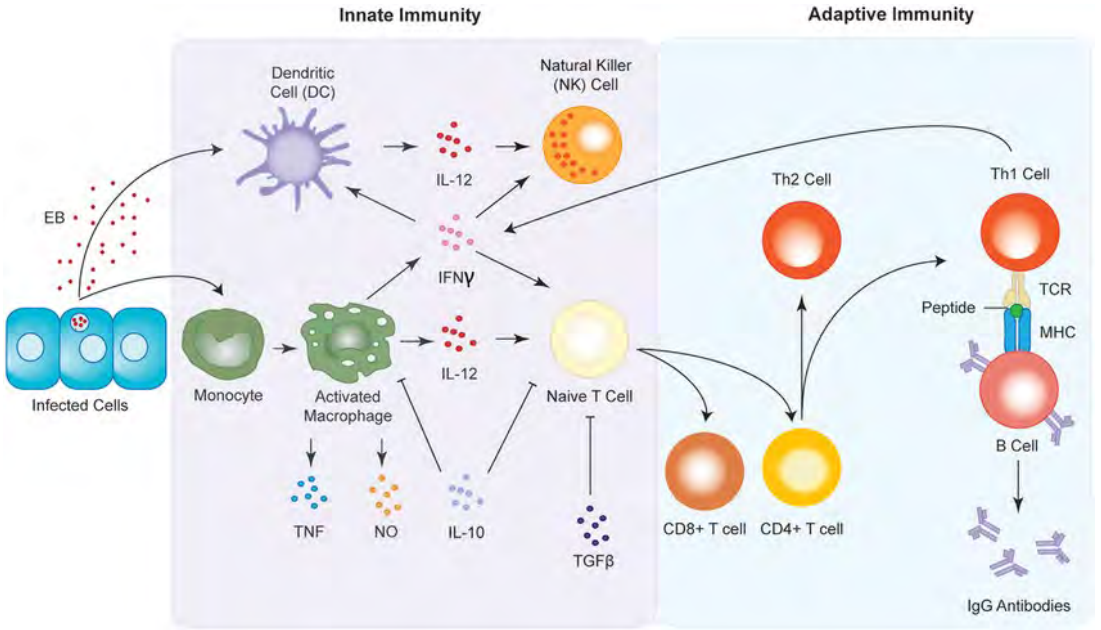
- **Neutralizing antibody** titres **did not differ between the two trial arms** despite the transfusion of convalescent plasma.
- **Participants had higher antibody** positivity and median neutralizing antibody titres **than the donors** of convalescent plasma.
- The **difference in age and severity of illness** between participants, with **donors being younger and having milder disease**, could have driven this difference.
- Potentially **no benefit of convalescent plasma collected from young survivors of mild covid-19** and administered to elderly patients with moderate or severe disease who have a robust antibody response.

Agarwal, September 2020

Pattern of immune response

Patients with good immune status can eliminate the infection at early stage (without having to produce high antibodies)





Khader et al: J Clin Invest
DOI: 10.1172/JCI128877

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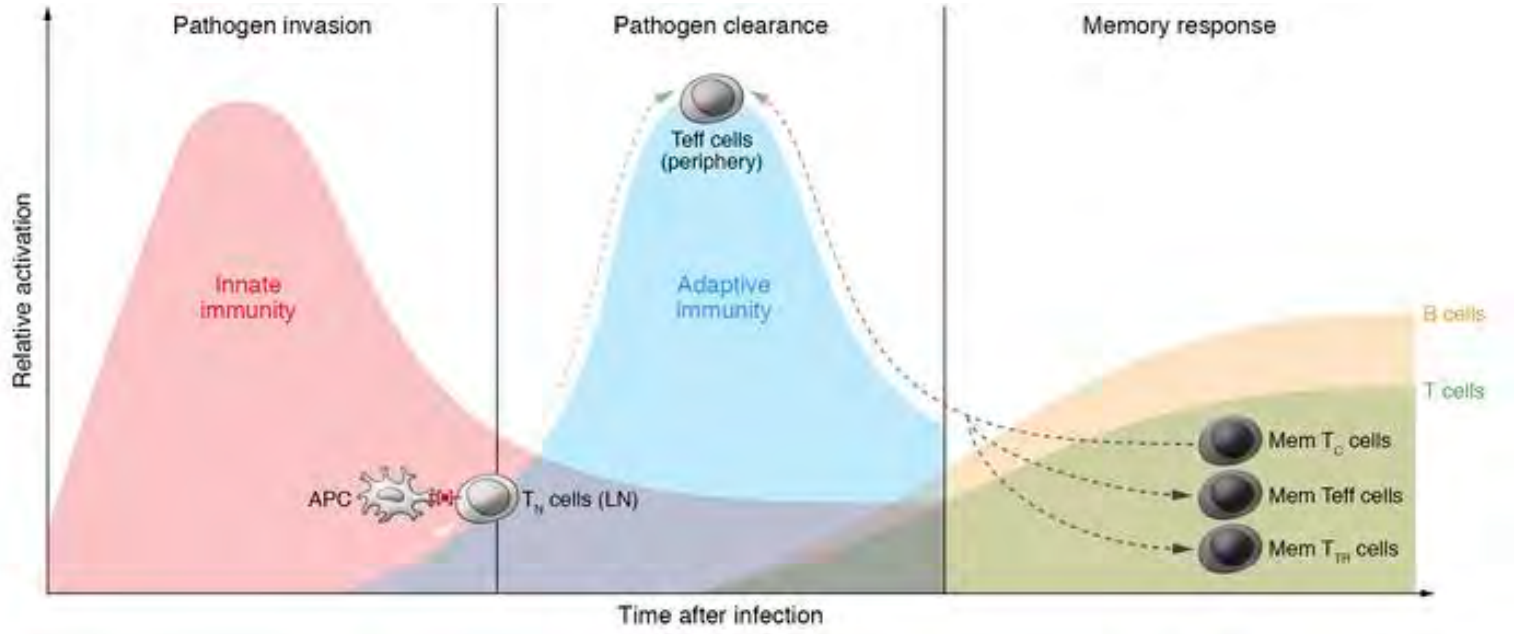


Early phase, Patients can recover by innate immunity
Start to produce antibodies

Antibodies reach peak levels
(if successful, clinical condition will progress)

Memory cells will be formed
(which will generate antibodies if the same antigens are present)

Khader et al: J Clin Invest
DOI: 10.1172/JCI128877

A randomized trial comparing convalescent plasma with standard of care in patients hospitalized for COVID-19 - ConCOVID trial (NETHERLAND)

- **Study population:**
  - 86 patients hospitalized with COVID-19 in the Netherlands who had been symptomatic for a median 10 days at the time of enrollment received convalescent plasma with antibody titers of >1:80 dilution and standard of care, or standard of care alone.
  - Standard of care included chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra or other medications.
- **Key findings:**
  - 53 of 66 patients had anti-SARS-CoV-2 antibodies at time of enrollment into the study.
  - A SARS-CoV-2 plaque reduction neutralization test (PRNT) revealed neutralizing antibodies in 44/56 (79%) patients tested, comparable to the 115 donors (1:160 vs. 1:160, p=0.40).
  - No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.58) observed between plasma-treated patients and those on standard of care.
  - The trial was halted early due to concerns about convalescent plasma's lack of benefit.
- **Overall,**
  - **P**atients with COVID-19 may have antibody titers and still be symptomatic.
  - Antibody titers should be checked in patients prior to the administration of convalescent plasma

(Gharbharan, July 2020)

A randomized trial comparing convalescent plasma with standard of care in patients hospitalized for COVID-19 - ConCOVID trial (NETHERLAND)

Around 60% of the donors had antibody titers less than 1:320, which could be linked to the fact that most of them had a substantially milder disease episode. This again provides support to the hypothesis that a more severe course of the disease is linked to a better antibody response, although without more evidence this is just yet another conjecture. The CONCOVID team also raises the

A solution may be to actively recruit recovered patients who had more severe COVID-19 disease as donor, as they have been shown to have higher antibody levels

(Gharbharan, July 2020)

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*

January 7, 2021

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

Plasma with IgG titers of 1:3200 or higher reduced the risk of severe respiratory disease by 73%

Hospitalized patients with high titers should be identified for future plasma donations

Outline

- **Pathogenesis of Covid-19**
- Therapy of COVID-19: Convalescent plasma is an option
- Convalescent plasma – donor's side
- **Convalescent Plasma – patient's side**

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

CONCLUSION AND RELEVANCE Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference.

TRIAL REGISTRATION Chinese Clinical Trial Registry: ChiCTR2000029757

JAMA. doi:10.1001/jama.2020.10044
Published online June 3, 2020.

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma

- Treatment with CP may benefit patients with moderate and severe COVID-19
- The success of CP therapy are in correlation with higher IgG levels against the spike protein which serves as a surrogate marker for neutralizing antibodies

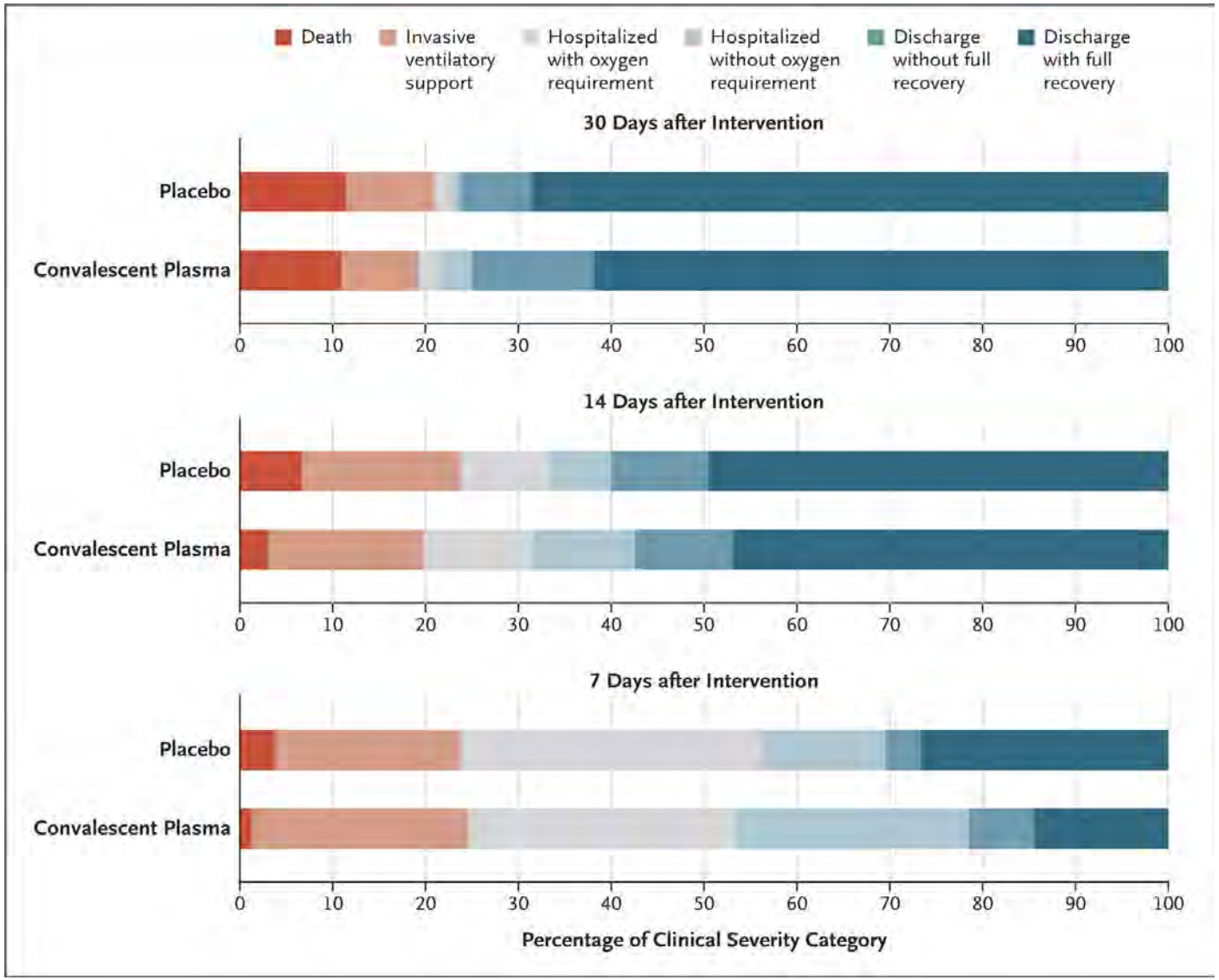
(Maor et al (Israel)., 2020)

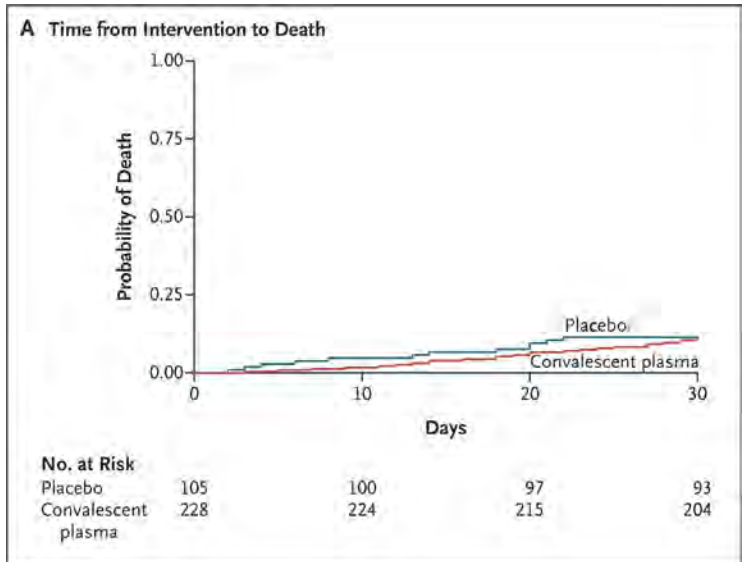
A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia – PlasmAr ClinicalTrials.gov number, NCT04383535

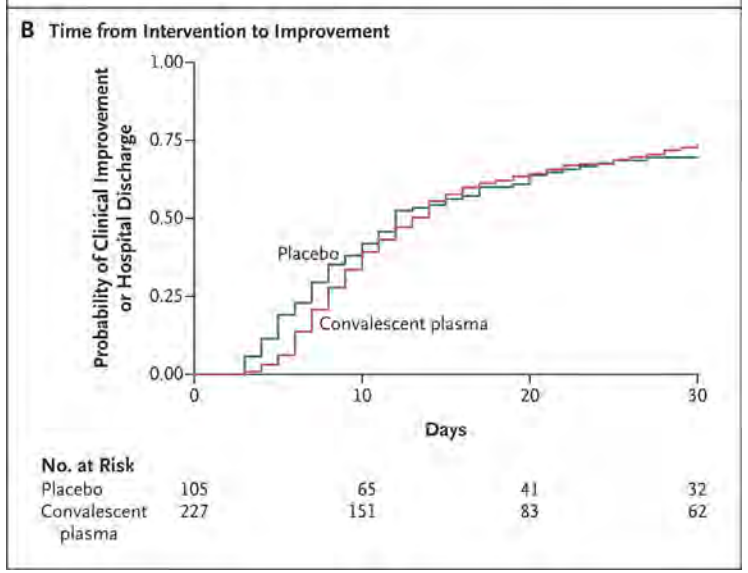
- **Study population:**
  - 333 hospitalized patients with severe COVID-19 across 12 clinical sites in **Argentina**.
  - 228 patients were randomized to the intervention arm, and 105 to the control arm
- **Primary endpoint:**
  - Composite outcome of clinical status 30 days after intervention, represented by six ordinal categories adapted from WHO.
- **Key findings:**
  - At day 30, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (odds ratio, 0.83 (95% confidence interval [CI], 0.52 to 1.35; P=0.46)
  - Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of −0.46% (95% CI, −7.8 to 6.8)
  - The infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies (interquartile range, 1:800 to 1:3200].
- **Limitations:**
  - This study only enrolled severe COVID-19 pneumonia patients, therefore the conclusion cannot be extrapolated to mild-moderate COVID-19 cases
  - Measurement of antibody titer prior to plasma administration cannot be obtained in 113 patients (35,4% of total participants)

(Simonovich et al (Argentina)., NEJM, 2020)

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia – PlasmAr ClinicalTrials.gov number, NCT04383535







Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial - ConPlas-19 Trial (SPAIN)

- **Study population:**
  - 81 patients hospitalized for COVID-19 in 14 Spanish hospitals.
    - The goal enrollment was 278 patients.
  - 38 were randomized to convalescent plasma (1 unit = 250-300 mL) + standard of care; 43 were randomized to standard of care.

(Avendano-Sola, September 2020).

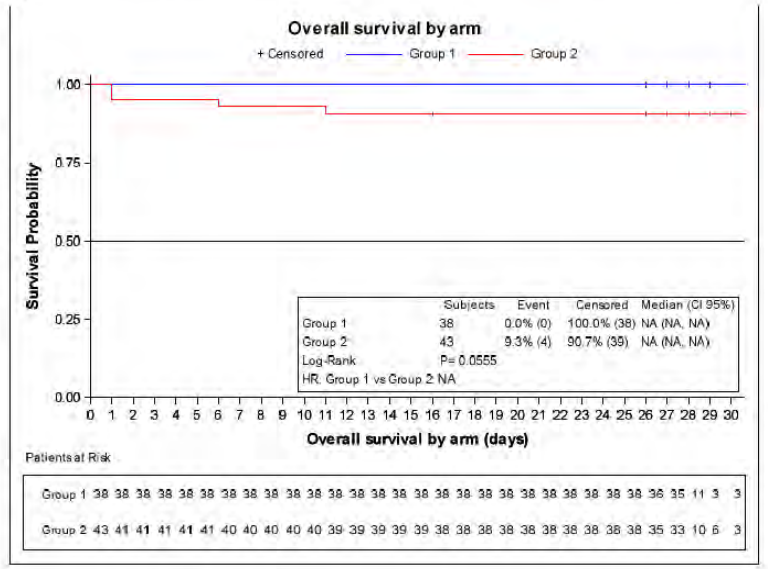
ConPlas -19 – Cont.

- **Key findings:**
  - Median time interval between symptom onset and randomization was 8 days.
  - At baseline 40 out of 81 patients (49.4%) tested positive for anti-SARS-CoV-2 IgG antibodies.
  - Patients assigned to convalescent plasma had a lower rate of worsening at 15 days than patients receiving standard of care only.
  - There were no patients progressing to mechanical ventilation or death among the 38 patients assigned to receive plasma (0%) versus 6 of 43 patients (14%) progressing in control arm.
  - Mortality rates were 0% vs. 9.3% at days 15 and 29 for the active and control groups, respectively.

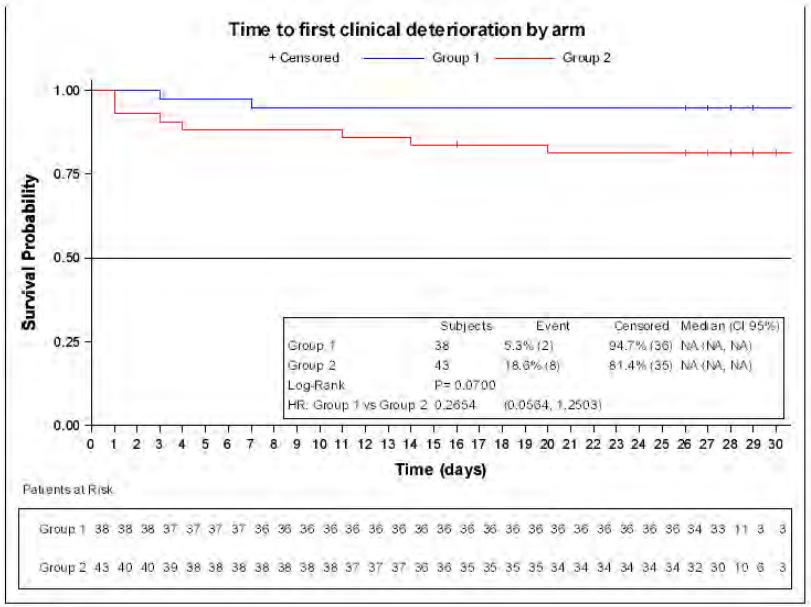
(Avendano-Sola, September 2020).

Figure 2. Kaplan-Meier estimates of secondary outcomes. A) Overall survival. Time to event curves for B) first clinical deterioration, C) first improvement of one category and D) Discharge.

A)



B)



ConPlas -19 – Cont.

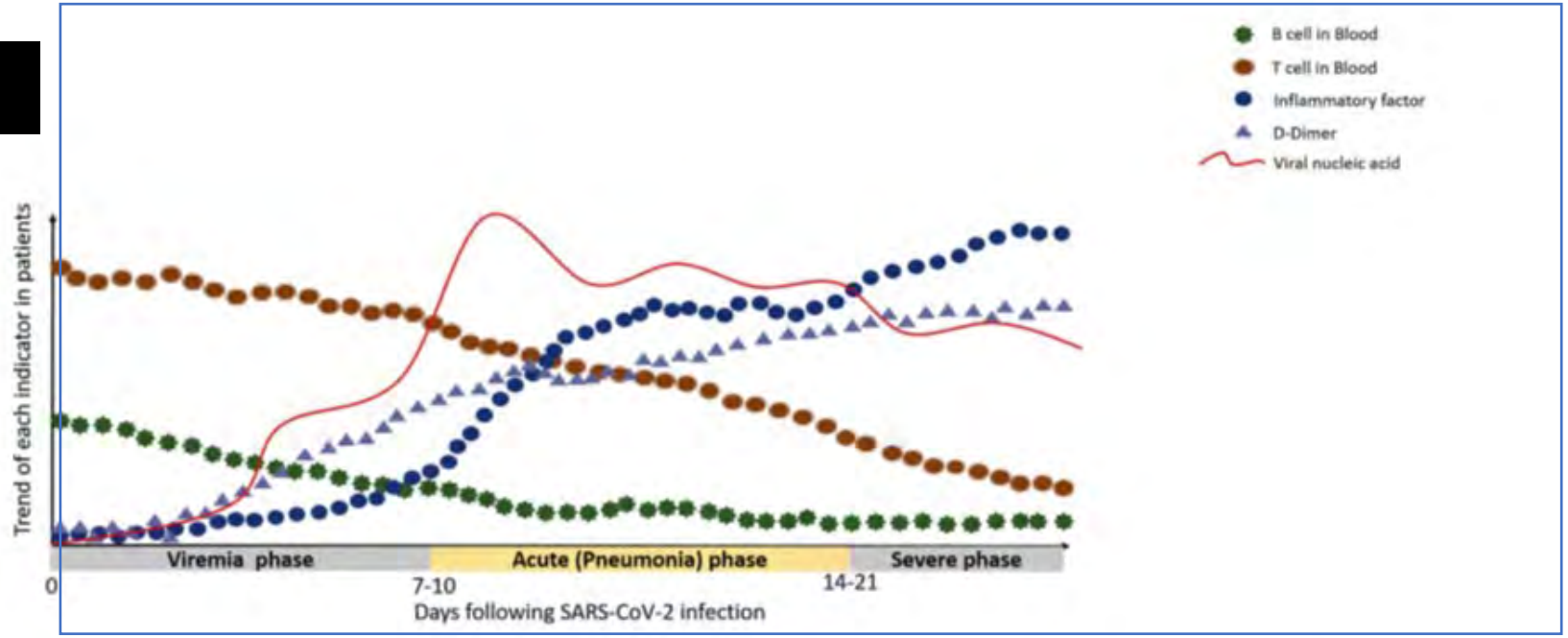
- **Limitations:**
  - The trial was stopped early due to low enrollment; of a planned 278 patients, only 81 were enrolled.
  - Baseline characteristics of patients not provided.
  - The patients received convalescent plasma over a week after symptom onset; this may be too late to see a significant effect.
  - The titer of neutralizing antibodies was not obtained when the convalescent plasma units were obtained and were not used to select donors or units.
  - Half of the patients were already IgG positive at the time of enrollment and may have had less of a benefit from convalescent plasma.
  - The real-world clinical implications of the primary endpoint is not clear.

Overall, in this open-label randomized study, the administration of convalescent plasma was associated with a reduction in the probability of clinical deterioration, ICU admission, or death in hospitalized COVID-19 patients who **did not require highflow oxygen devices or mechanical ventilation**.

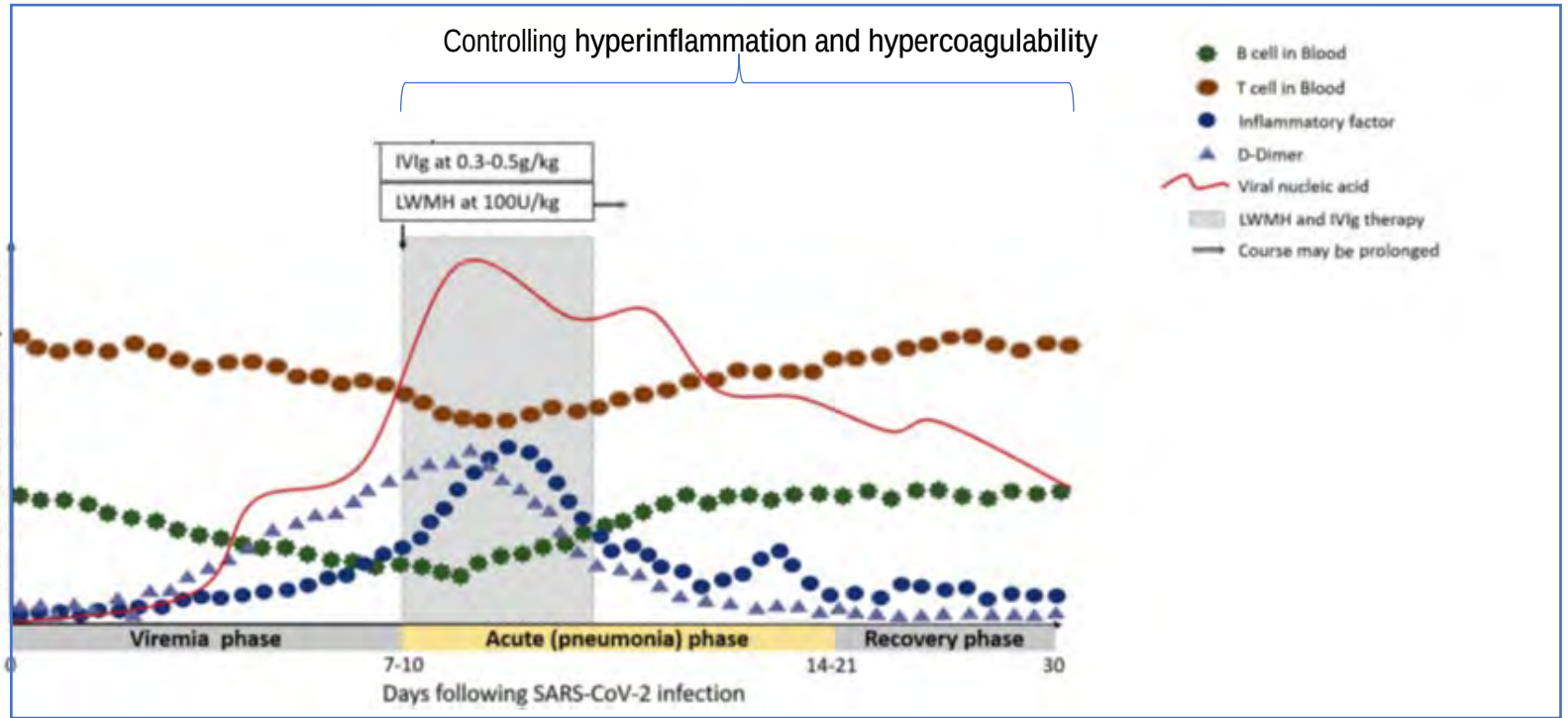
However, caution must be undertaken when interpreting the results, as the study was stopped early and under-powered

(Avendano-Sola, September 2020).

Timing of CP intervention:



Treat before disease worsening

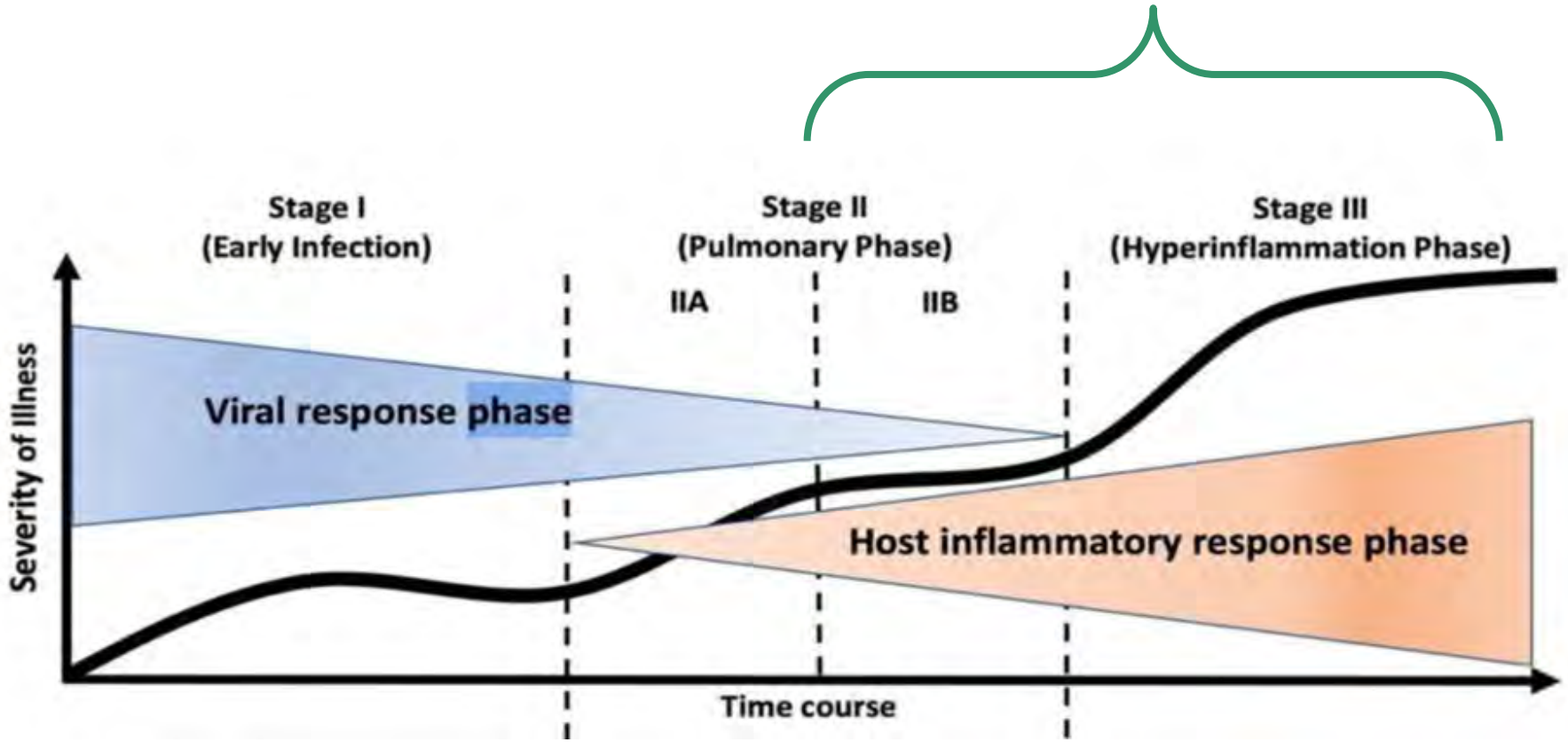


Wei Cao and Taisheng Li. COVID-19: towards understanding of pathogenesis Cell Research (2020) 30:367–369;

Timing of CP intervention:

Pathophysiological approach

Not too early, not too late



Hasan K. Siddiqi MD MSCR Mandeep R. Mehra MD MSc COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal Journal of Heart and Lung Transplantation(2020) doi: https://doi.org/10.1016/j.healun.2020.03.012

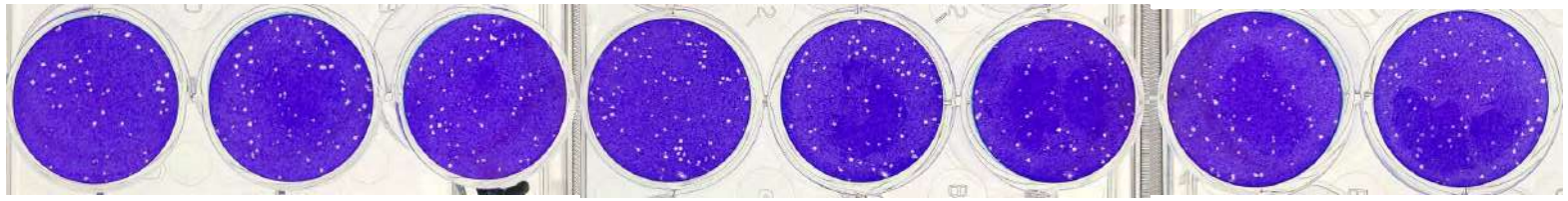
Outline

- **Pathogenesis of Covid-19**
- Therapy of COVID-19: Convalescent plasma is an option
- Convalescent plasma – donor's side
- Convalescent Plasma – patient's side
- **The need for antibody testing**

Uji PRNT: Mengukur antibodi dalam Plasma Konvalesen dalam menetralisasi virus SARS-CoV-2

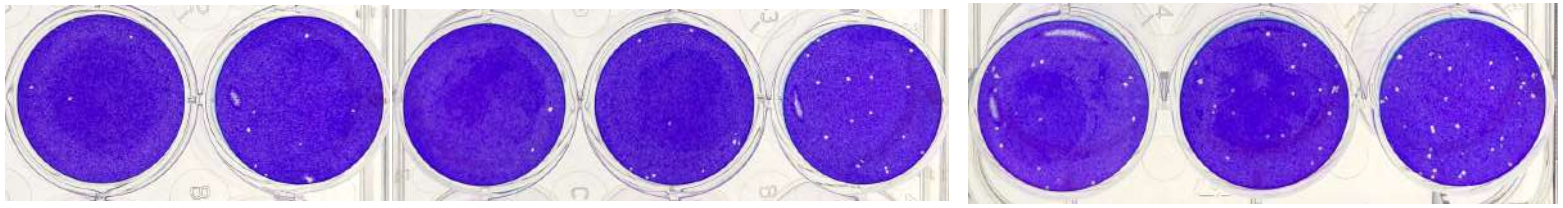
Pengenceran plasma:	10	20	40	80	160	320	640	1280

Plasma sehat
(belum memiliki antibodi)



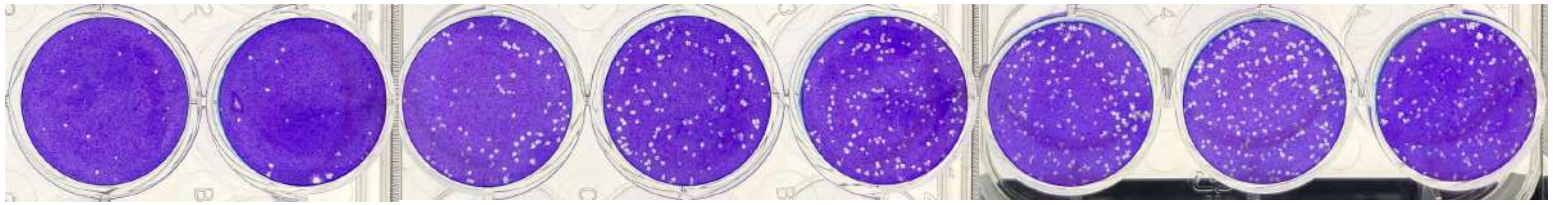
Titer : 1:640

Plasma Penyintas COVID-19 berat
(Kadar antibodi spesifik **tinggi**)
→ Titer PRNT 1:640



Titer : 1:20

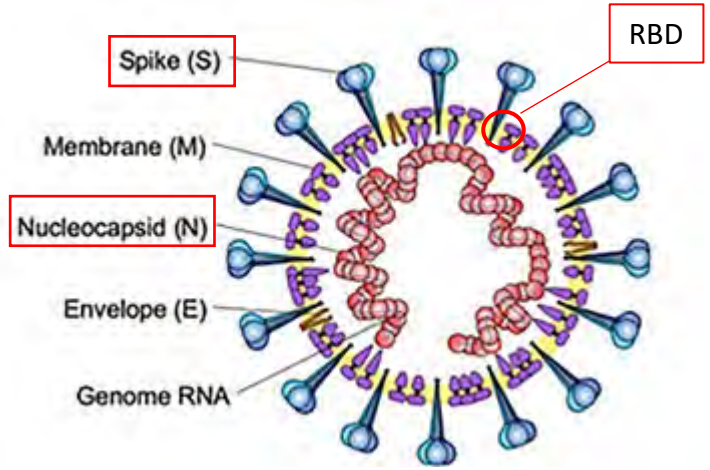
Plasma Penyintas Covid-19 ringan
(Kadar antibodi spesifik **rendah**)
→ Titer PRNT 1:20



Severe Acute Respiratory Syndrome Coronavirus 2–Specific Antibody Responses in Coronavirus Disease Patients

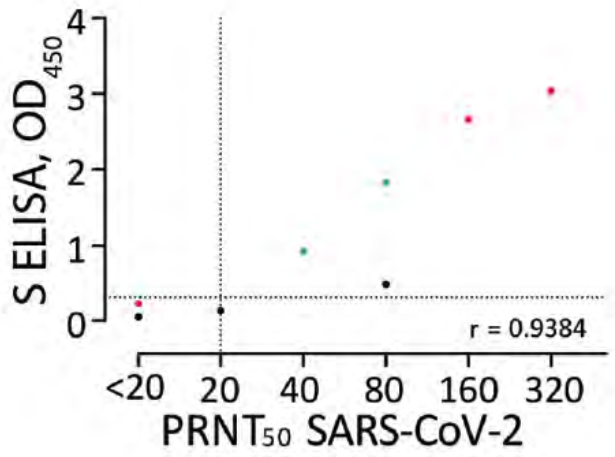
Nisreen M.A. Okba,[1] Marcel A. Müller,[1] Wentao Li,[1] Chunyan Wang, Corine H. GeurtsvanKessel, Victor M. Corman, Mart M. Lamers, Reina S. Sikkema, Erwin de Bruin, Felicity D. Chandler, Yazdan Yazdanpanah, Quentin Le Hingrat, Diane Descamps, Nadhira Houhou-Fidouh, Chantal B.E.M. Reusken, Berend-Jan Bosch, Christian Drosten, Marion P.G. Koopmans, Bart L. Haagmans

Emerging Infectious Diseases • Vol. 26, No. 7, July 2020

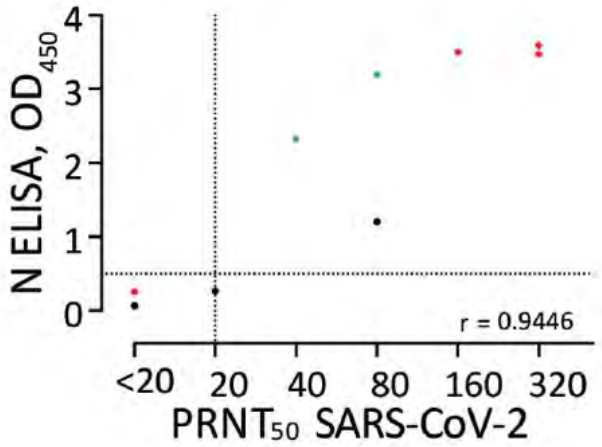


Correlations between ODs of ELISAs and PRNT results

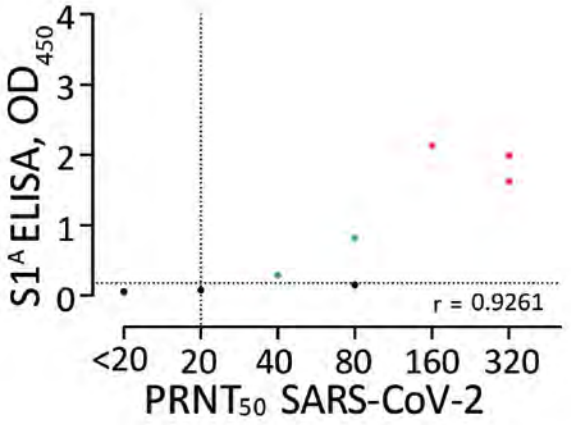
S protein vs $PRNT_{50}$



N protein vs $PRNT_{50}$



RBD protein vs $PRNT_{50}$



Severe
Mild, patient 1
Mild, patient 2

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2020)

DOI: 10.1111/vox.12970

ORIGINAL PAPER

Guidance for the procurement of COVID-19 convalescent plasma: differences between high- and low-middle-income countries

Evan M. Bloch,[1,†] Ruchika Goel,[1,2,†] Silvano Wendel,[3] Thierry Burnouf,[4,5] Arwa Z. Al-Riyami,[6] Ai Leen Ang,[7] Vincenzo DeAngelis,[8] Larry J. Dumont,[9,10,11] Kevin Land,[12,13] Cheuk-kwong Lee,[14,15] Adaeze Oreh,[16] Gopal Patidar,[17] Steven L. Spitalnik,[18] Marion Vermeulen,[19] Salwa Hindawi,[20] Karin Van den Berg,[19] Pierre Tiberghien,[21] Hans Vrielink,[22] Pampee Young,[23] Dana Devine[24,25,*] & Cynthia So – Osman[22,26,*]

- Convalescent donor testing for neutralizing antibody in donor selection.
  - Gold standard: plaque reduction neutralization test (PRNT) which requires a viable isolate, replication-competent cell lines, and skilled personnel.
  - Alternatively, using enzyme linked immunosorbent assay (ELISA) targeting the recombinant receptor binding domains (RBDs) of the virus

- Testing of neutralizing antibody is being developed and soon will be available

Outline

- **Pathogenesis of Covid-19**
- Therapy of COVID-19: Convalescent plasma is an option
- Convalescent plasma – donor's side
- Convalescent Plasma – patient's side
- The need for antibody testing
- **Conclusion**

Kesimpulan

1. Terapi diperlukan PK sebagai Opsi Terapi Tambahan
2. Efektivitas lebih baik pada penderita COVID1- derajat sedang dibanding derajat berat
3. Beberapa donor tidak / kurang memiliki antibody COVID-19
4. Beberapa pasien sudah memiliki antibody titer tinggi, sebelum mendapat terapi PK (sudah membentuk antibodi endogen → terutama yang sudah dirawat dlm jangka waktu lama)
5. Perlu ditetapkan kriteria:
   - Donor: prekualifikasi sebelum mendonor
   - Pasien: indikasi dan cara pemberian
6. Perlu dibuat protokol berdasarkan **Uji Klinik** (Randomized control: terapi dengan vs tanpa PK), yang mendapat Persetujuan Regulator sebagai Terapi PK

Rekomendasi

1. **Stockpiling** Plasma Konvalesen
   - Rekrutmen Penyintas COVID-19 RS dan masyarakat
   - Seleksi calon donor (sebaiknya bukan ‘mild’) dan tes kadar Antibodi
   - Dibuat jejaring Bank Plasma (update tiap hari)

2. Sosialisasi dan Koordinasi dengan Rumah Sakit:
   - Tim Medis dan Administrasi (KIE pada Tim Medis)
     - Penjelasan tentang PK (merupakan ‘terapi tambahan’, bukan ‘terapi pengganti’; dan belum menjadi Standar Terapi
     - Saat pemberian: pasien derajat sedang / mengarah ke berat (belum memasuki fase kritis)

3. Dukungan pada Uji Klinik yang sedang berjalan untuk mendapat Protokol Terapi PK

Thank you