Passive immunotherapy to treat COVID-19

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4eme Journées de la Fédération d'Immunologie Médicale
19 Novembre 2020

Passive immunotherapy by transferring humoral immunity

Available therapeutic options to manage COVID-19 immunopathology and deter viral propagation

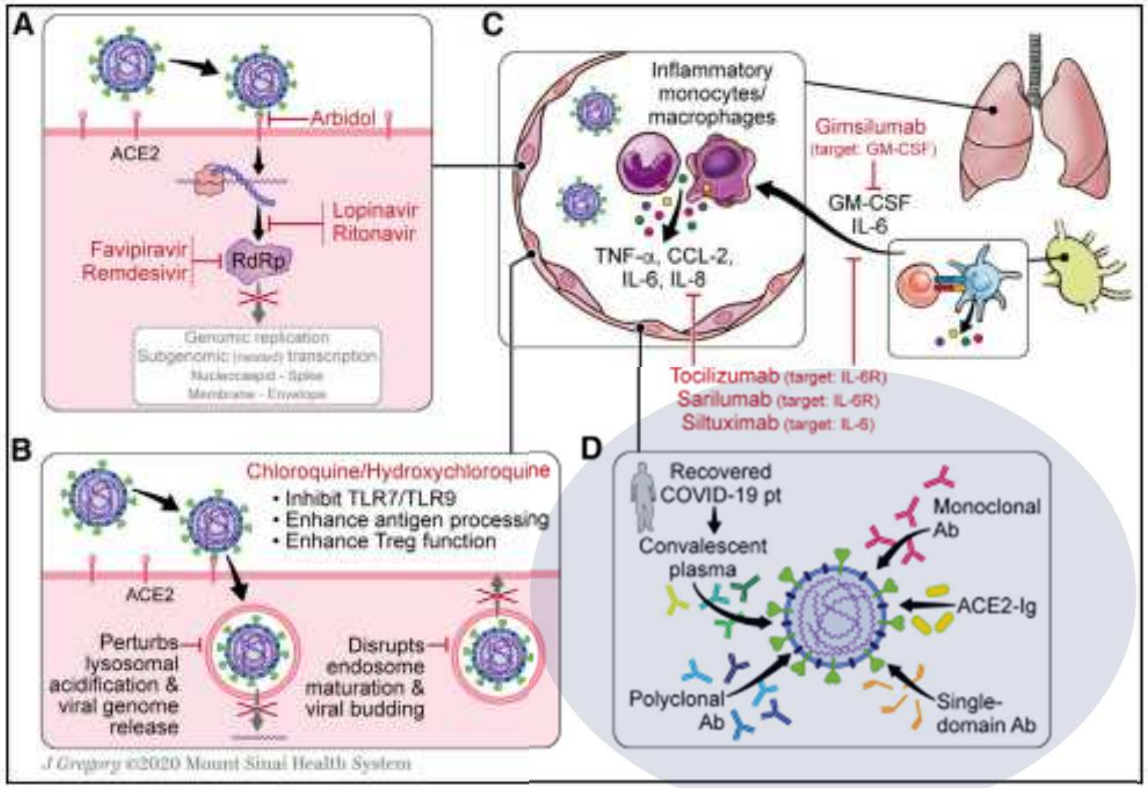

Figure 6. Available Therapeutic Options to Manage COVID-19 Immunopathology and to Deter Viral Propagation

(A) Rdrp inhibitors (remdesivir, favipiravir), protease inhibitors (lopinavir/ritonavir), and antifusion inhibitors (arbidol) are currently being investigated in their efficacy in controlling SARS-CoV-2 infections.

(B) CQ and HCQ increase the pH within lysosomes, impairing viral transit through the endolysosomal pathway. Reduced proteolytic function within lysosomes augments antigen processing for presentation on MHC complexes and increases CTLA4 expression on Tregs.

(C) Antagonism of IL-6 signaling pathway and of other cytokine-/chemokine-associated targets has been proposed to control COVID-19 CRS. These include secreted factors like GM-CSF that contribute to the recruitment of inflammatory monocytes and macrophages.

(D) Several potential sources of SARS-CoV-2 neutralizing antibodies are currently under investigation, including monoclonal antibodies, polyclonal antibodies, and convalescent plasma from recovered COVID-19 patients.

GM-CSF, granulocyte-macrophage colony-stimulating factor; CQ, chloroquine; HCQ, hydroxychloroquine; RdRp, RNA-dependent RNA polymerase.

Vabret et al, Cell, 2020

Passive immunotherapy to treat infectious diseases

Adolf von Behring (1854 –1917), was a German physiologist who received the **1901 Nobel Prize in Physiology or Medicine**, the first one awarded in that field, for his discovery of a **diphtheria antitoxin** and the demonstration, with Kitasato Shibasaburo, that such antitoxin (diphtheria and tetanus) could allow for the transfer of anti-infectious immunity

Also other prominent researchers in the field: Paul Erhlich; Charles Richet: sérum anti staphylocoque serum (1888), anti tuberculosis serum (1890); Albert Calmette: anti venom serum (1890); Emile Roux: sérum antidiphtérique (1894)

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- Hyperimmunoglobulin: hepatitis B, tetanos, diphteria, CMV, …

03 INDICATIONS THERAPEUTIQUES HAS

« Immunoprophylaxie de l'hépatite B :
- en cas de contamination accidentelle chez les sujets non immunisés (y compris lorsque la vaccination est incomplète ou inconnue)
- chez les hémodialysés en attente de l'efficacité de la vaccination
- chez le nouveau-né en cas de mère porteuse du virus de l'hépatite B
- chez les patients n'ayant pas développé de réponse immunitaire après vaccination contre le virus de l'hépatite B (anticorps contre l'hépatite B non détectables) et qui ont besoin d'une protection continue contre cette maladie. »

HAS - Direction de l'Evaluation Médicale, Economique et de Santé Publique 4/14
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vacc
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prote

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Avis2

Immunoglobuline humaine tétanique

Indication :

- Prophylaxie du tétanos en cas de plaie souillée chez les sujets dont la vaccination est incomplète, trop ancienne ou inconnue.
- Traitement du tétanos déclarée.

Passive immunotherapy to treat infectious diseases

- Convalescent plasma (CP) treatment, i.e. passive polyclonal antibody administration to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology (Mair-Jenkins J et al, J Infect Dis. 2015).
- A number of CP studies, unfortunately all inadequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish Influenza A (H1N1) infections in 1915-1917, the more recent Influenza A (H1N1)pdm09 infections in 2009/2010 as well SARS-CoV infections in 2003.
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Antiviral treatment of Argentine hemorrhagic fever[1]

TABLE I—MORTALITY IN PATIENTS WITH AHF TREATED WITH IMMUNE OR NORMAL PLASMA

Treatment	Total cases	Improved	Died	Mortality (%)
Immune plasma	91	90	1	1·1
Normal plasma	97	81	16	16·5
Total	188	171	17	—

χ_2=13·53; p<0·01

Maiztegui et al, Lancet, 1979
Enria et al, Lancet, 1984
Enria an Maitzegui, Antivir Res, 1994

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Dose of neutralizing antibodies in treatment of AHF with immune plasma prospective study (1982–92)

Outcome	TU/kg		
	1000–1999	2000–2999	3000–3999
Died	2	3	5
Improved	24	46	908
Total	26	49	913
Mortality	7.69%	6.12%	0.55%

X^2: 26.32; P = 0.0002.

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Morta

X^2: 26

Mortality in AHF patients-treated with immune plasma after 8 days of illness

Outcome	Immune plasma	
	yes	no
Improved	40	74
Died	21	31
Total	61	105
Mortality	34%	30%

X^2: 0.23; P = 0.63.

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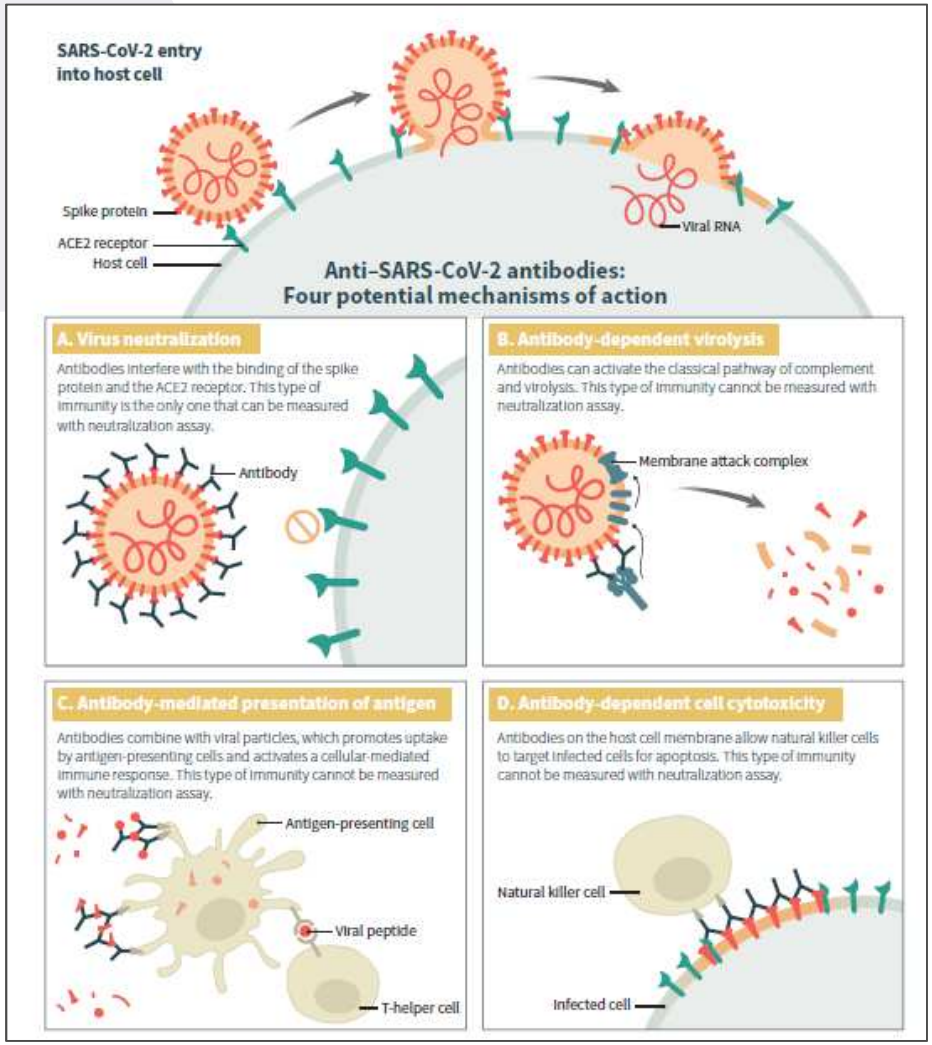
Ab response to SARS-CoV-2



Devasenapathy et al, CMAJ 2020

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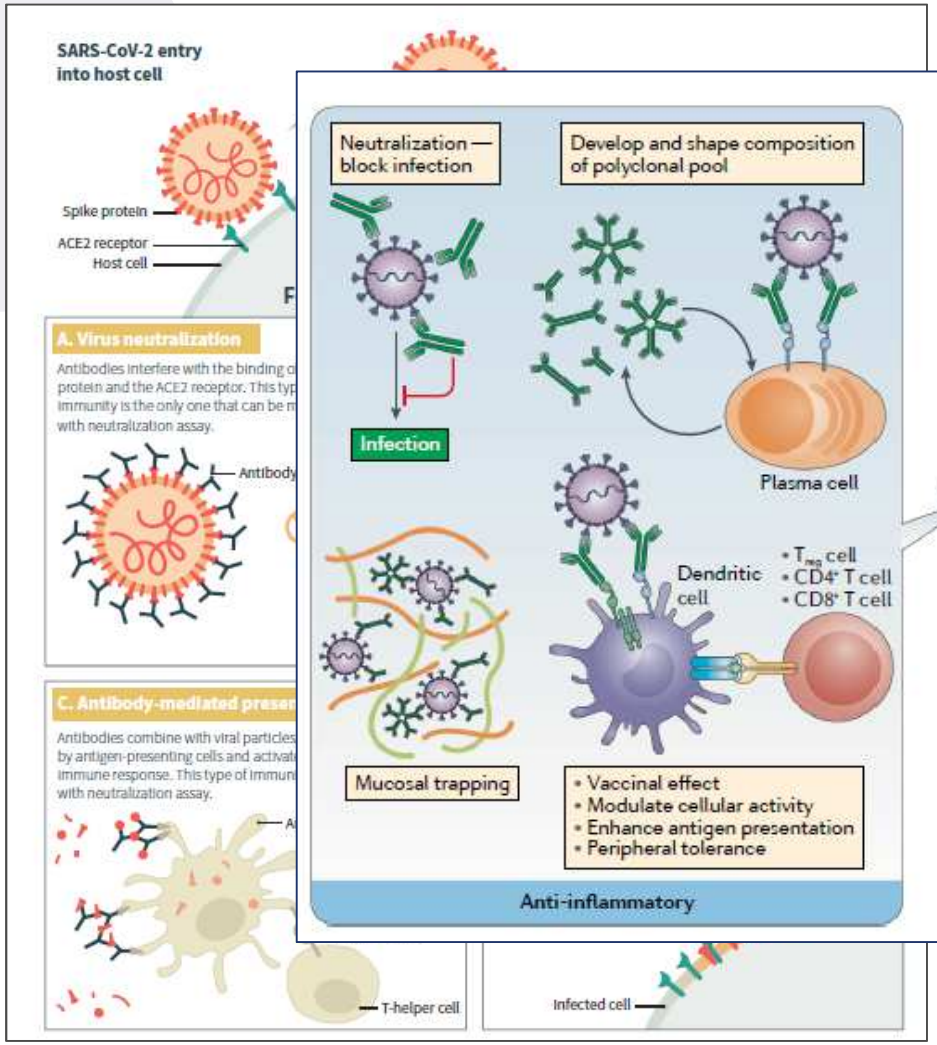

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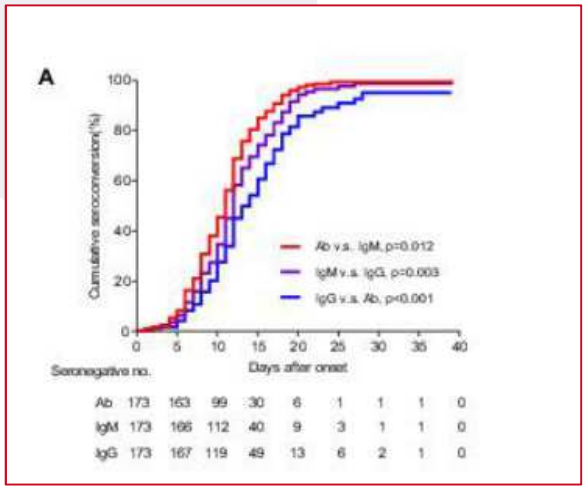
Zohar and Alter, Nature Rev Immunol, 2020

Antibody-dependant enhancement / Enhanced respiratory disease



Abraham et al, Nature Rev Immunol 2020

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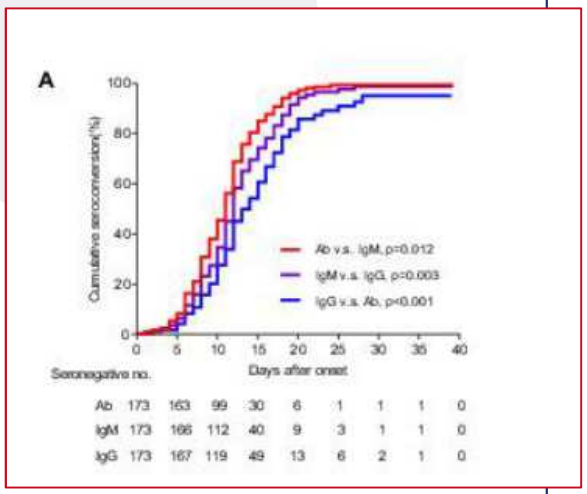

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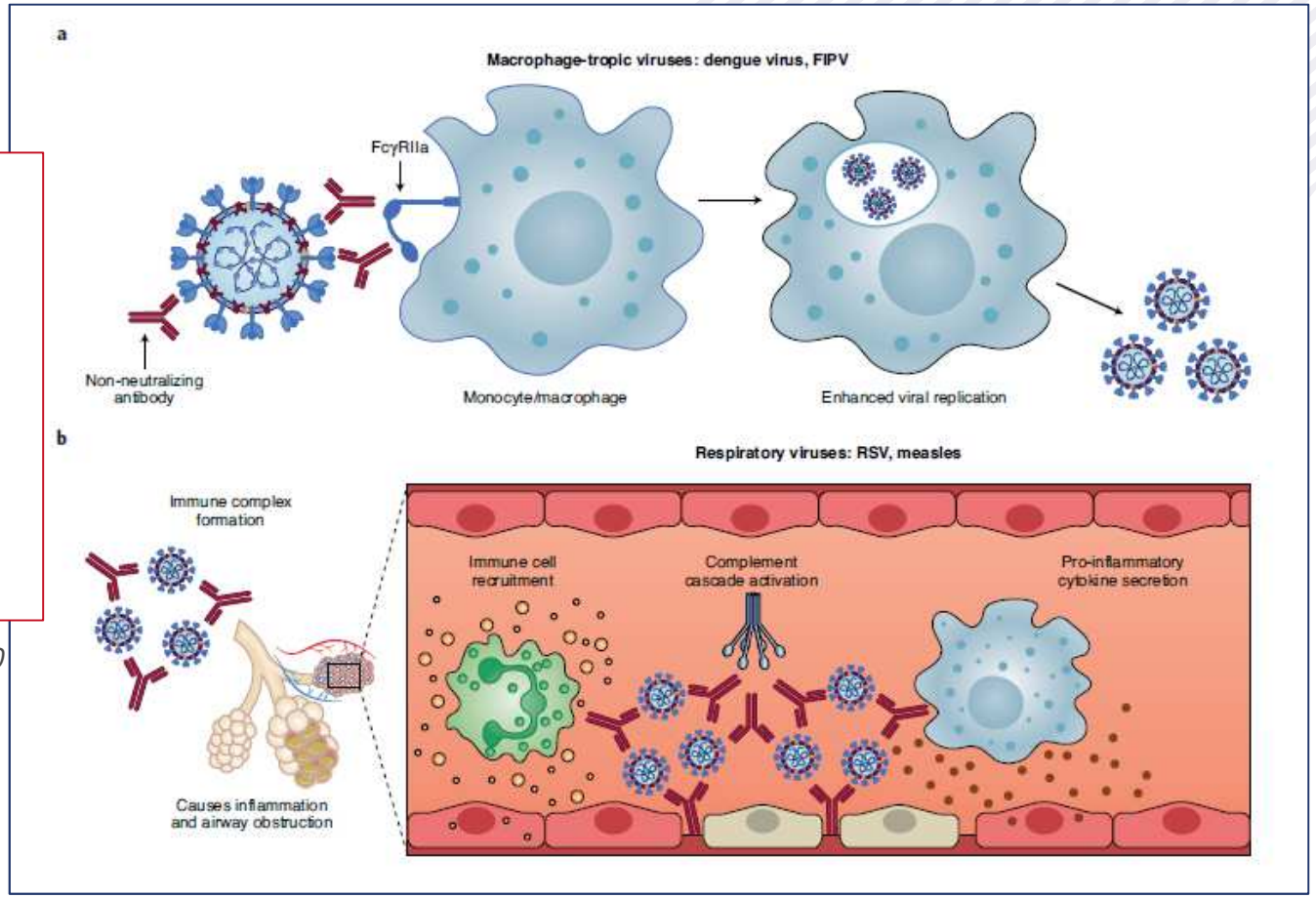

Fig. 1 | Two main ADE mechanisms in viral disease. a, For macrophage-tropic viruses such as dengue virus and FIPV, non-neutralizing or sub-neutralizing antibodies cause increased viral infection of monocytes or macrophages via FcγRIIa-mediated endocytosis, resulting in more severe disease. **b**, For non-macrophage-tropic respiratory viruses such as RSV and measles, non-neutralizing antibodies can form immune complexes with viral antigens inside airway tissues, resulting in the secretion of pro-inflammatory cytokines, immune cell recruitment and activation of the complement cascade within lung tissue. The ensuing inflammation can lead to airway obstruction and can cause acute respiratory distress syndrome in severe cases. COVID-19 immunopathology studies are still ongoing and the latest available data suggest that human macrophage infection by SARS-CoV-2 is unproductive. Existing evidence suggests that immune complex formation, complement deposition and local immune activation present the most likely ADE mechanisms in COVID-19 immunopathology. Figure created using BioRender.com.

Lee et al, Nature Microbiol, 2020

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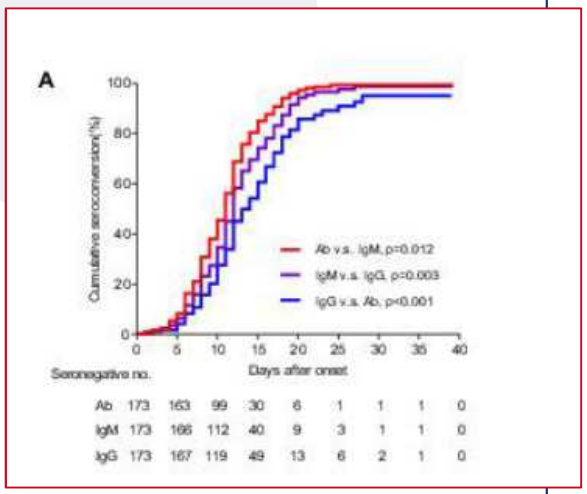

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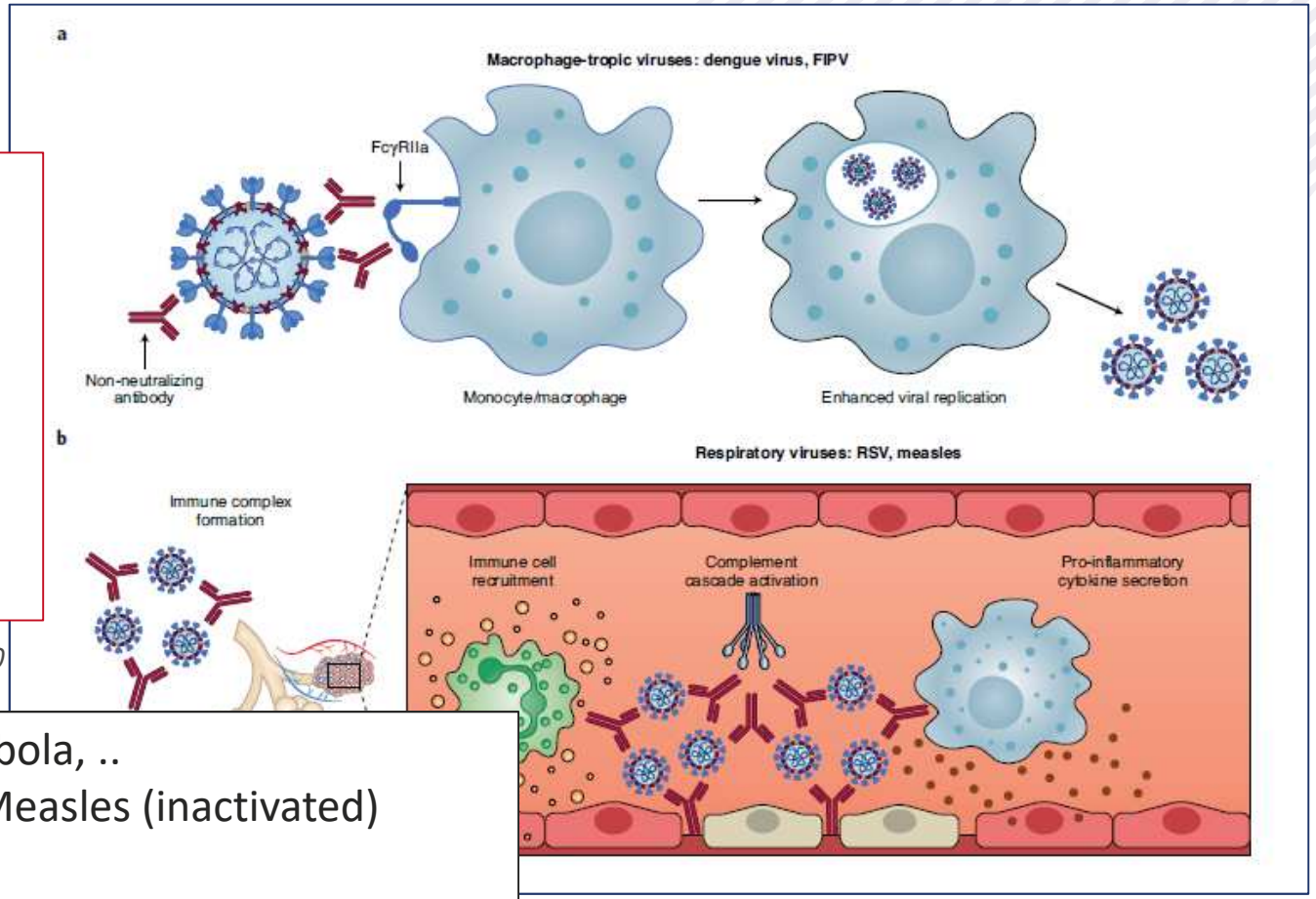

- Dengue, HIV, Ebola, ..
- Dengue, RSV, Measles (inactivated) vaccines
- Coronavirus : Cat FIPV vaccine, SARS-CoV vaccin in the mouse
- Risk mitigation: high titer neutralizing Ab, anti-spike specificity, Th1 response

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Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection

Liu et al, JCI, 2009

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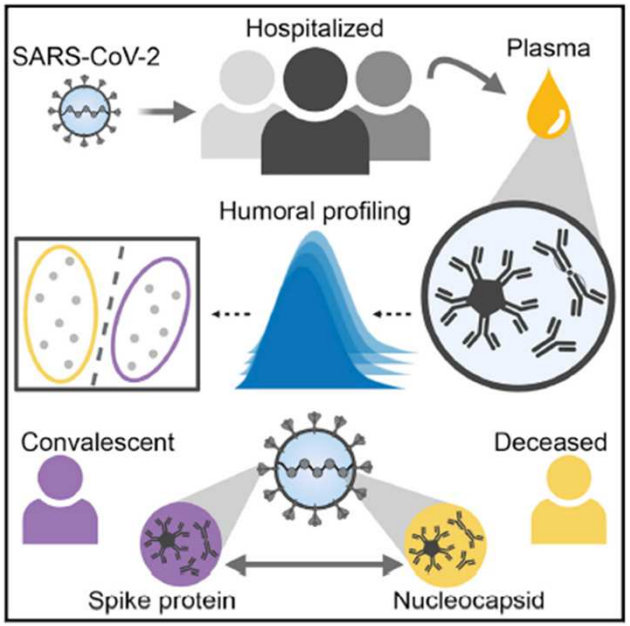
Distinct Early Serological Signatures Track with SARS-CoV-2 Survival

Atyeo et al, Immunity, 2020



Highlights

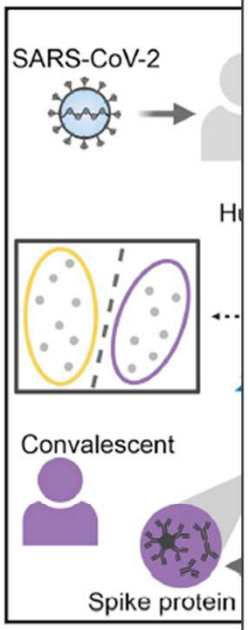
- Limited early differences were observed in titers and neutralization across groups
- Five antibody features could collectively differentiate convalescents and deceased
- A shift in the balance of spike versus nucleocapsid immunity separated the groups
- Spike-specific phagocytic and complement fixing activity was enriched in convalescents

Anti-spike IgG causes severe acute lung injury by skewing m during acute SARS-

Liu et al, JCI, 2009

Distinct Early Serological Signatures Track with SARS-CoV-2 Surviv

Atyeo et al, Immunity, 202



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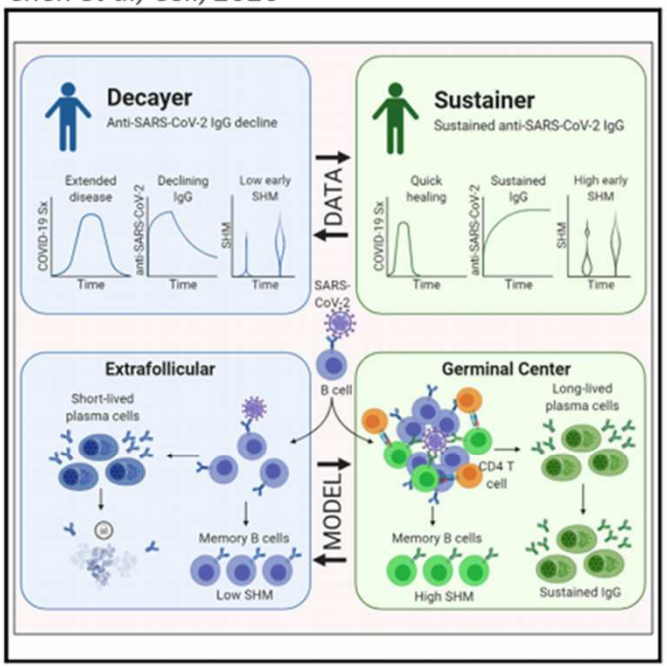
Quick COVID-19 Healers Sustain Anti-SARS-CoV-2 Antibody Production

Chen et al, Cell, 2020



Highlights

- SARS-CoV-2 antibody responses range from negligible to robust in mild COVID-19
- Some individuals maintain stable or increased SARS-CoV-2 IgG, while most decline
- Those who sustain virus-specific IgG production tend to have shorter disease courses
- Virus-specific B cells from "sustainers" have more SHM early after disease resolution

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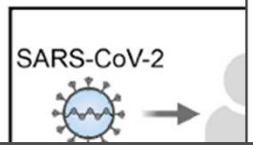

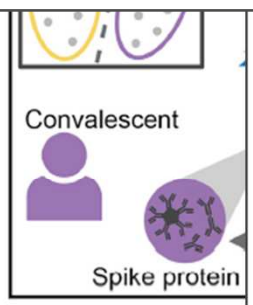

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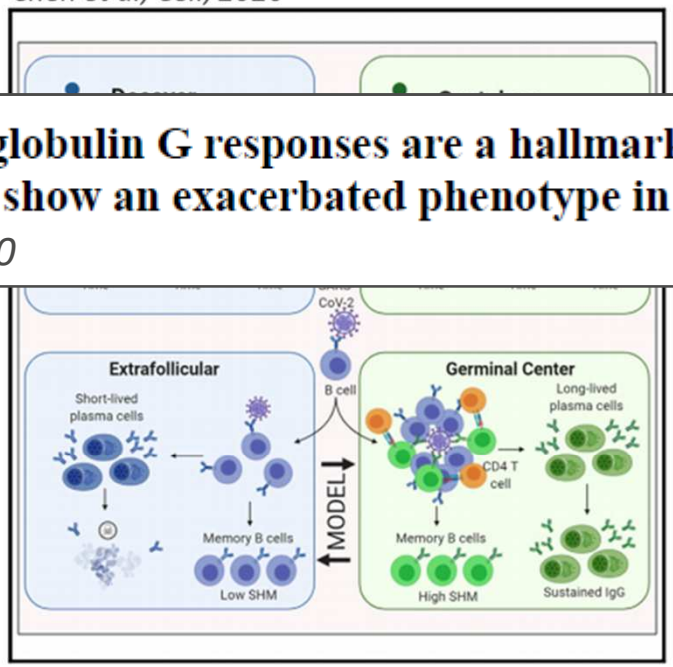

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Afucosylated immunoglobulin G responses are a hallmark of enveloped virus infections and show an exacerbated phenotype in COVID-19

Larsen et al, BioRxiv, 2020

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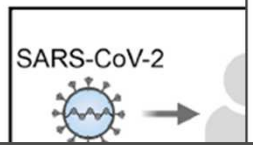

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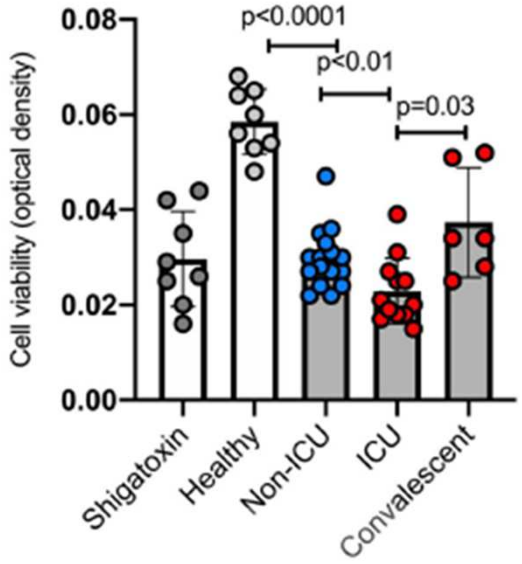
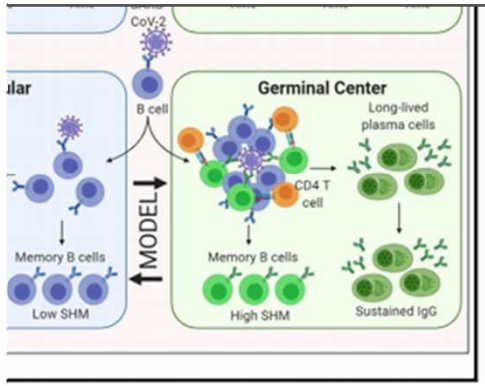
Rauch et al, Circulation, 2020





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SARS-CoV-2

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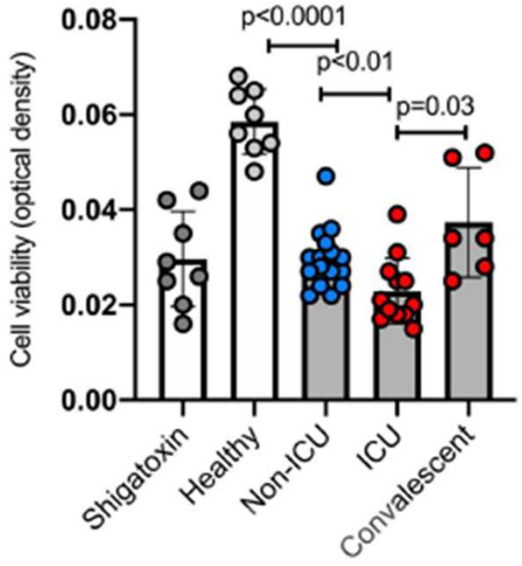


- Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19 (Kaneko et al , Cell)
- Extrafollicular B cell responses with neutralizing antibodies and morbidity in COVID-19 (Woodruff et al Nature Immunology, 2020)
- Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19 (Zuo et al, Science Translational Medicine, 2020)
- Auto-antibodies against type I IFNs in patients with life-threatening COVID-19 (Bastard et al, Science, 2020)

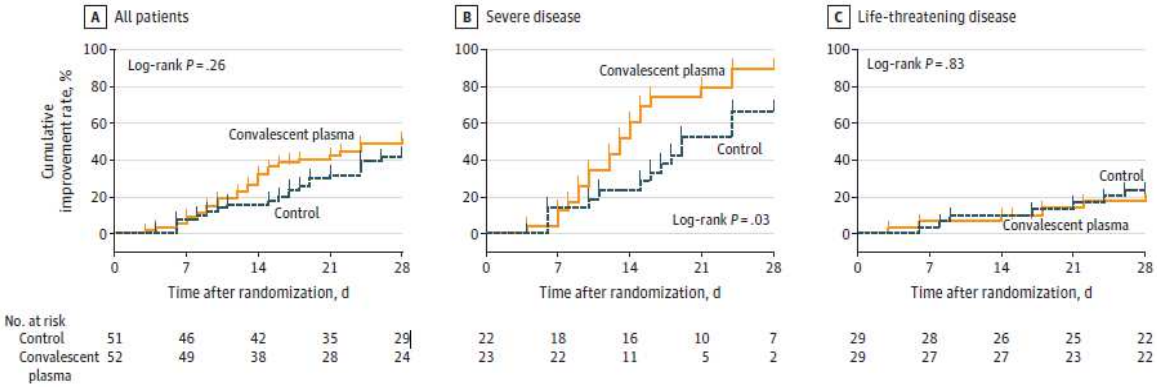
Passive immunotherapy to treat COVID-19

COVID-19 convalescent plasma - Results

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

Li et al, JAMA, 2020)

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



The cumulative improvement rate is the percentage of patients who experienced a 2-point improvement or were discharged alive from the hospital. Ticks on the curves indicate censored events. All patients who did not reach clinical improvement were observed for the full 28-day period or until death. COVID-19 indicates coronavirus disease 2019.

The median (IQR) follow-up times for the convalescent plasma group and control group, respectively, were 15 (10-28) days and 24 (13-28) days overall; 13 (10-16) and 18.5 (11-26) days among those with severe COVID-19; and 28 (12-28) and 26 (15-28) days among those with life-threatening COVID-19.

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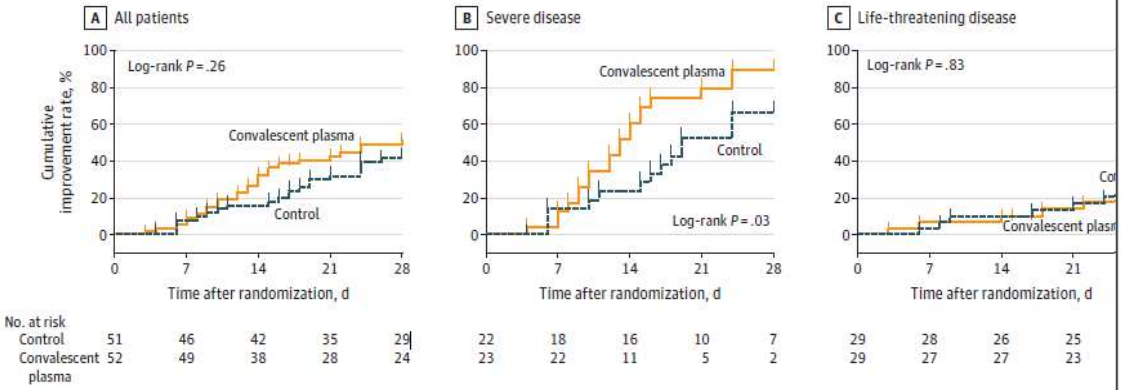

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Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study

Liu et al, Nature Medicine

Figure 2. Survival Probability

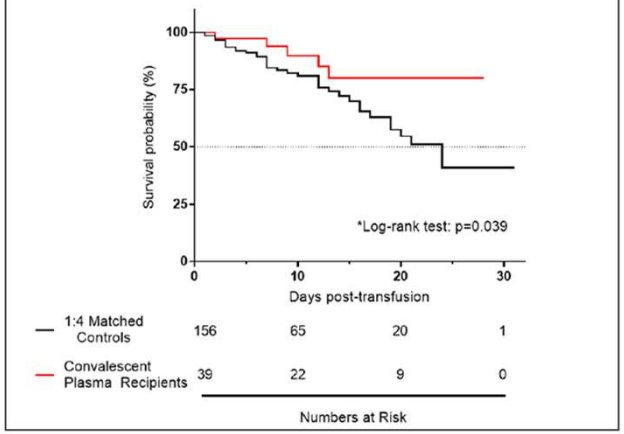
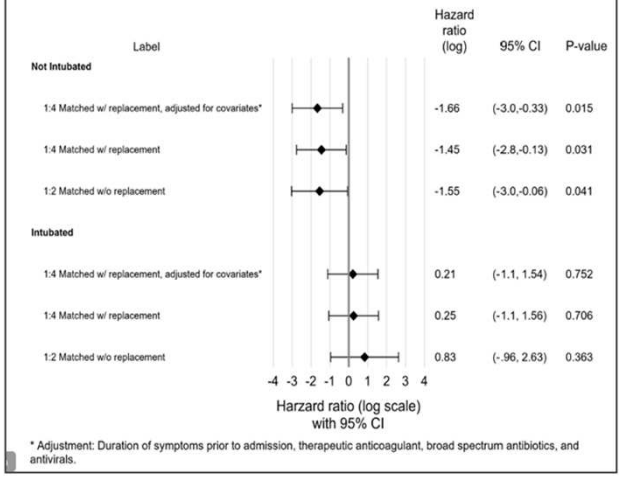


Figure 3. Hazard ratios for in-hospital mortality



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COVID-19 convalescent plasma - Results

Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy

Joyner et al, medRxiv

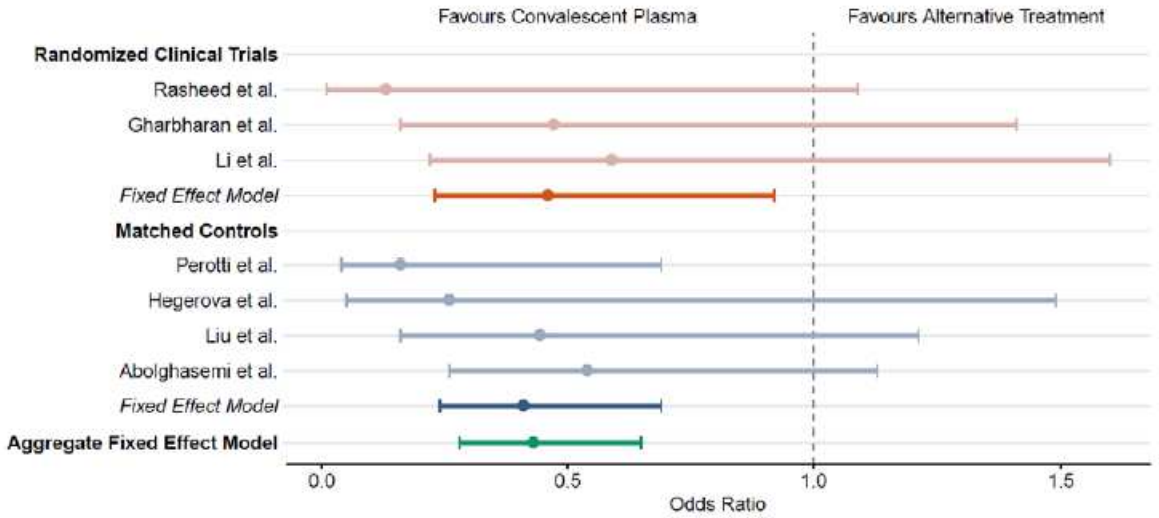

Figure 1. The impact of human convalescent plasma therapy on COVID-19 patient mortality. Forest plot illustrating odds ratios (OR) and 95% confidence intervals for controlled studies and aggregate fixed effect models. Randomized clinical trials including Rasheed et al.[10], Gharbharan et al.[8], and Li et al.[7] are represented in orange. Matched controlled studies including Perotti et al.[13], Hegerova et al.[11], Liu et al.[12], and Abolghasemi et al.[14] are represented in blue. Aggregate fixed effect models for each study type are represented by shaded hues. The overall aggregate fixed effect model is represented in teal.

Passive immunotherapy to treat COVID-19

COVID-19 convalescent plasma - Results

Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality

Salazar et al, Am J Pathol, 2020

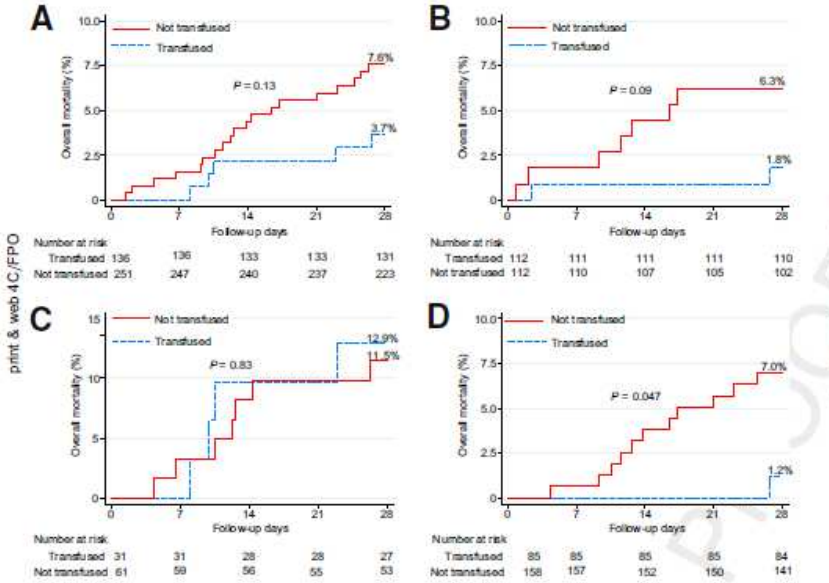

Figure 2 Kaplan-Meier curves for mortality within 28 days post-day 0 for secondary matched cohorts. **A:** All secondary matched patients. **B:** Secondary matched patients transfused within 72 hours of admission. **C:** Secondary matched patients transfused >72 hours after admission. **D:** Secondary matched patients transfused within 72 hours of admission with plasma with anti–receptor binding domain IgG titer ≥1:1350.

Passive immunotherapy to treat COVID-19

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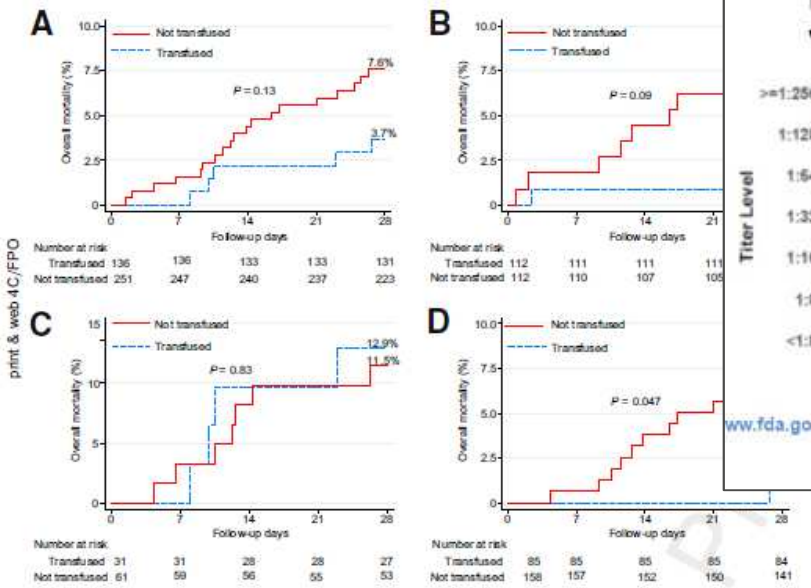
Salazar et al, Am J Pathol, 2020



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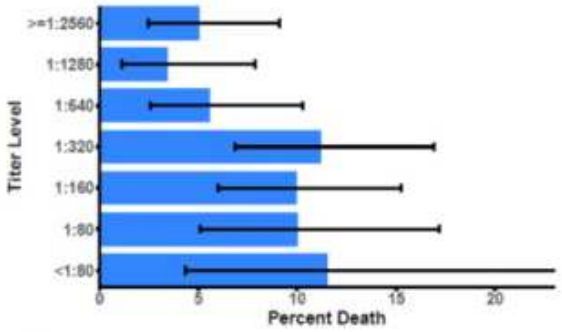
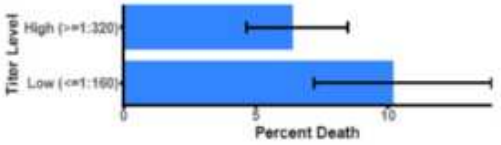
FDA

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

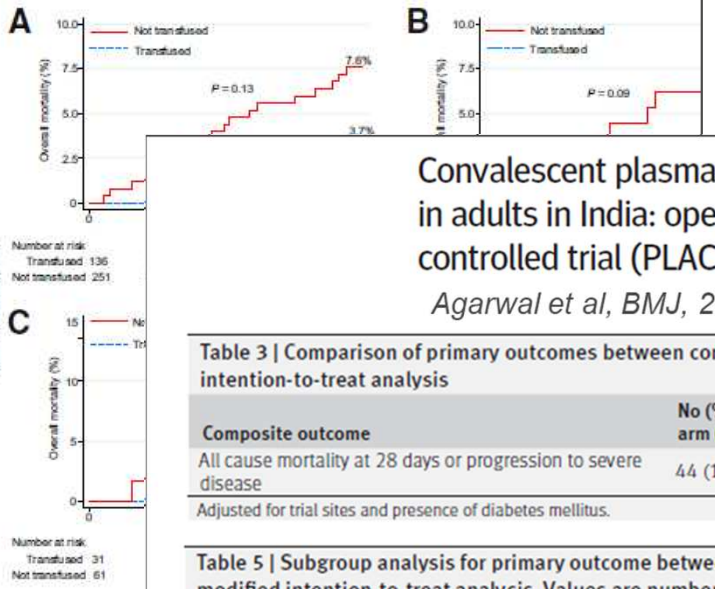
ww.fda.gov

Passive immunotherapy to treat COVID-19

COVID-19 convalescent plasma - Results

Treatment of Coronavirus Disease 2019 Patients with Convalescent Signal of Significantly Dec

Salazar et al, Am J Pathol, 2020



COVID-19 Convalescent Plasma Reduction in Death at 7 Days

FDA

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

Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)

Agarwal et al, BMJ, 2020

Table 3 | Comparison of primary outcomes between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in intention-to-treat analysis

Composite outcome	No (%) in intervention arm (n=235)	No (%) in control arm (n=229)	Unadjusted risk difference (95% CI)	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)
All cause mortality at 28 days or progression to severe disease	44 (19)	41 (18)	0.008 (−0.062 to 0.078)	1.04 (0.71 to 1.54)	1.07 (0.73 to 1.58)

Adjusted for trial sites and presence of diabetes mellitus.

Table 5 | Subgroup analysis for primary outcome between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in modified intention-to-treat analysis. Values are numbers (percentages) unless stated otherwise

Composite outcome	Intervention arm (detectable NAbs in CP)* (n=160)	Control arm (n=229)	Unadjusted risk ratio (95% CI)	Intervention arm (NAbs ≥1:80 in CP)* (n=67)	Unadjusted risk ratio (95% CI)	Intervention arm (undetectable NAb in CP)* (n=64)	Unadjusted risk ratio (95% CI)
All cause mortality at 28 days or progression to severe disease	27 (17)	41 (18)	0.94 (0.61 to 1.47)	12 (18)	1.0004 (0.56 to 1.79)	13 (20)	1.13 (0.65 to 1.98)

Nab=neutralising antibodies; CP=convalescent plasma.
*Comparator was best standard of care.

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

Joyner et al, JCI, 2020

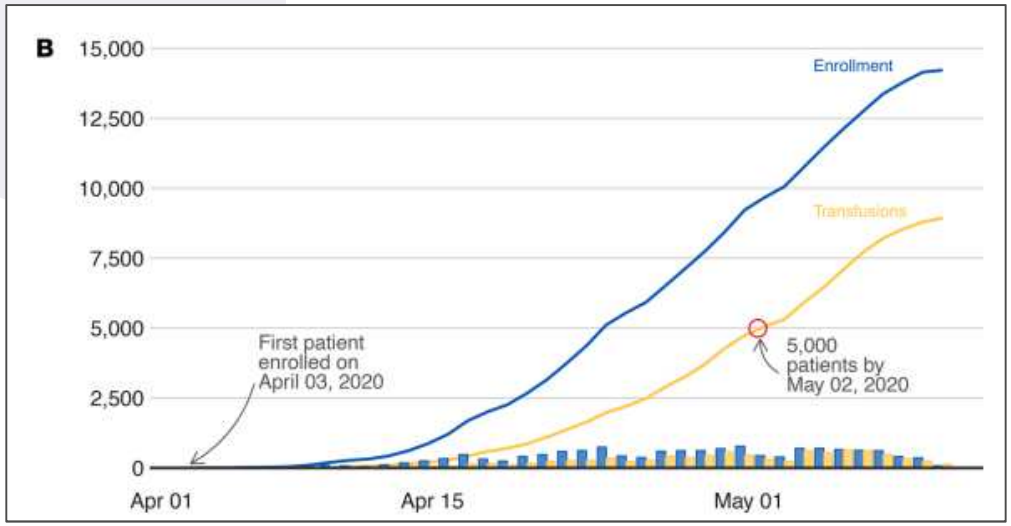

Table 2. Serious adverse event characteristics (n = 5,000)

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.

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

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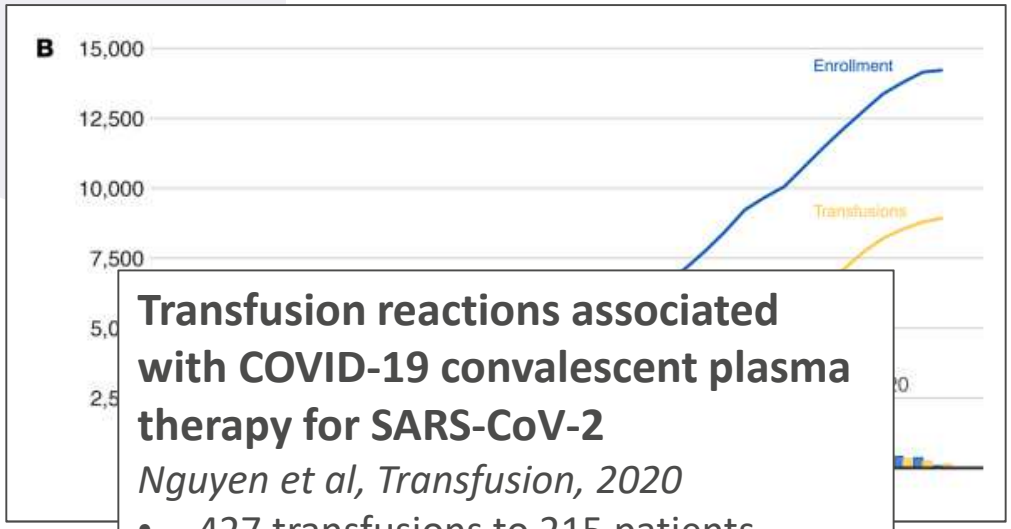

Transfusion reactions associated with COVID-19 convalescent plasma therapy for SARS-CoV-2

Nguyen et al, Transfusion, 2020

- 427 transfusions to 215 patients
- 55 reactions (12,9% incidence), among which 13 (3,1%) were attributed to transfusion (FNRH, TACO mainly)
- 42 reactions (fever, hypoxia) (9,8%) were attributed to underlying disease

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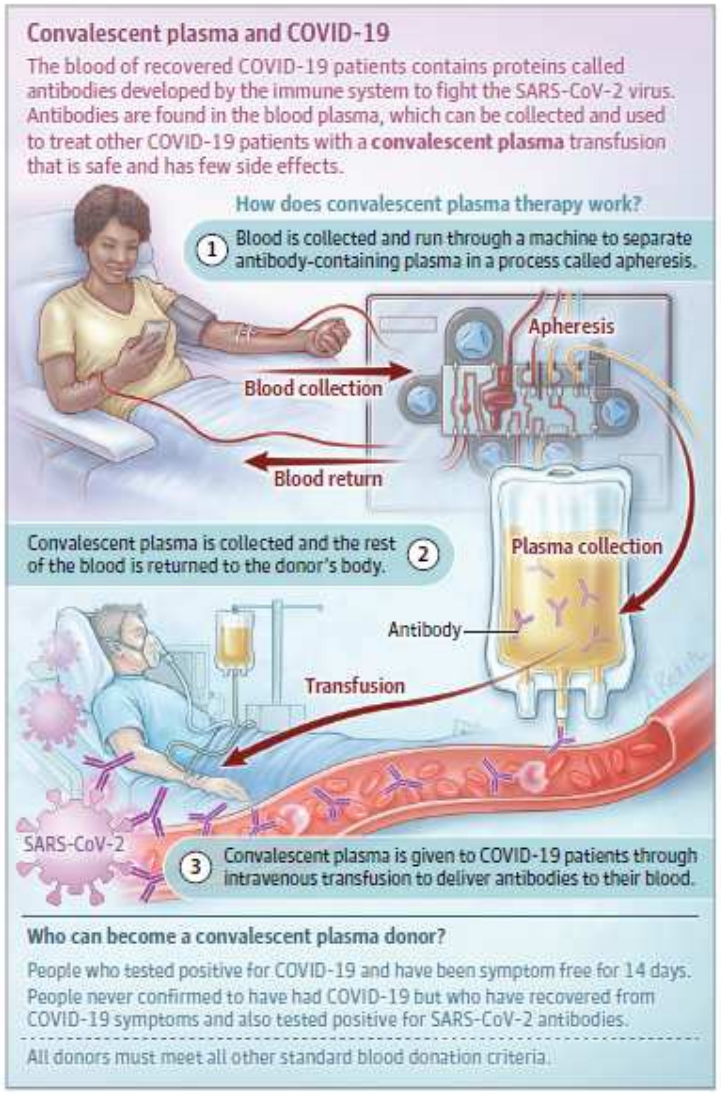
Passive immunotherapy to treat COVID-19

COVID-19 convalescent donors

JAMA patient page



Convalescent donor selection

Standard eligibility criteria, including a delay of 14 days since COVID-19 symptoms resolution (fever, dyspnea)

Apheresis : standard procedure, 650 ml

Frequency : up to 3 times with a minimum of 15 days interval (per standard regulation)

Donor qualification:

Neutralizing activity titer >= 1/40 (*Xavier De Lamballerie*) and/or Euroimmun Elisa ratio > 5,6 (*Pierre Gallian, Sophie Lecam*)

Plasma:

Pathogen reduced (Intercept) and cryopreserved for use as:

- Convalescent plasma (neutralizing titer >= 1/40)
- Standard plasma (neutralizing titer < 1/40)

From 07/04 to 12/06:

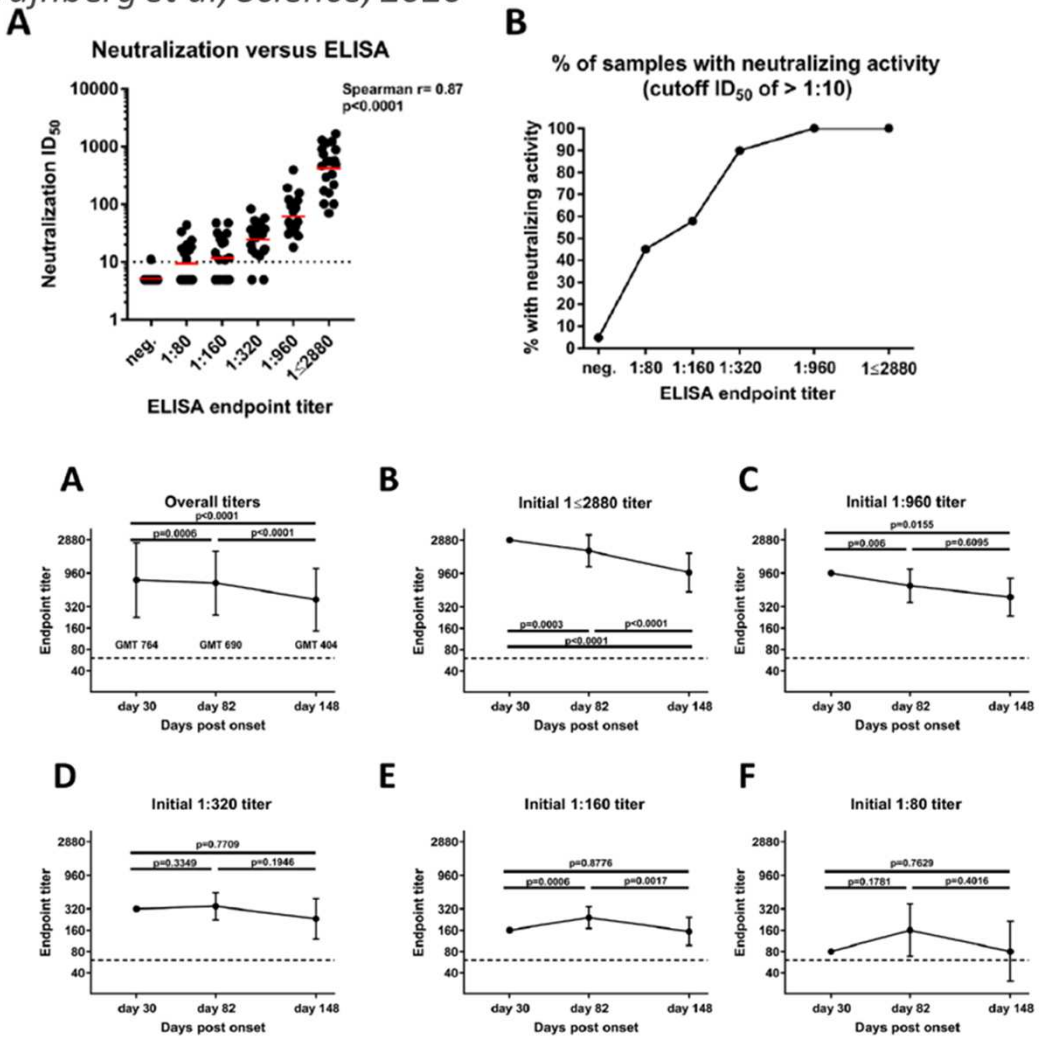
- 2869 plasma donations (apheresis)
- 64 to 55% qualified donations (76% among PCR+ donors)
- 4700 qualified convalescent plasma units (200 to 220 ml/unit)

Reinitiation of convalescent plasma collection since 26/10

Characterization and duration of the anti-SARS-CoV-2 Ab response

Robust neutralizing antibodies to SARS-CoV-2 infection persist for months

Wajnberg et al, Science, 2020



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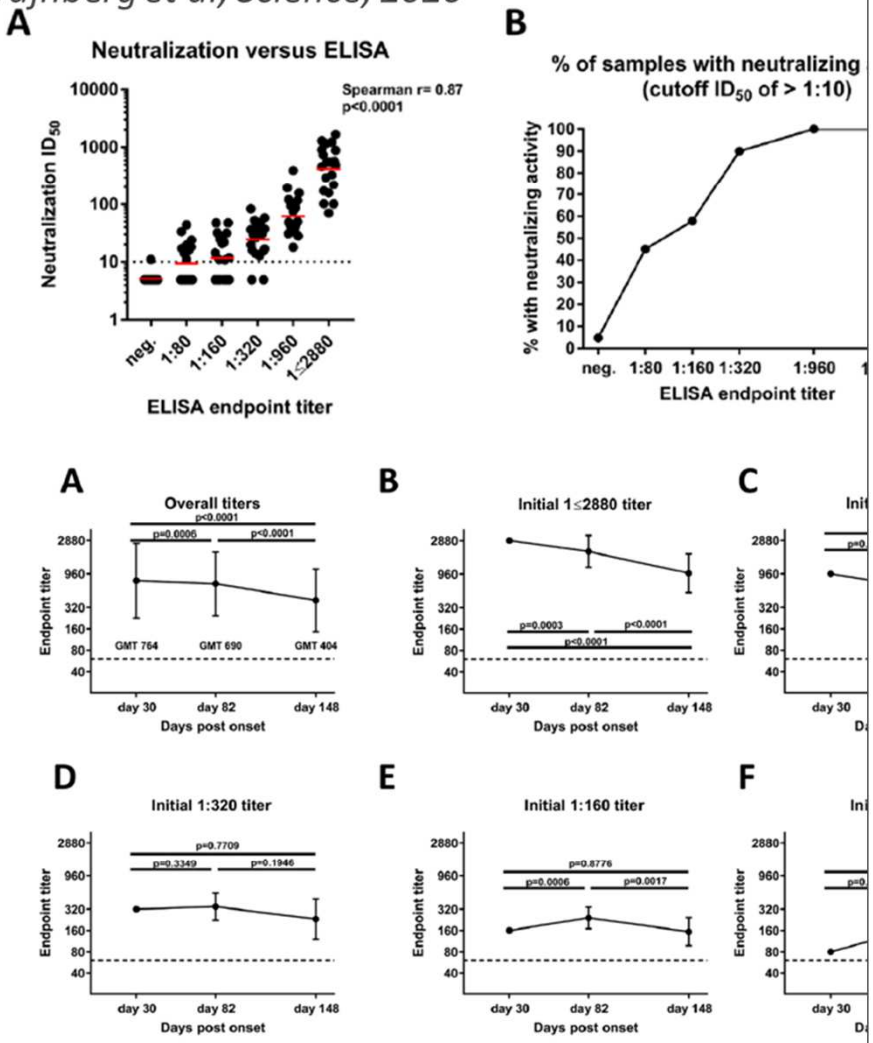


Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients

Iyer et al, Science Immunol, 2020

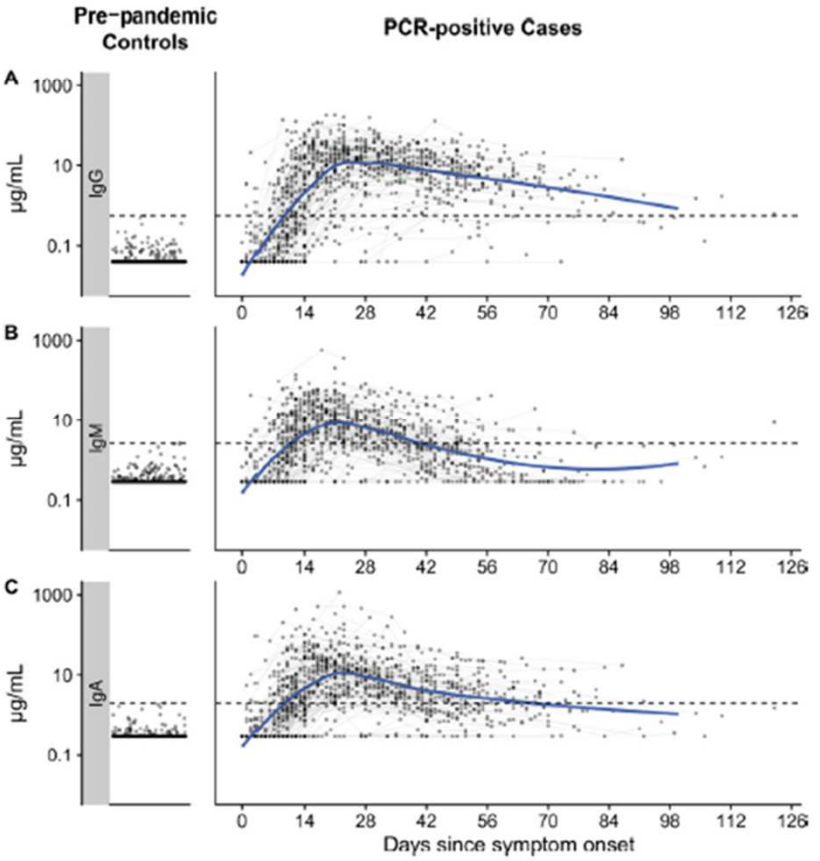
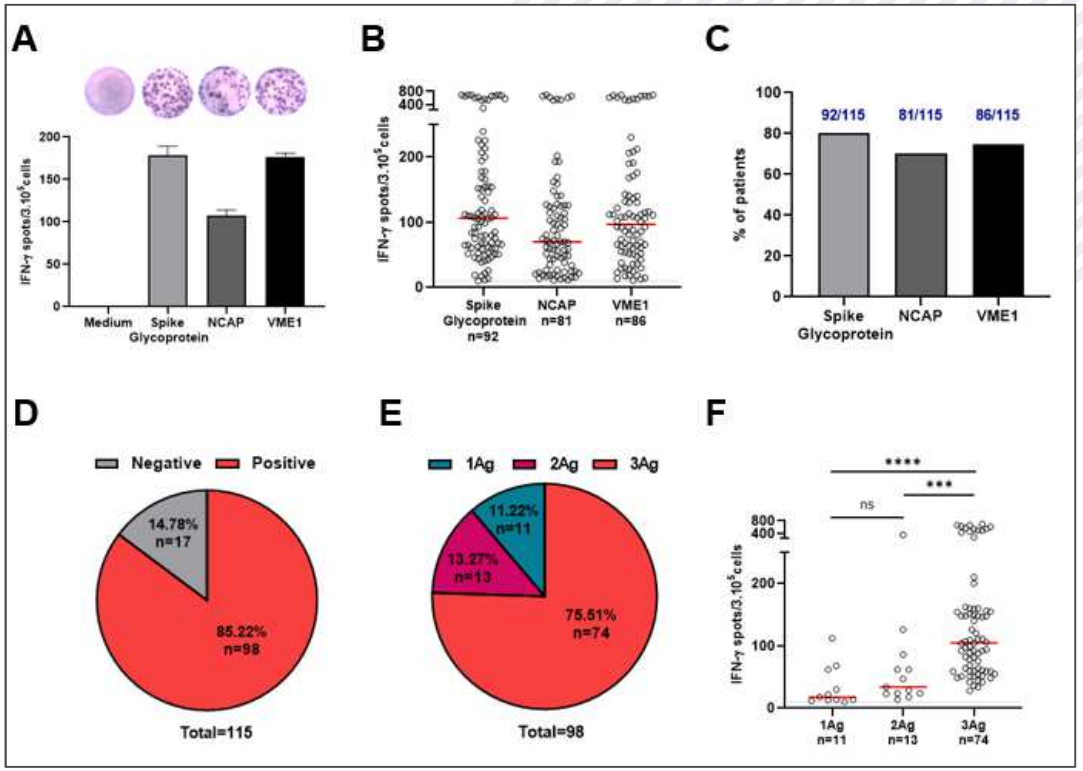


Fig. 1. Measurement of IgG, IgM, IgA against SARS-CoV-2 spike protein receptor binding domain among pre-pandemic controls and PCR positive cases. Each dot represents a unique measurement of an isotype (Row A: IgG, Row B: IgM, Row C: IgA) in pre-pandemic controls (left panels) and PCR positive cases (right panels). The blue line is a loess smooth nonparametric function. Black dashed lines indicate the maximum concentration (µg/mL) found among pre-pandemic controls (IgG: 0.57, IgM: 2.63, IgA: 2.02). Horizontal jitter was introduced into the pre-pandemic controls. The limit of detection (µg/mL) was 0.04 for IgG, 0.28 for IgM, and 0.30 for IgA.

T-cell responses in COVID-19 convalescent plasma donors



Olivier Adotevi et al, unpublished

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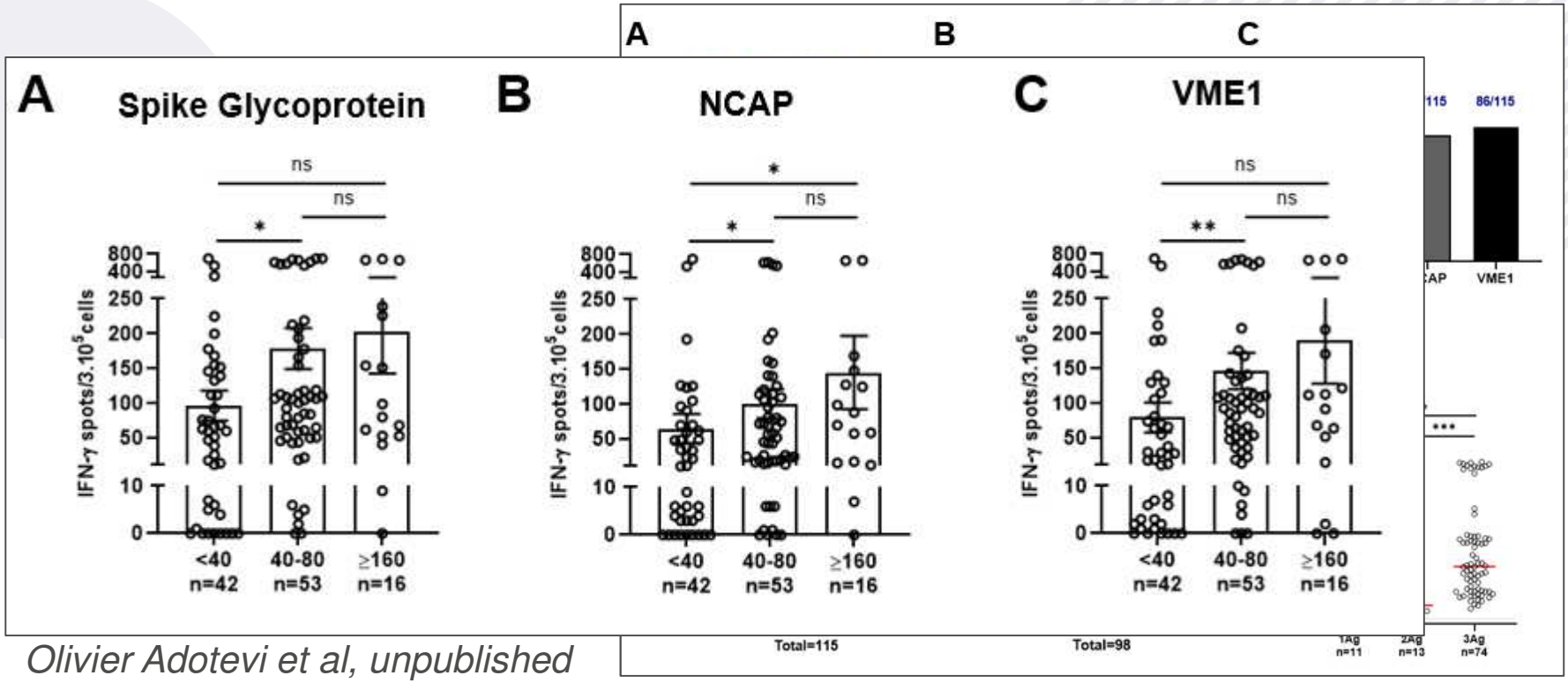

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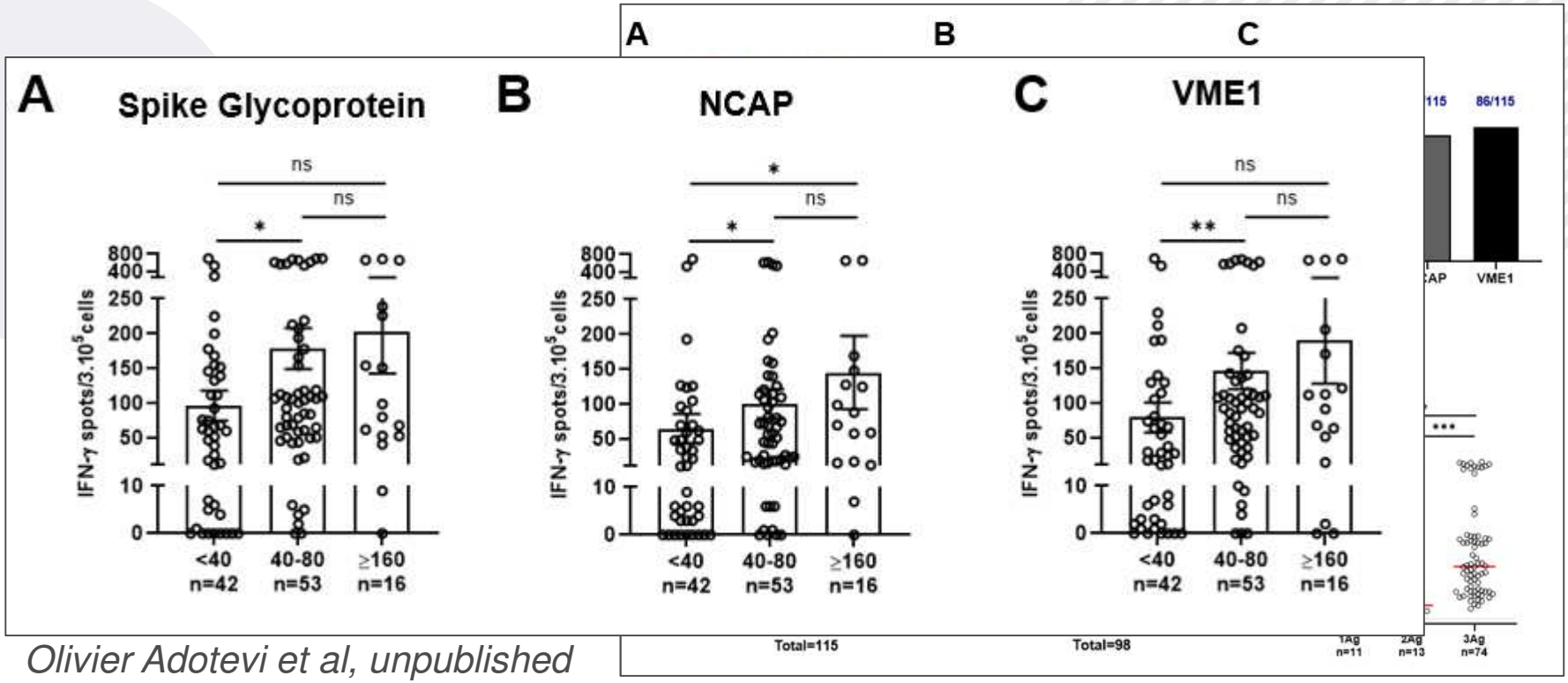


Olivier Adotevi et al, unpublished

On-going as well:

- Inflammatory mediators in convalescent plasma (*Fabrice Cognasse et al; Paul Bastard, Jean-Laurent Casanova et al)*
- ABO group (*Gallian et al, Antiviral Res*) and anti-A/B Ab profil in convalescent donors (*France Pirenne, Jacques Chiaroni et al*)
- Characterization of the anti-SARS-CoV-2 Ab response (*Pierre Gallian, Xavier De Lamballerie et al, on-going; Pascal Morel et al*)

CORIMUNO - CORIPLASM Trial

- **Promoter:** AP-HP, in collaboration with Etablissement Français du Sang, IHU Méditerranée Infection, REACTing Inserm.
- **Principal investigator:** Karine Lacombe, Sorbonne Université, IPLESP UMR-S1136
- **Plasma administration:** Two units of plasma (400-440 ml/day) as soon as possible, 2 days in a row (4 units total), at the latest on day 10 and 11 after onset of symptoms.
- **Primary endpoints:**
    1. Survival without needs of ventilator utilization (including non- invasive ventilation) or of other immunomodulatory agents at day 14
    2. Early end point : WHO progression scale >=7 at day 4 after plasma transfusion
- **Inclusion Criteria:** Patients included in the CORIMUNO-19 cohort* with the specific following criteria:
    - Mild severity (grade 4 or 5) as described in the WHO scale
    - Hospitalized and less than 10 days after onset of symptoms
- **Immunomonitoring**: Ab (Xavier De Lamballerie, Pierre Gallian, France Pirenne), T-cell (Yves Levy), inflammation (Fabrice Cognasse)
- **As of November 17th, 2020**

  15 clinical sites open

  40 patients included

Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19

PROTOCOLE D'UTILISATION THERAPEUTIQUE

24 avril 2020

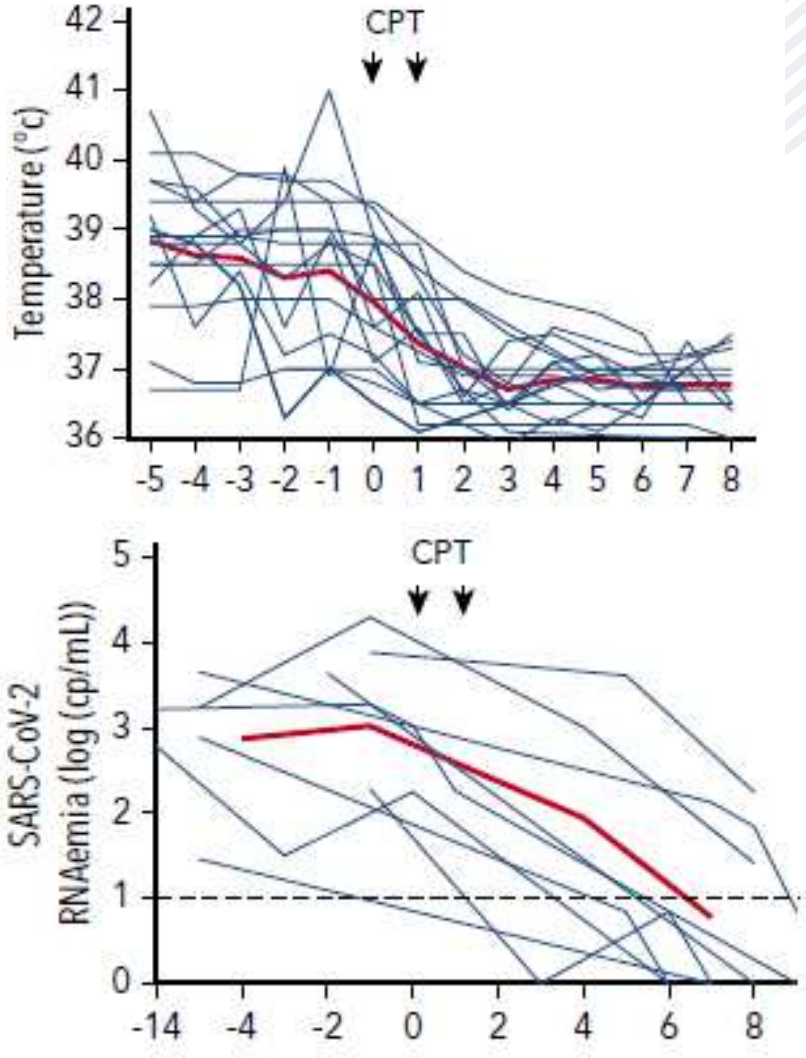
Plasma convalescent COVID-19

Infection par le coronavirus SARS-CoV-2 (maladie COVID-19)

Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19

Hueso et al, Blood

- Seventeen patients with B-cell lymphopenia (15 patients with prior Rituximab treatment) and prolonged COVID-19 symptoms, negative immunoglobulin G (IgG)-IgM SARS-CoV-2 serology, and positive RNAemia were transfused with 4 units of COVID-19 convalescent plasma.
- Within 48 hours of transfusion: striking improvement of clinical symptoms in 16 out 17 patients.
- All 10 oxygen-dependent patients could be weaned from the oxygen mask or noninvasive ventilation.
- One patient requiring ventilation died of bacterial pneumonia
- SARS-CoV-2 RNAemia decreased to below the sensitivity threshold in 9/9 evaluated patients.
- Virus-specific T-cell responses were present in 3/3 (*Lucienne Chatenoud et al*)
- No adverse event was reported.



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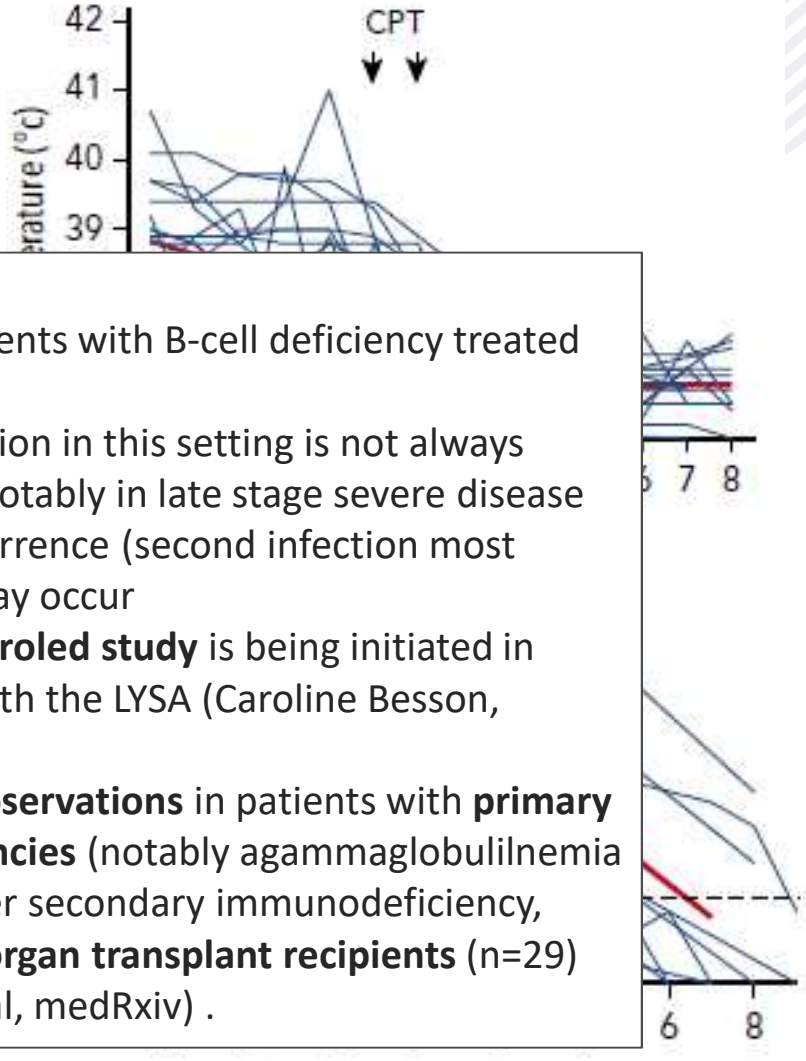


Up to now :

- Over 50 patients with B-cell deficiency treated by CCP
- CCP transfusion in this setting is not always successful, notably in late stage severe disease
- Disease recurrence (second infection most probably) may occur

A matched controled study is being initiated in collaboration with the LYSA (Caroline Besson, Vincent Ribrag).

Approaching observations in patients with **primary immunodeficiencies** (notably agammaglobulilnemia (n=-6)) and other secondary immunodeficiency, including **solid organ transplant recipients** (n=29) (Senefeld et et al, medRxiv) .

EUROPEAN BLOOD ALLIANCE

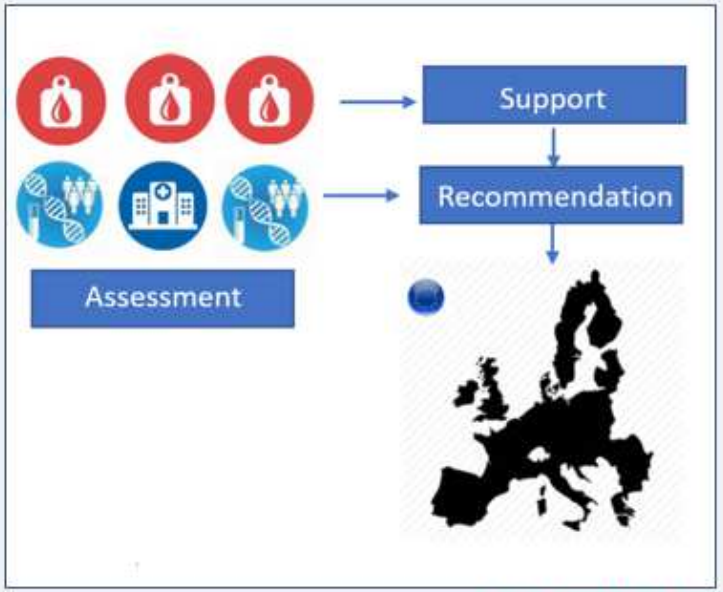
SUPPORT-E

Supporting high quality evaluation of COVID-19 convalescent plasma throughout Europe

SUPPORTing high quality evaluation of covid-19 convalescent plasma throughout EUROPE

SUPPORT-E objectives:

- support high quality clinical evaluation of COVID-19 convalescent plasma (CCP)
- achieve a consensus on the appropriate use of CCP in the treatment of COVID-19 across EU Member States
- promote best practices regarding convalescent plasma use in the current health crisis as well as in subsequent crisis involving novel pathogens



Funded by The European Union

The content of this presentation reflects only the author's view and that the Commission is not responsible for any use that may be made of the information it contains. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 101015756

Safe blood for Europe

Passive immunotherapy to treat COVID-19

Anti-SARS-CoV-2 hyperimmune immunoglobulin (hIVIG)

- High titer anti-SARS-CoV-2 IgG (five fold concentration increase?)
- Requires a large number of donations (extraction capacity: 4g IgG / liter of plasma)

CoVig-19 Plasma Alliance international consortium: lead by Takeda and CSL Behring (with Biotest, BPL, LFB, Octapharma and Sanquin)

- ITAC randomized clinical trial (NIH)(USA currently, England, Denmark, Japan, Greece planned)
- IvIG/standard of care vs standard of care; 500 patients, «early » (≤ 12 days of symptoms), Remdesevir in both treatment arms
- Primary endoint: patient clinical status at day 7 of treatment
- Initiated in 10/2020, scheduled end: 01/2021

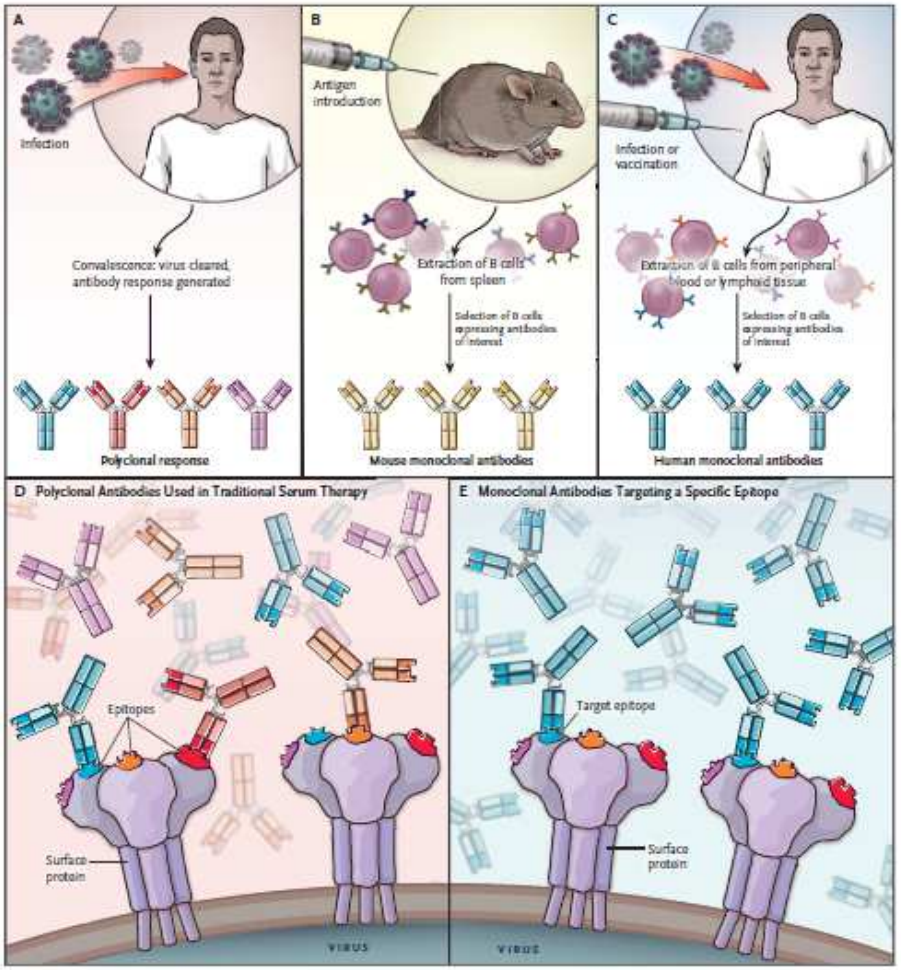
Kamada: completion of a phase 1/2 trial in Israel

- Hospitalized, non ventilated patients
- Symptom improvement in 11 /12 patients within 24 hours to 48 hours and discharged from hospital within 4.5 days (press release, Kanada)

Sanquin: (Netherlands) has just produced a 1rst batch of hIVIG

Passive immunotherapy to treat COVID-19

Monoclonal antibodies



Monoclonal Antibody Therapy.

Panel A shows early techniques to collect polyclonal serum from individuals recovering from disease after infectious virus is cleared and antibody response has been generated. Panel B shows monoclonal antibody isolation from mice, using antigen introduction into mice, collection of B cells from mouse spleens, and production of fully mouse, antigen-specific monoclonal antibodies. Panel C shows a technique for isolation of monoclonal antibodies from humans, using antigen introduction (through natural infection or immunization), collection of immune cells from peripheral blood or lymphoid tissue, selection of B cells expressing antibodies of interest (e.g., using flow cytometry), and production of fully human, antigen-specific monoclonal antibodies. Panel D shows polyclonal antibodies binding diverse regions or epitopes on the virion, whereas Panel E shows monoclonal antibodies representing a single antibody that targets a single epitope.

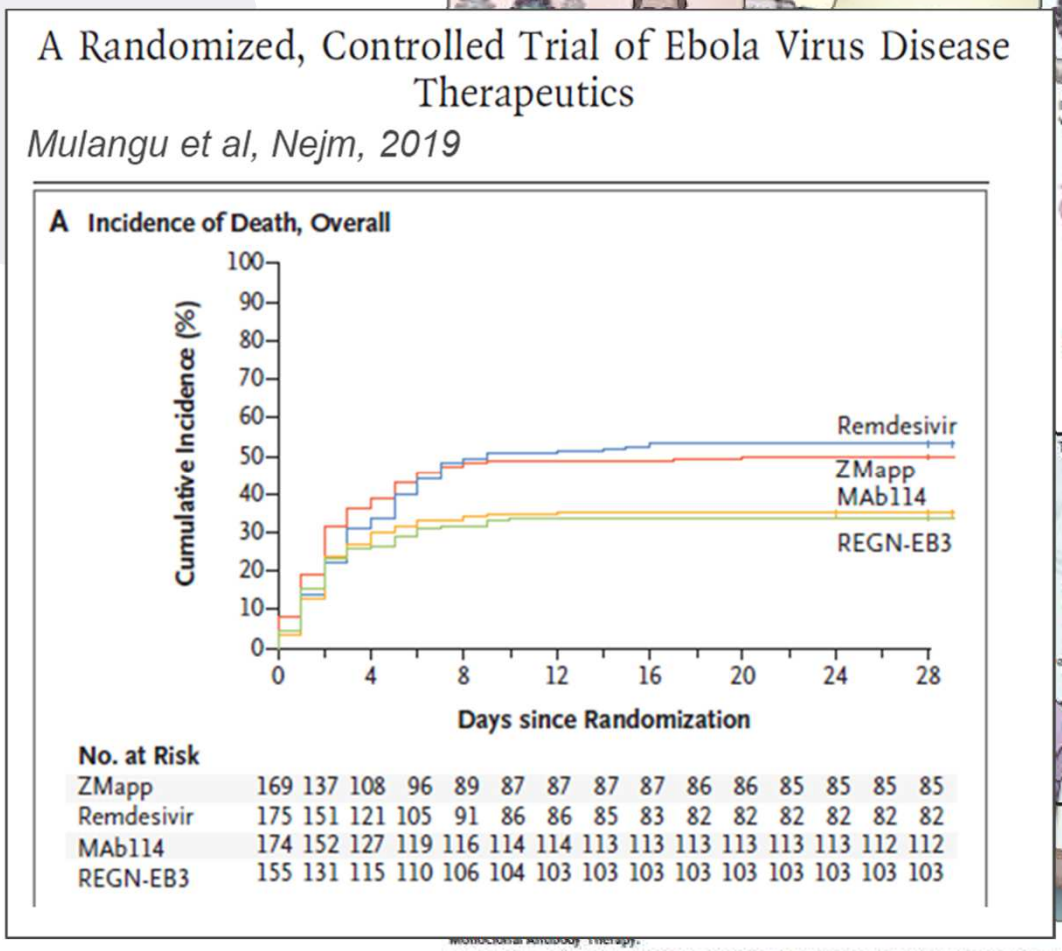
Marston et al, NEJM, 2020

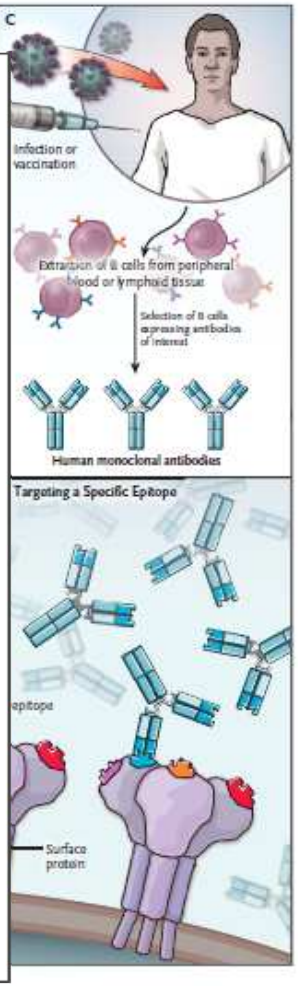
Passive immunotherapy to treat COVID-19

Monoclonal antibodies

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

Mulangu et al, Nejm, 2019





Panel A shows early techniques to collect polyclonal serum from individuals recovering from disease after infectious virus is cleared and antibody response has been generated. Panel B shows monoclonal antibody isolation from mice, using antigen introduction into mice, collection of B cells from mouse spleens, and production of fully mouse, antigen-specific monoclonal antibodies. Panel C shows a technique for isolation of monoclonal antibodies from humans, using antigen introduction (through natural infection or immunization), collection of immune cells from peripheral blood or lymphoid tissue, selection of B cells expressing antibodies of interest (e.g., using flow cytometry), and production of fully human, antigen-specific monoclonal antibodies. Panel D shows polyclonal antibodies binding diverse regions or epitopes on the virion, whereas Panel E shows monoclonal antibodies representing a single antibody that targets a single epitope.

Marston et al, NEJM, 2020

Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model

- Cohort of convalescent patients
- Antibody neutralization assays
- High-throughput antibody generation pipeline
- Rapid screening of more than 1800 antibodies
- Animal model to test protection.

- Isolation of neutralizing antibodies to two epitopes on RBD and to distinct non-RBD epitopes on the spike protein
- Demonstration that passive transfer of a nAb provides disease protection in hamsters.

Rogers et al, Science 2020

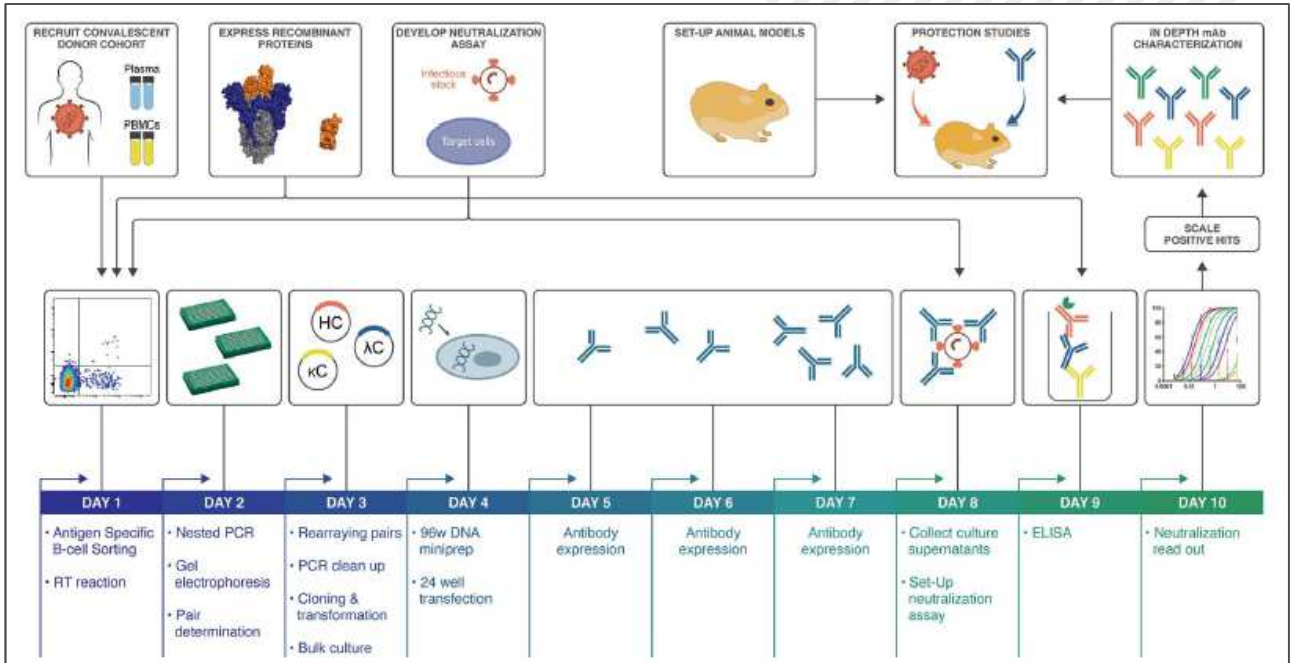


Fig. 1. SARS-CoV-2 neutralizing antibody isolation strategy. A natural infection cohort was established to collect plasma and PBMC samples from individuals who recovered from COVID-19. In parallel, functional assays were developed to rapidly screen plasma samples for SARS-CoV-2 neutralizing activity. SARS-CoV-2 recombinant surface proteins were also produced for use as baits in single-memory B cell sorting and downstream functional characterization of isolated mAbs. Finally, a Syrian hamster animal model was set up to evaluate mAb passive immunization and protection. The standard mAb isolation pipeline was optimized to facilitate high-throughput amplification, cloning, expression, and functional screening of hundreds of unpurified Ab heavy and light chain pairs isolated from each of several selected neutralizers in only 10 days. Selected pairs were scaled up to purify IgG for validation and characterization experiments. Potent neutralizing mAbs were selected to evaluate protection in the Syrian hamster model. HC, heavy chain; κC, kappa light chain; λC, lambda light chain; RT, reverse transcriptase.

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Chen et al, NEJM, 2020

- Ongoing randomized phase 2 (Blaze) trial
- Outpatients with recently diagnosed mild or moderate Covid-19 (less than 3 days since positive SARS-CoV-2 testing),
- Single iv infusion of of LY-CoV555 (anti-spike, derived from a human convalescent plasma) in one of three doses (n=309) or placebo (n=153)
- No reported serious adverse events

Primary outcome		
Mean change from baseline in viral load at day 11	−3.47	
	700 mg, −3.67	−0.20 (−0.66 to 0.25)
	2800 mg, −4.00	−0.53 (−0.98 to −0.08)
	7000 mg, −3.38	0.09 (−0.37 to 0.55)
	Pooled doses, −3.70	−0.22 (−0.60 to 0.15)

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

* Data for patients who presented to the emergency department are included in this category.

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Chen et al, NEJM, 2020

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Mean change from baseline in viral load at day 11	−3.47	
	700 mg, −3.67	−0.20 (−0.66 to 0.25)
	2800 mg, −4.00	−0.53 (−0.98 to −0.08)
	70	5)
	Pool	5)

Ly-CoV555+Ly-CoV016: 85,5% reduction in hospitalization (similar trial setting)(Eli Lilly press release)

Later administration of (hospitalized patients) of **Ly-CoV555**: trial interrupted (for futility?)

Table 3. Hospitalization.*

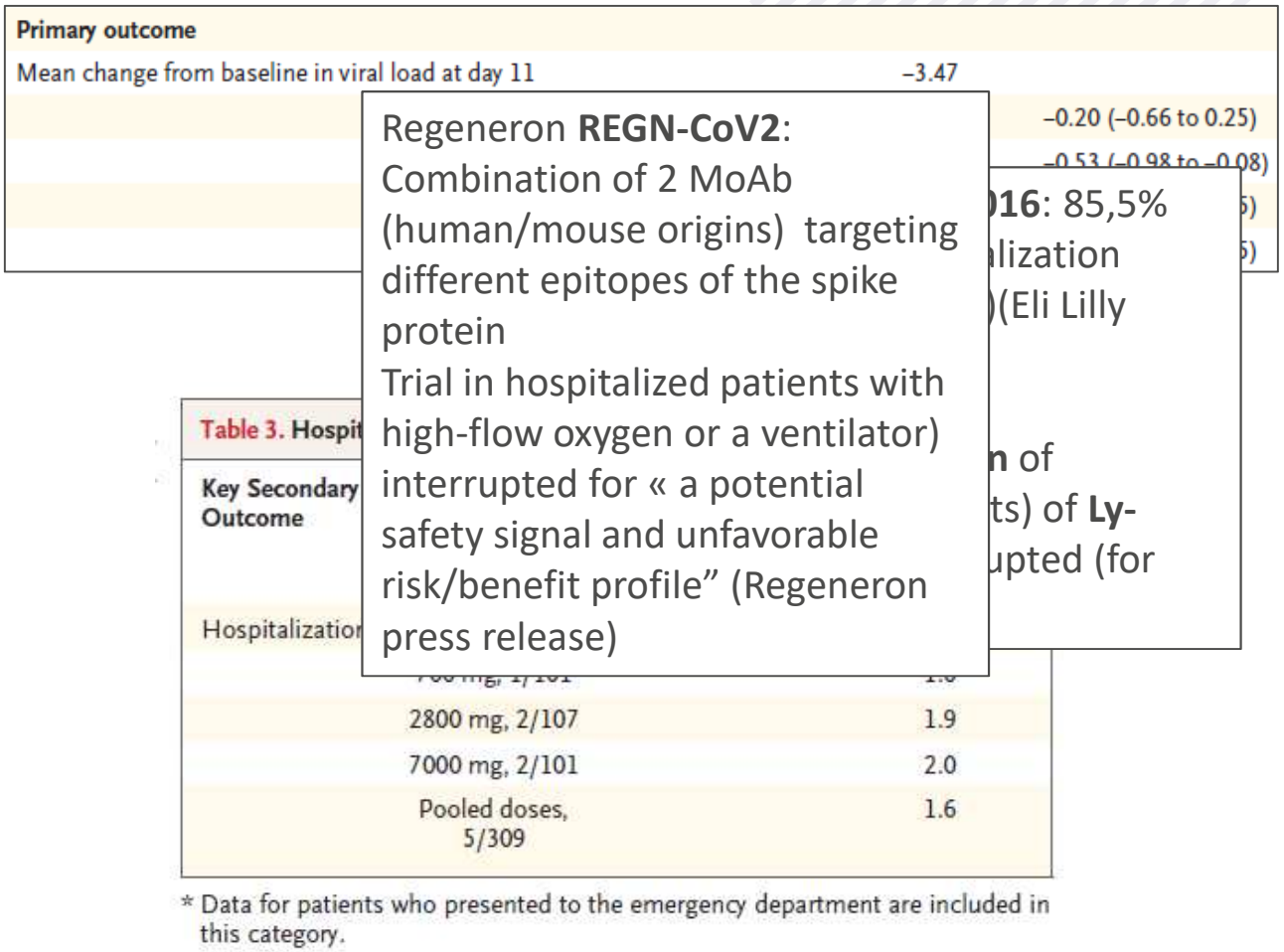
Key Secondary Outcome	LY-CoV555	
	no. of patients	
Hospitalization		
	700 mg, 1/101	1.0
	2800 mg, 2/107	1.9
	7000 mg, 2/101	2.0
	Pooled doses, 5/309	1.6

* Data for patients who presented to the emergency department are included in this category.

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Chen et al, NEJM, 2020

- Ongoing randomized phase 2 (Blaze) trial
- Outpatients with recently diagnosed mild or moderate Covid-19 (less than 3 days since positive SARS-CoV-2 testing),
- Single iv infusion of of LY-CoV555 (anti-spike, derived from a human convalescent plasma) in one of three doses (n=309) or placebo (n=153)
- No reported serious adverse events



Primary outcome	
Mean change from baseline in viral load at day 11	−3.47
	−0.20 (−0.66 to 0.25)

Regeneron **REGN-CoV2**: Combination of 2 MoAb (human/mouse origins) targeting different epitopes of the spike protein
Trial in hospitalized patients with high-flow oxygen or a ventilator) interrupted for « a potential safety signal and unfavorable risk/benefit profile" (Regeneron press release)

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Key Secondary Outcome	
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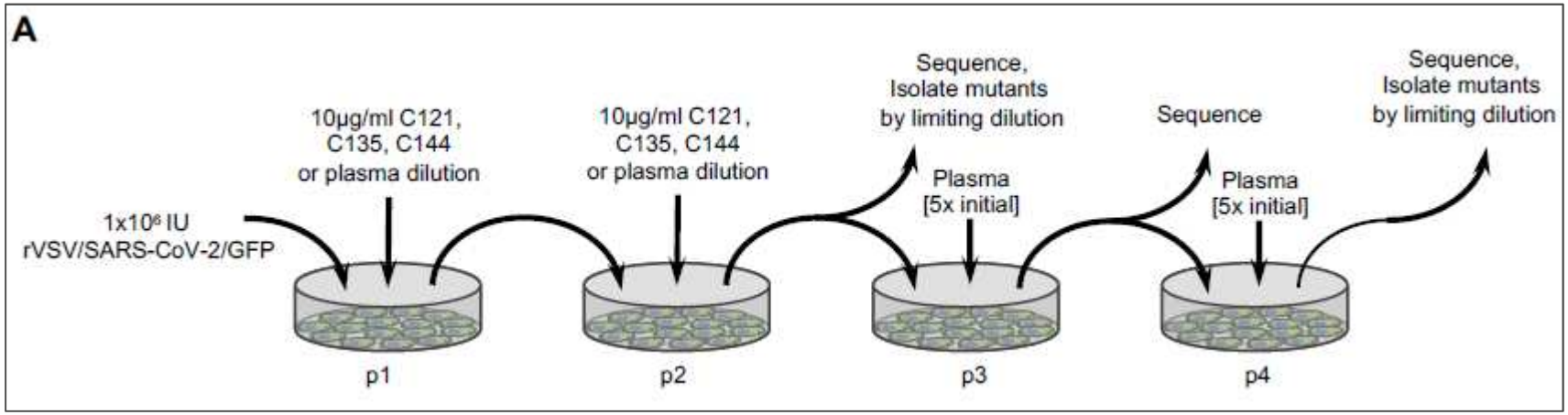
Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants

Weisblum et al, Elife, 2020

- Use a recombinant chimeric VSV/SARS-CoV-2 reporter virus
- Demonstration that functional SARS-CoV-2 S protein variants with mutations in the RBD and N-terminal domain that confer resistance to MoAb or convalescent plasma can be readily selected.
- SARS-CoV-2 S variants that resist commonly elicited neutralizing antibodies are now present at low frequencies in circulating SARS-CoV-2 populations



- Blaze trial: % resistant variants higher in the AcMo treatment arm? 8 vs 6%?

- New mutation of coronavirus found in mink farms in Denmark: implications for human health and treatment?
- Mutations that could affect the efficiency of vaccines as well as passive immunotherapy approaches

Passive immunotherapy to treat COVID-19

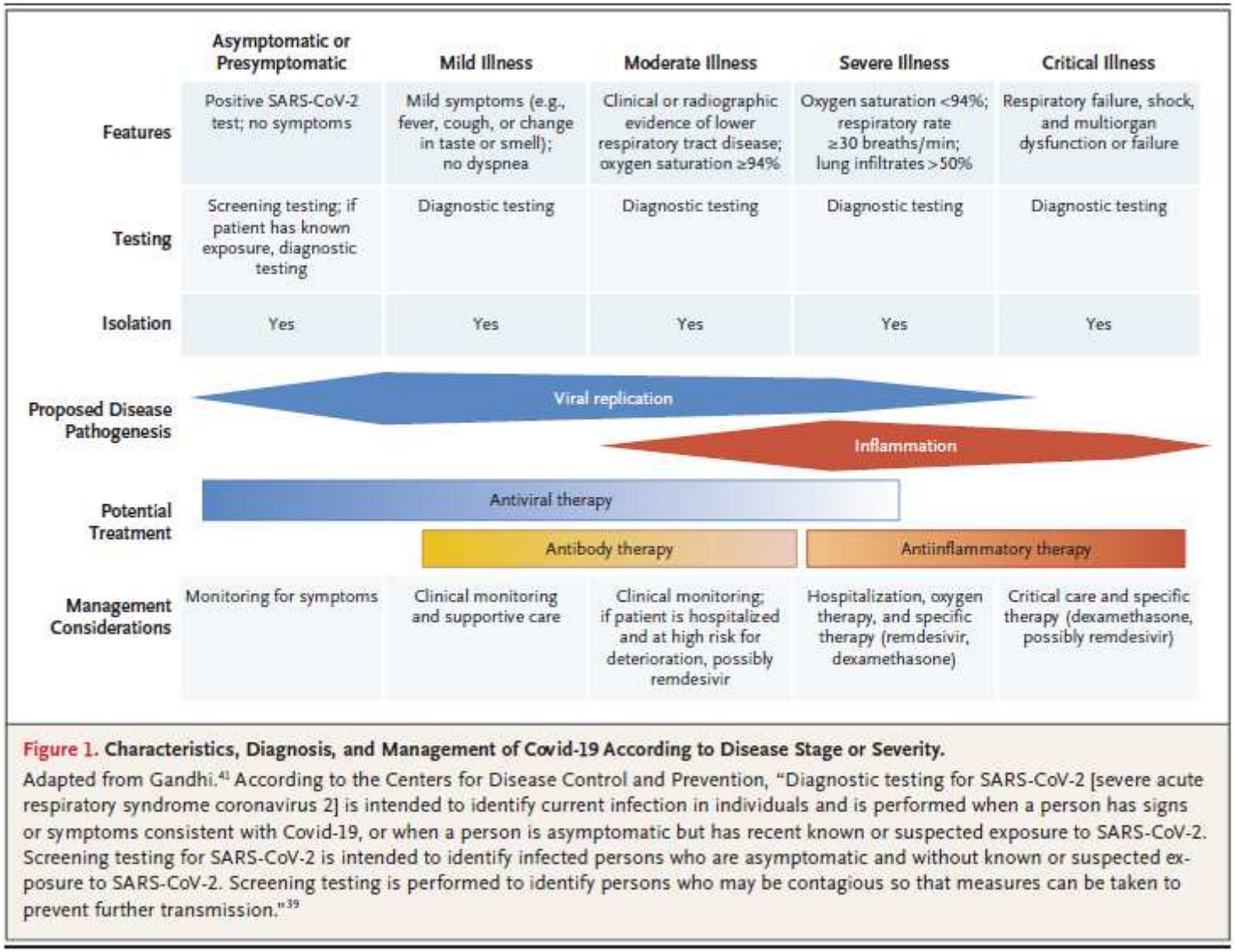
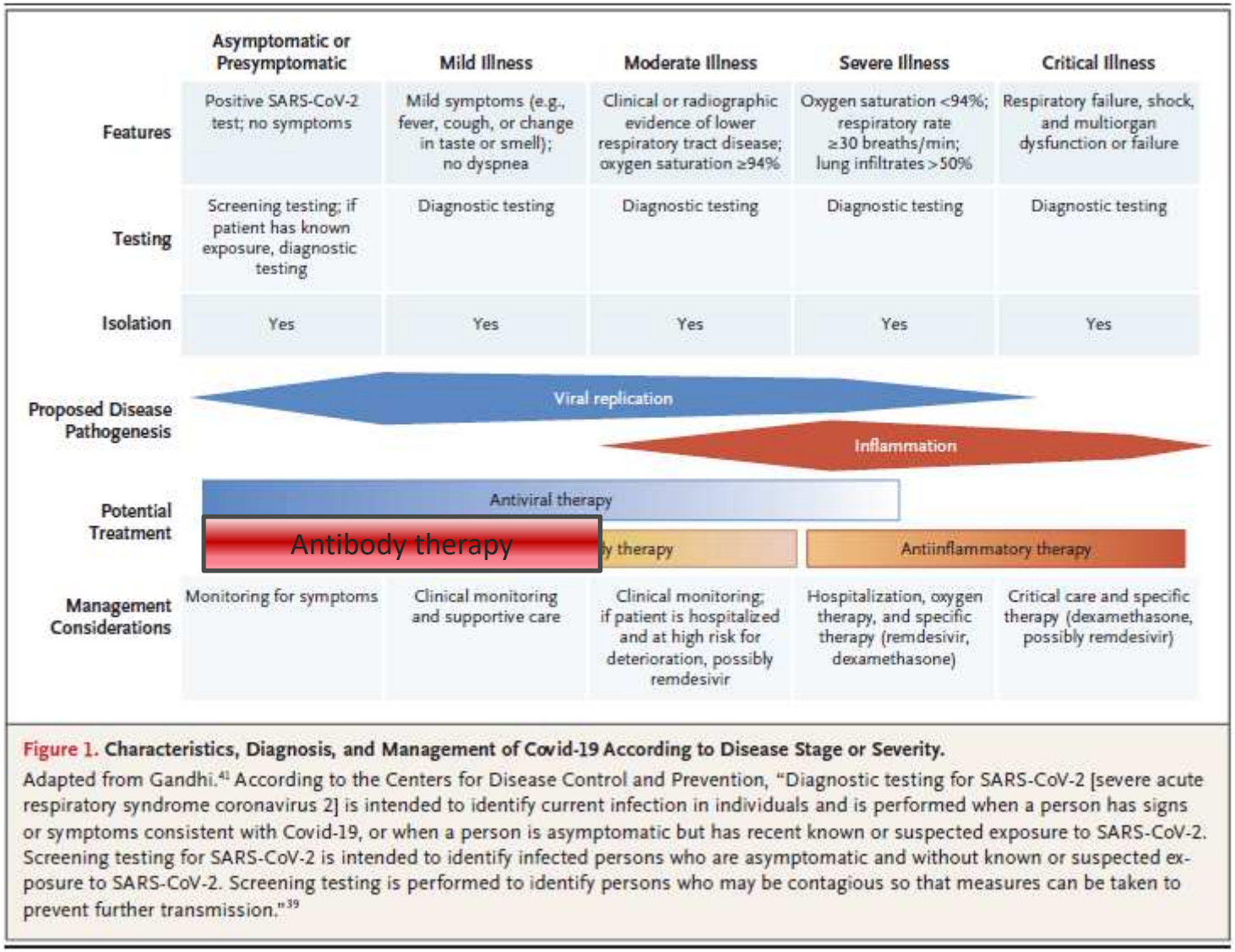


Figure 1. Characteristics, Diagnosis, and Management of Covid-19 According to Disease Stage or Severity.

Adapted from Gandhi.[41] According to the Centers for Disease Control and Prevention, "Diagnostic testing for SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2] is intended to identify current infection in individuals and is performed when a person has signs or symptoms consistent with Covid-19, or when a person is asymptomatic but has recent known or suspected exposure to SARS-CoV-2. Screening testing for SARS-CoV-2 is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2. Screening testing is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission."[39]

Gandhi et al, NEJM, 2020

Passive immunotherapy to treat COVID-19



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Gandhi et al, NEJM, 2020

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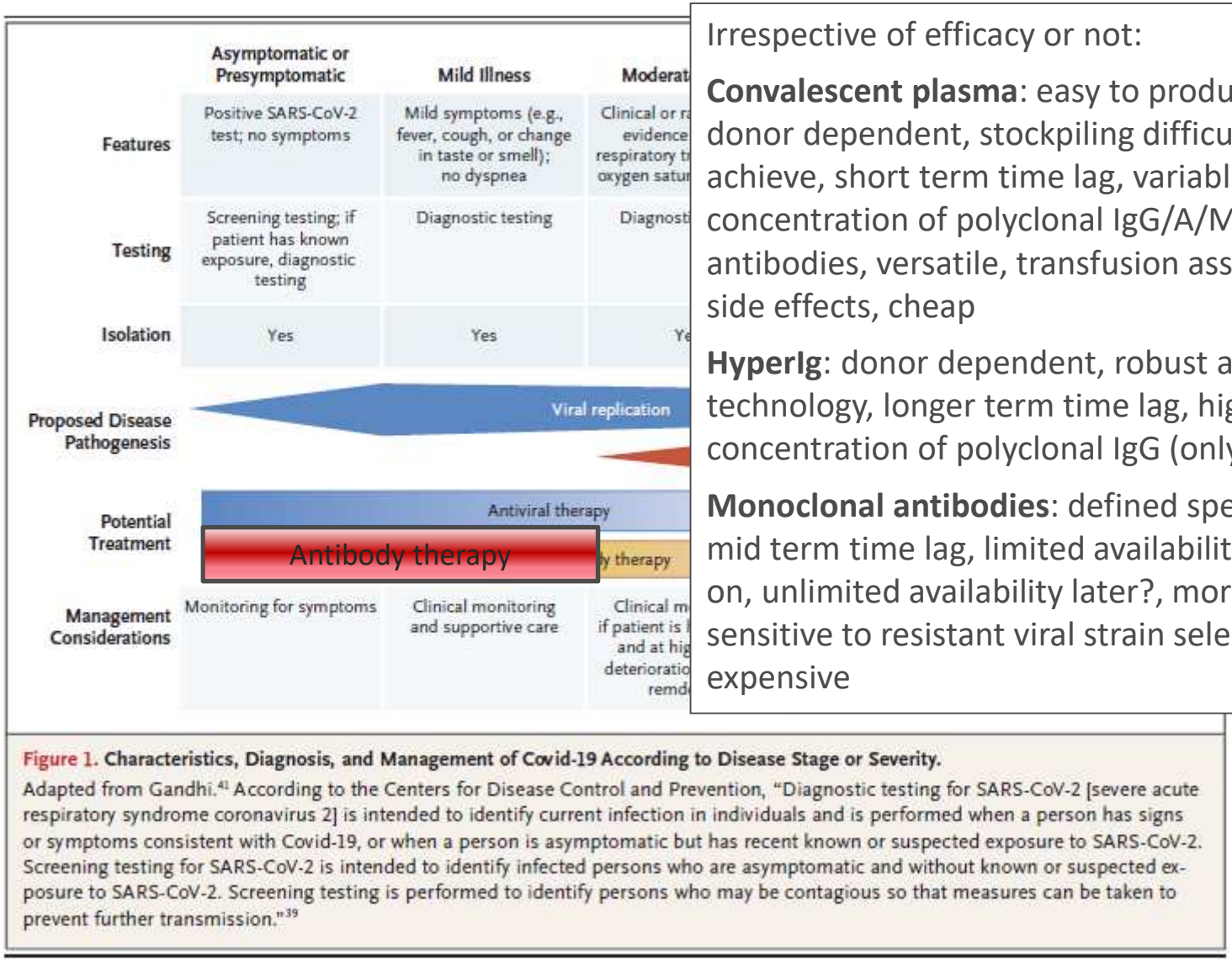

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Irrespective of efficacy or not:

Convalescent plasma: easy to produce, donor dependent, stockpiling difficult to achieve, short term time lag, variable concentration of polyclonal IgG/A/M, antibodies, versatile, transfusion associated side effects, cheap

HyperIg: donor dependent, robust and safe technology, longer term time lag, high concentration of polyclonal IgG (only)

Monoclonal antibodies: defined specificity, mid term time lag, limited availability early on, unlimited availability later?, more sensitive to resistant viral strain selection, expensive

Gandhi et al, NEJM, 2020

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Yazdan Yazdanpanah, APHP Bichat / REACTing

And last but not least!, our blood donors