Available Therapies and Vaccination in COVID-19 patients with Kidney Disease

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No Disclosures

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Covid-19 therapy: Attacking the virus and the inflammatory response

Coronavirus pandemic

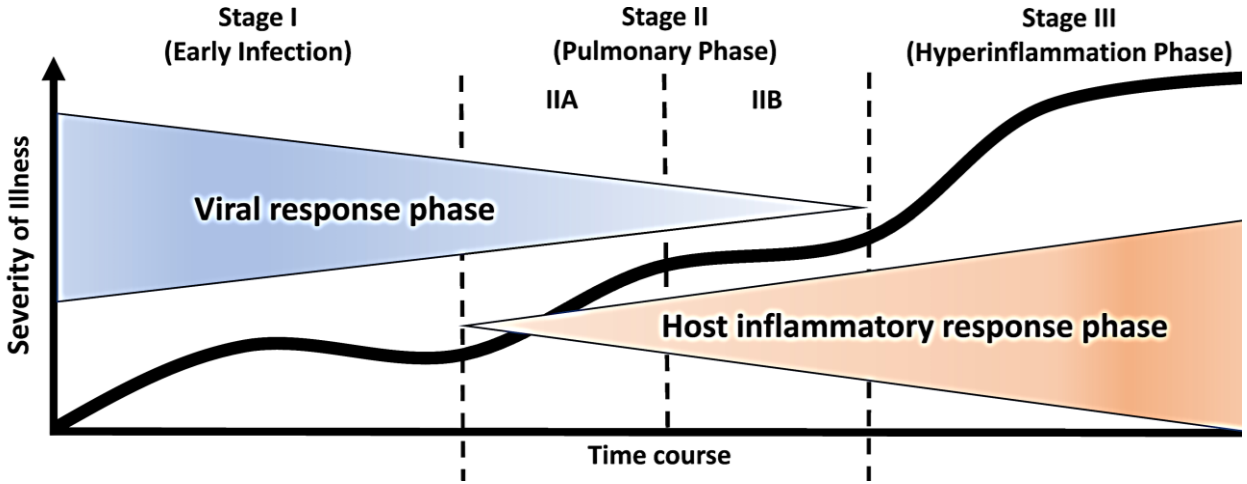
Coronavirus whistleblower doctor dies in Wuhan hospital

Passing of Li Wenliang sparks outpouring of grief and anger in China

Li Wenliang raised the alarm over some new pneumonia cases in an online chat group with medics that was shared widely

James Kynge in Hong Kong and **Nian Liu** in Beijing FEBRUARY 6 2020

Anti-viral agents **Anti-inflammatory agents**



https://www.jhltonline.org/article/S1053-2498(20)31473-X/fulltext

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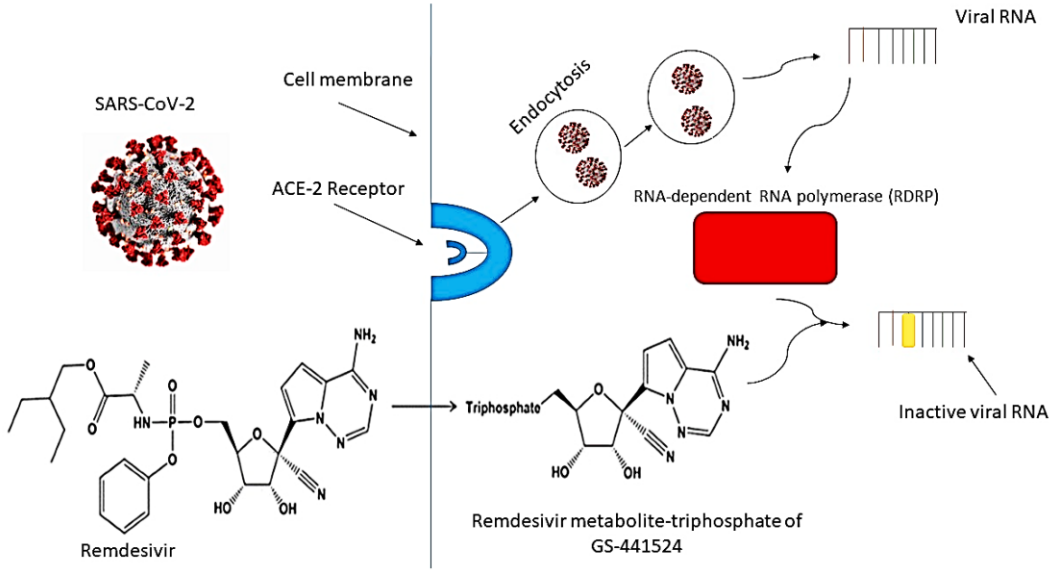
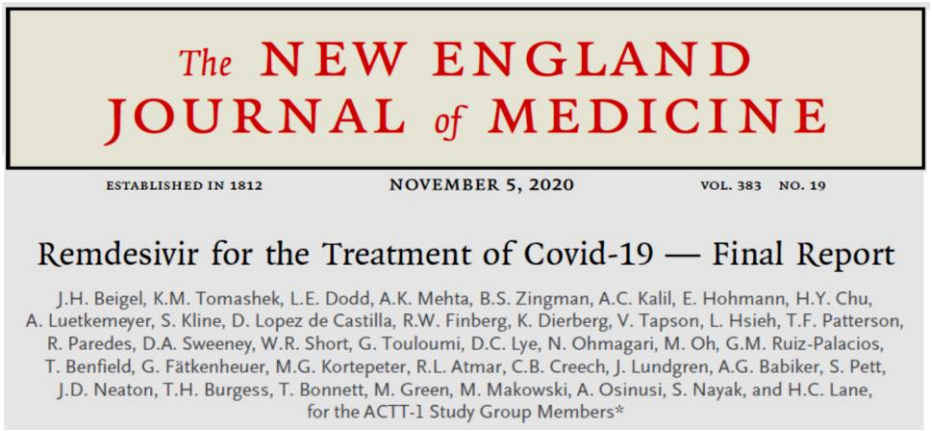
FDA approved therapy for Covid-19

- Remdesivir
  - Anti-viral - approved 10/2020
    - Prodrug – adenosine analog inhibitor of viral RNA polymerase
  - Effect: Shorter time to improvement, symptomatic improvement.
  - Indication: Oxygen requirement (non-invasive ventilation).
  - Not recommended: creatinine clearance <30 mL/min, renal replacement therapy.



https://www.mdpi.com/2218-0532/88/2/29/htm



The NEW ENGLAND JOURNAL of MEDICINE

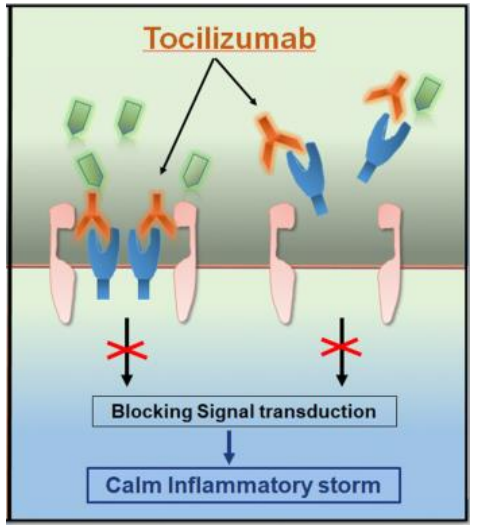
ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

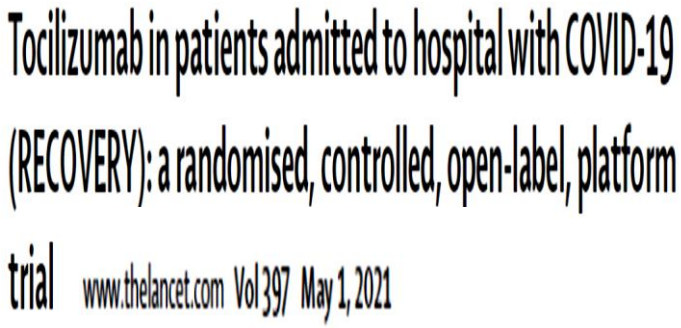
J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Repurposed drugs for Covid-19

- Dexamethasone
  - Anti-inflammatory drug
  - RECOVERY trial
    - Reduced mortality: Mechanical ventilation, oxygen support.
- Tocilizumab
  - IL-6 inhibitor
  - RECOVERY trial
    - Reduced mortality: Hypoxia (O_2<92%), including those on corticosteroids.



https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-020-02339-3



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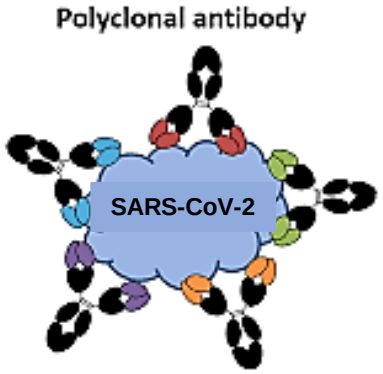
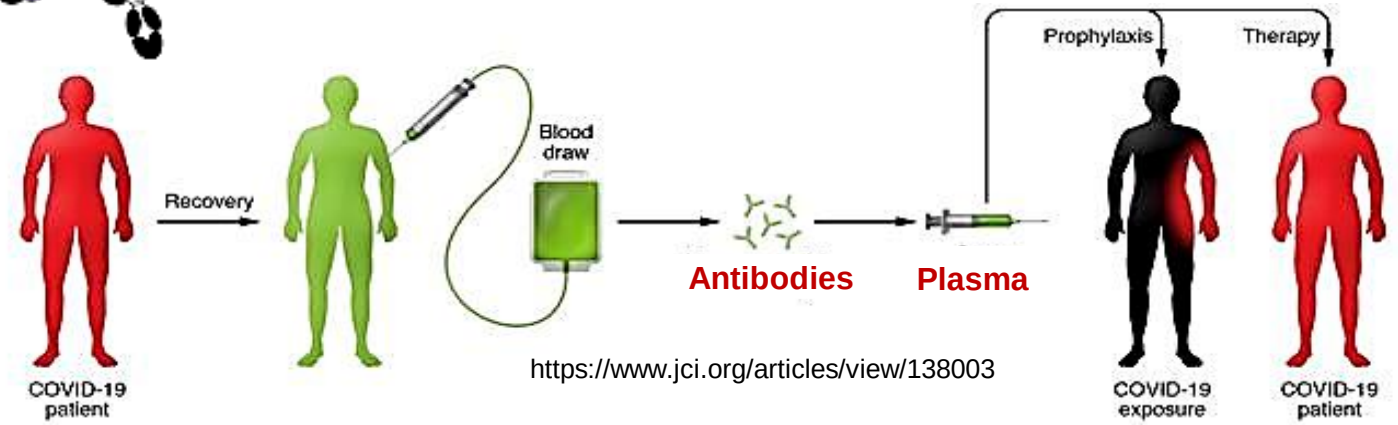


Covid-19 convalescent plasma (CCP)

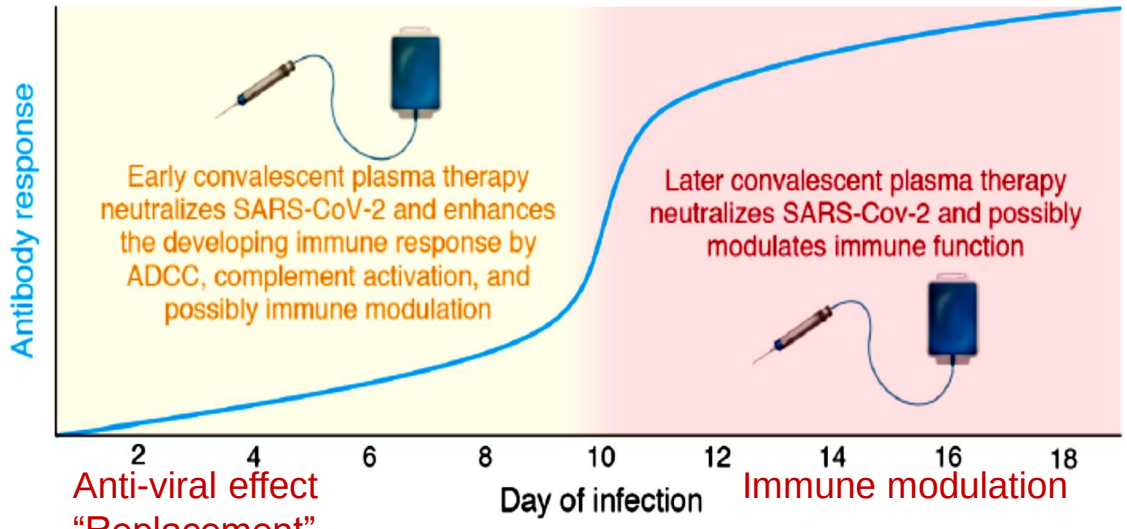
FDA emergency use authorization (EUA): August 2020, revised February 2021

https://www.fda.gov/media/141478/download

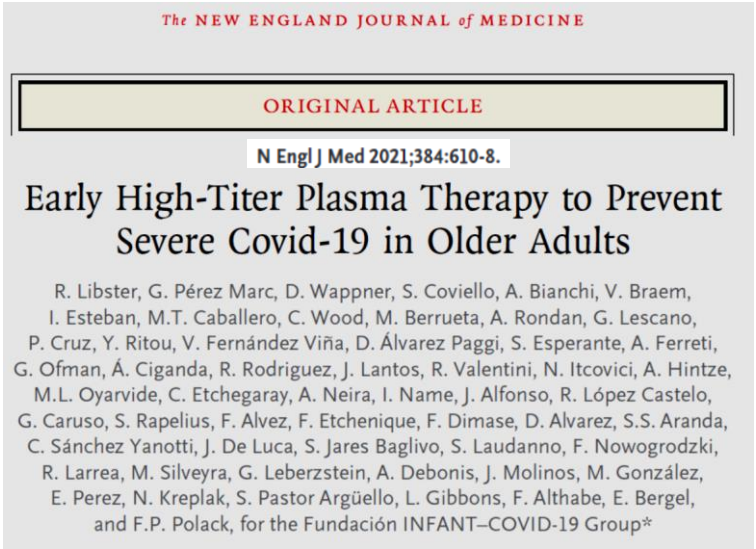


https://www.jci.org/articles/view/138003

- Hospitalized patients only.
- High titer SARS-CoV-2 IgG.
- Used early, non-intubated.
- Later in humoral immunodeficiency.



https://www.jci.org/articles/view/13976012



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Received: 25 August 2020 | Revised: 25 August 2020 | Accepted: 3 September 2020

DOI: 10.1111/ctr.14089

BRIEF COMMUNICATION

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Treatment with convalescent plasma in solid organ transplant recipients with COVID-19: Experience at large transplant center in New York City

- 13 patients
  - 5 kidney,
  - 1 liver-kidney, 1 kidney-pancreas
  - 4 liver
  - 1 heart
  - 10 steroids, 8 tacrolimus, 6 MMF
- Time to treatment
  - 5-31 days symptoms (median 8)
- Outcomes
  - 8 required less O_2 on day 7
  - 9 discharged, 1 in hospital
  - 3 died - treated late, ventilated/ICU

CCP had anti-inflammatory effect

Lab (median)	Pre-infusion (at day 0)	Post-Infusion (at day 7)
C-reactive protein (mg/L) Normal 0-5	124 (range 24.2-457)	58.5 (range 14.3-307.5)
Procalcitonin (ng/mL) Normal < 0.49	1.54 (range 0.29-14.2)	0.315 (range 0.02-4.29)
D-dimer (ug/mL) Normal 0-0.5	2.63 (range 0.41-16.64)	2.835 (range 0.48-8.85)
Ferritin (ng/mL) Normal 30-400	1096 (range 76-14 614)	805 (range 119-15 621)

https://onlinelibrary.wiley.com/doi/full/10.1111/ctr.14089

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Feasibility of Convalescent Plasma Therapy in Kidney Transplant Recipients With Severe COVID-19: A Single-Center Prospective Cohort Study

Akash Gupta,[1] Vivek B. Kute,[1] Himanshu V. Patel,[1] Divyesh P. Engineer,[1] Subho Banerjee,[1] Pranjal R. Modi,[2] Syed J. Rizvi,[2] Vineet V. Mishra,[3] Ansy H. Patel,[4] Vijay Navadiya[1]

Table 3. Clinical Symptoms and Laboratory Investigations at Days 0, 1, and 7 of Convalescent Plasma Transfusion

Characteristic	Patient Number									
	1	2	3	4	5	6	7	8	9	10
Fever										
Before plasma	+	+	-	+	-	+	+	+	+	+
After plasma	-	-	-	-	-	-	-	-	-	-
Pao_2/Fio_2, mm Hg										
Before plasma	124	140	136	153	110	130	70	156	92	116
After plasma	310	352	412	324	284	305	N/A	349	416	364
hsCRP, mg/L										
Before plasma	173.1	158.6	159.4	91.4	140	164.1	204	63.8	90.2	89
After plasma (D1)	19.9	23.7	27.9	23.6	45	39.5	145.8	22.7	35.7	34.5
After plasma (D7)	2.1	8.5	3.2	6.4	7.1	5.8	N/A	11.6	8.7	9.6
IL-6, pg/mL										
Before plasma	116.8	191.4	111.4	318.7	255.3	318.5	198	110	104	167
After plasma (D1)	59.95	36.23	17.91	121	41.5	165	78.8	34	24.54	28.59
After plasma (D7)	1.8	23.48	9.73	21.4	6.7	28.1	N/A	6.68	8.28	7.8

Increased O2

Decreased CRP

Decreased IL-6

Experimental and Clinical Transplantation (2021) 4: 304-309

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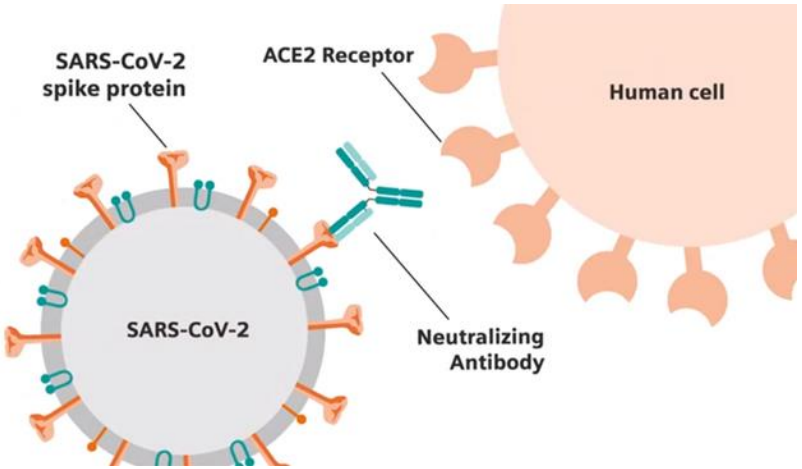
SARS-CoV-2 monoclonal antibodies

- Anti-viral mechanism
  - Bind spike protein block viral entry
- FDA EUAs for outpatient use
  - bamlanivimab/etesevimab (Lilly)
  - casirivimab/imdevimab (Regeneron)
- Efficacy
  - Reduce hospitalizations, severe disease
  - Especially in seronegative people
- Indications (adults)
  - SARS-CoV-2 positive
  - Symptoms ≤ 10 days
  - Not hospitalized
  - High risk for severe Covid-19
    - Body mass index (BMI) ≥35
    - CKD, immunocompromising condition, DM, ≥65
    - ≥55 with: Cardiovascular disease, *or* Hypertension, *or* COPD, *or* respiratory disease



bamlanivimab/etesevimab: Human IgG1κ – overlapping spike epitopes
https://jamanetwork.com/journals/jama/fullarticle/2775647
https://www.fda.gov/media/145801/download

casirivimab/imdevimab: Human IgG1κ – different spike epitopes
https://www.fda.gov/media/143892/download
https://www.nejm.org/doi/full/10.1056/NEJMoa2035002

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LETTER TO THE EDITOR

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Clinical Transplantation. 2021;35:e14245.
https://doi.org/10.1111/ctr.14245

Bamlanivimab for treatment of COVID-19 in solid organ transplant recipients: Early single-center experience

TABLE 1 Characteristics of Solid organ transplant recipients treated with Bamlanivimab

Age(years)/sex/ transplant type	Symptoms/days	Chest X-ray	SpO2 on ambient air	Other risk factors for progression	Follow-up (days)
58/M Liver	Nasal stuffiness 6 days	N/A	98%	Cardiac disease, Diabetes	27
60/M Liver	Cough 10 days	N/A	97%		27
56/M Kidney	Fever, Malaise 2 days	N/A	96%	BMI – 35 Diabetes, CKD	27
66/M Liver/kidney	Cough, SOB 3 days	Bilateral opacities	92%	Age >65 years	24
40/M Kidney	Fever, cough, diarrhea, malaise 1 day	Bilateral opacities	93%	Cardiac disease, CKD	21
51/M Heart	Fever, cough, nasal stuffiness 1 day	N/A	96%		20
62/M Kidney	Cough, nasal stuffiness 3 days	N/A	93%	Cardiac disease, Diabetes	20
55/M Kidney	Fever, cough 4 days	Clear	97%		20
41/M Kidney	Fever, malaise 1 day	N/A	98%		17
39/M Kidney	Loss of smell, malaise 2 days	N/A	96%	BMI - 35	14

- 11 SOT recipients
  - 5 kidney, 1 kidney/liver
- Interventions
  - Stopped/lowered MMF (40%)
  - Lowered calcineurin inhibitor (70%)
- Outcome
  - None required hospitalization

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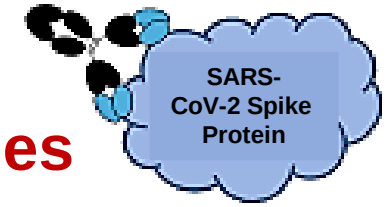
Benefits of CCP and monoclonal antibodies

Convalescent plasma

- Ready made, readily available.
- Can be deployed rapidly.
- Might be only antiviral available in resource limited settings.
- Relatively inexpensive.
- Only immediately available agent for variants.
- Likely effective in immune deficiency.

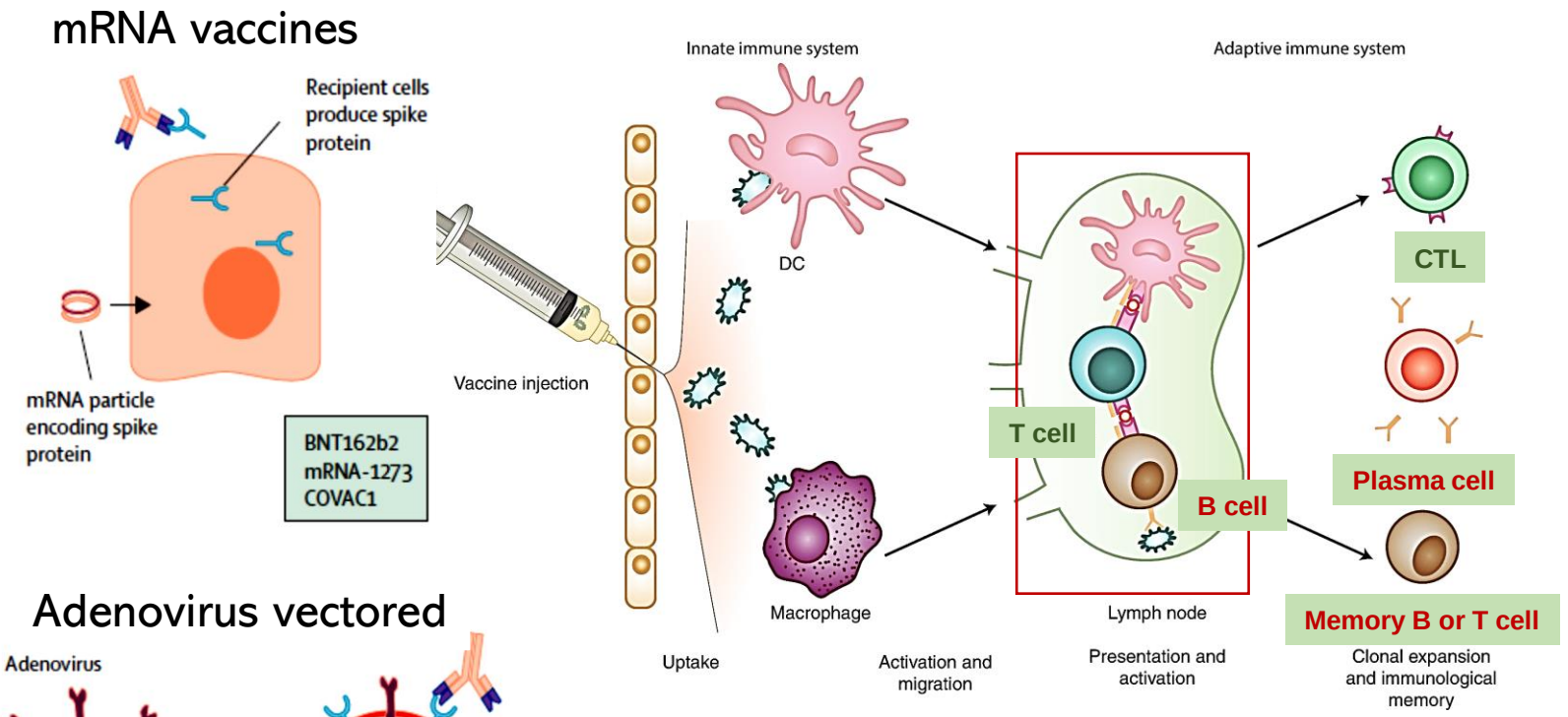


Monoclonal antibodies

- Require ‘manufacture’.
- Take time to produce to scale, resources and cost (they are expensive) limit availability.
- Susceptible to viral escape, emergence of resistance.
- Potential for SQ administration.
- Smaller volume load, not blood product.

SARS-CoV-2 vaccines with FDA EUAs

- mRNA
  - Packaged in liposomes
  - Spike protein mRNA
  - Highly immunogenic
  - Highly effective - prevent severe disease and death
- Adenovirus vectored
  - Nonreplicating
  - Encode spike protein
  - Highly immunogenic
  - Highly effective - prevent severe disease and death



https://link.springer.com/chapter/10.1007/978-3-030-00710-2_14

www.thelancet.com/gastrohep Vol 6 March 2021

Moderna: https://www.fda.gov/media/144637/download

Pfizer: https://www.fda.gov/media/144413/download

Janssen: https://www.fda.gov/media/146304/download

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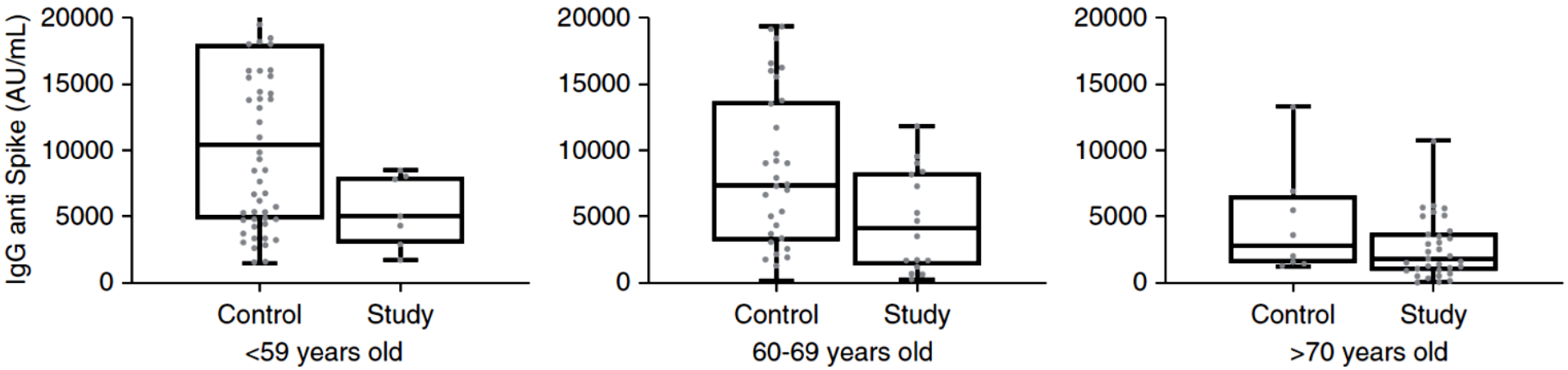
Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis

Ayelet Grupper,[1,2] Nechama Sharon,[3,4] Talya Finn,[4,5] Regev Cohen,[4,5] Meital Israel,[4,6] Amir Agbaria,[4,6] Yoav Rechavi,[2,3] Idit F. Schwartz,[1,2] Doron Schwartz,[1,2] Yonatan Lellouch,[4,7] and Moshe Shashar[1,4,6]

CJASN ePress. Published on April 6, 2021 as doi: 10.2215/CJN.03500321

Spike protein IgG assay



N= 95 controls, N= 56 dialysis patients, stratified by age

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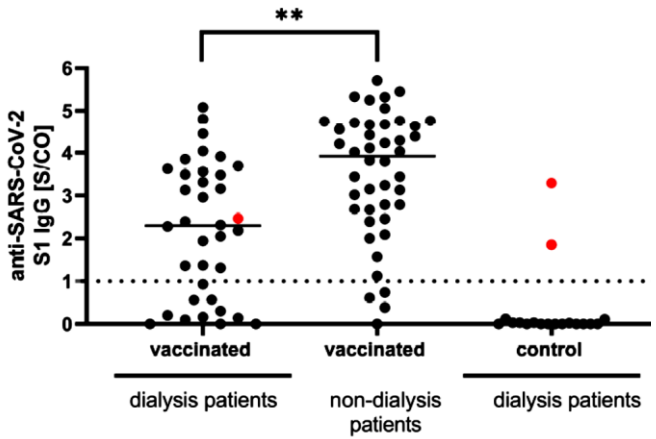
Immunogenicity of COVID-19 Tozinameran Vaccination in Patients on Chronic Dialysis

Eva Schrezenmeier[1]*, MD; Leon Bergfeld[2]*, MD; David Hillus[3]*, MD; Joerg-Detlev Lippert[4], MD; Ulrike Weber[1], MD; Pinkus Tober-Lau[3], MD; Irmgard Landgraf[5], MD; Tatjana Schwarz[2], PhD; Kai Kappert[6], MD; Ana-Luisa Stefanski[1], MD; Arne Sattler[7], PhD; Katja Kotsch, PhD[7], Thomas Doerner[8], MD; Leif Erik Sander[3], MD; Klemens Budde[1], MD; Fabian Halleck[1], MD; Florian Kurth[3,9]*, MD; Victor Max Corman[2]*, PhD; Mira Choi[1]*, MD

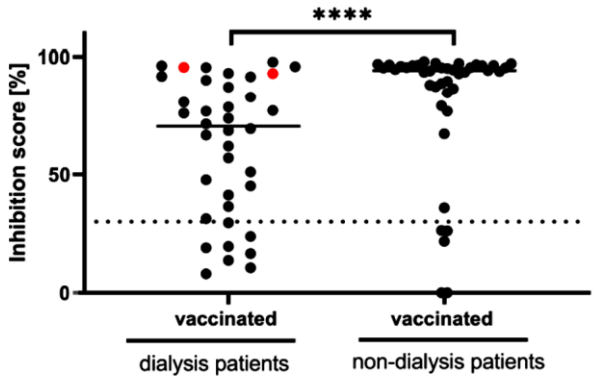
https://www.medrxiv.org/content/10.1101/2021.03.31.21254683v1

Spike protein IgG assay

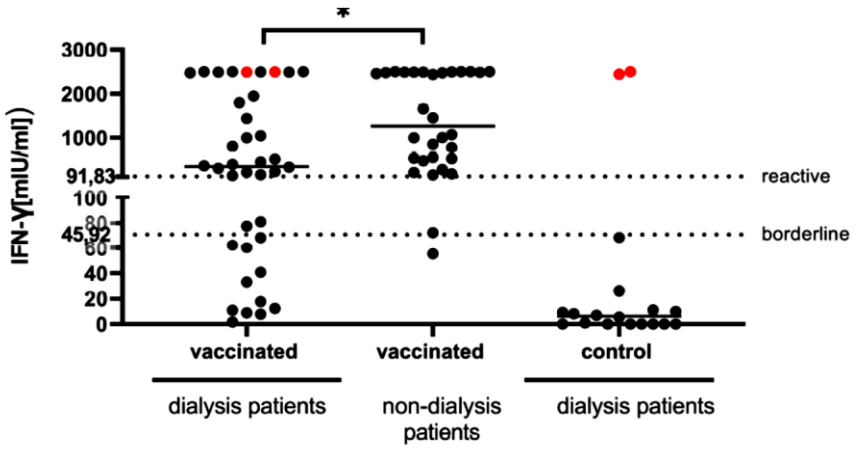


N=36 N=44 N=18

Neutralization assay



Measure of cellular function
Interferon-gamma release assay



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Immunogenicity of SARS-CoV-2 Vaccine in Dialysis

https://www.medrxiv.org/content/10.1101/2021.04.08.21254779v1.full.pdf

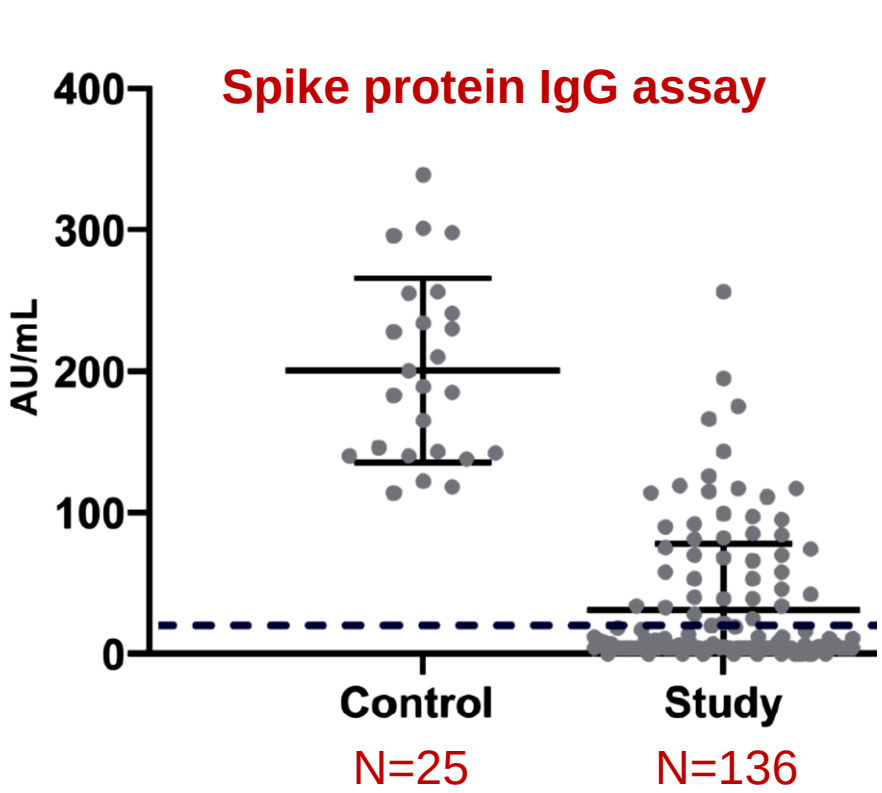
Authors: Eduardo Lacson, Jr., M.D.,M.P.H.,[1,2] Christos P. Argyropoulos, M.D.,[3] Harold J. Manley, PharmD,[2] Gideon Aweh, M.S.,[2] Andrew I. Chin, M.D.,[4] Loay H. Salman, M.D., M.B.A.,[5] Caroline M. Hsu, M.D.,[1] Doug S. Johnson, M.D.,[2] Daniel E. Weiner M.D.[1]

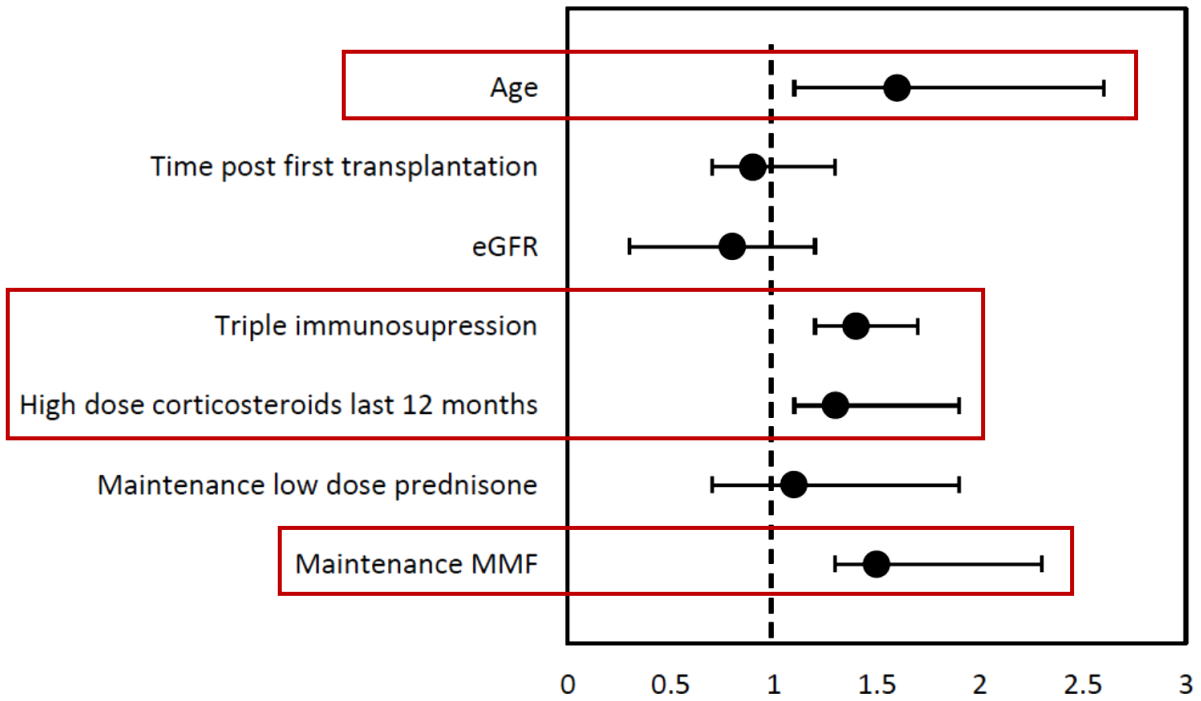
- Retrospective EMR study of vaccine response
- 186 dialysis patients @ 32 clinics, 8 states
  - Median age 68 years; 47% women; 21% Black
  - 97.3% hemodialysis: 26% LTCF; 97% in-center hemodialysis
  - Responders: 165/186: 88%
  - Univariate non-responders: Female; shorter vintage (39 v 61 months); immunosuppressive therapy; receipt of another vaccine within 2 weeks; hospitalization within 14 days; CHF

Reduced humoral response to mRNA SARS-Cov-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus.

Ayelet Grupper[1,2], Liane Rabinowich[2,3], Doron Schwartz[1], Idit F. Schwartz[1], Merav Ben-Yehoyada[3], Moshe Shashar[5], Eugene Katchman[4], Tami Halperin[4], Dan Turner[4], Yaacov Goykhman[2], Oren Shibolet[2,3], Sharon Levy[2,3], Inbal Houri[2,3], Roni Baruch[1,2], Helena Katchman[2,3]

https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajt.16615





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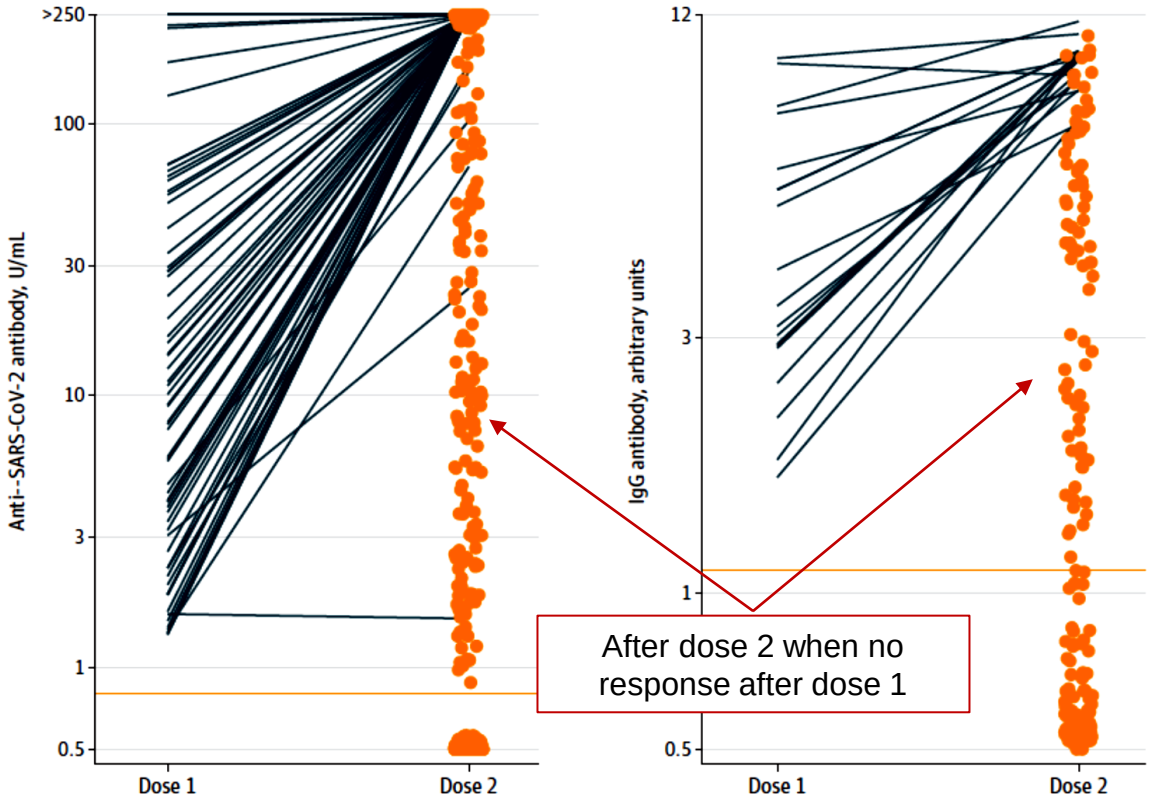
Letters

RESEARCH LETTER JAMA Published online May 5, 2021

Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients

Receptor binding domain IgG

Spike protein IgG



N = 658

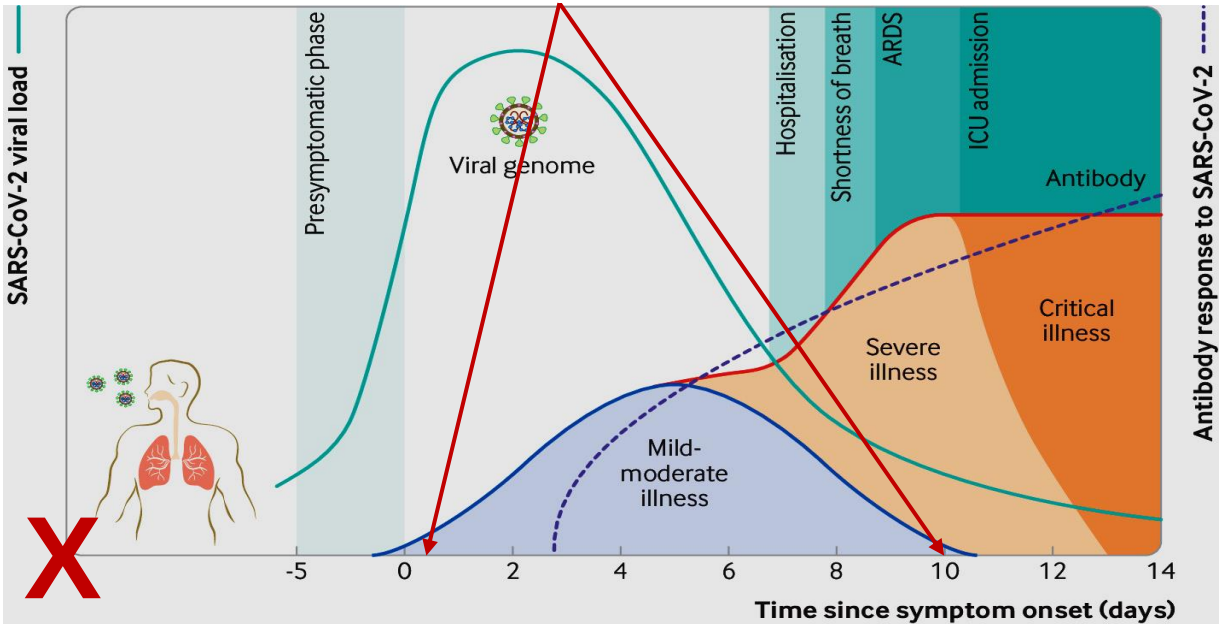
Table. Demographic and Clinical Characteristics of Study Participants, Stratified by Immune Response to the 2 Doses of SARS-CoV-2 mRNA Vaccine

	No. (%) by postvaccination antibody response			
	Dose 1− Dose 2−	Dose 1− Dose 2+	Dose 1+ Dose 2+	*P* value
No.	301 (46)	259 (39)	98 (15)	
Age category, y[a]				
18-39	46 (41)	35 (31)	32 (28)	.002[b]
40-59	86 (42)	94 (46)	26 (13)	
≥60	169 (50)	129 (38)	40 (12)	
Organ[f]				
Kidney	168 (52)	118 (37)	36 (11)	<.001[d]
Liver	26 (20)	62 (48)	41 (32)	
Heart	42 (43)	45 (46)	10 (10)	
Lung	43 (61)	22 (31)	6 (8)	
Pancreas	4 (80)	1 (20)	0	
Other multiorgan	15 (58)	7 (27)	4 (15)	
Years since transplant[g]				
<3	114 (63)	54 (30)	13 (7)	.001[b]
3-6	69 (50)	53 (39)	15 (11)	
7-11	54 (38)	61 (43)	26 (18)	
≥12	62 (33)	85 (45)	43 (23)	
Maintenance immunosuppression regimen				
Includes antimetabolite[h]	268 (57)	167 (35)	38 (8)	<.001[d]
Does not include antimetabolite[i]	33 (18)	92 (50)	60 (32)	
Vaccine[i]				
mRNA-1273 (Moderna)	124 (40)	116 (38)	67 (22)	<.001[d]
BNT162b2 (Pfizer-BioNTech)	175 (51)	138 (40)	29 (8)	

Covid-19 therapies and SARS-CoV-2 vaccines in patients with kidney disease

- Chronic kidney disease and dialysis
  - Vaccination is essential.
  - Outpatients with symptoms ≤10 days - Mab cocktail.
  - Inpatients: per protocols.
- Transplant
  - Current vaccines are likely to be poorly immunogenic.
  - Hopefully, prophylaxis with CCP or Mabs is on the horizon.
  - Inpatients: per protocols.

Immediate/early
Treatment with Mabs



Prevention with vaccine or prophylaxis

Virology, Transmission, and Pathogenesis of SARS-CoV-2 / BMJ 2020

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