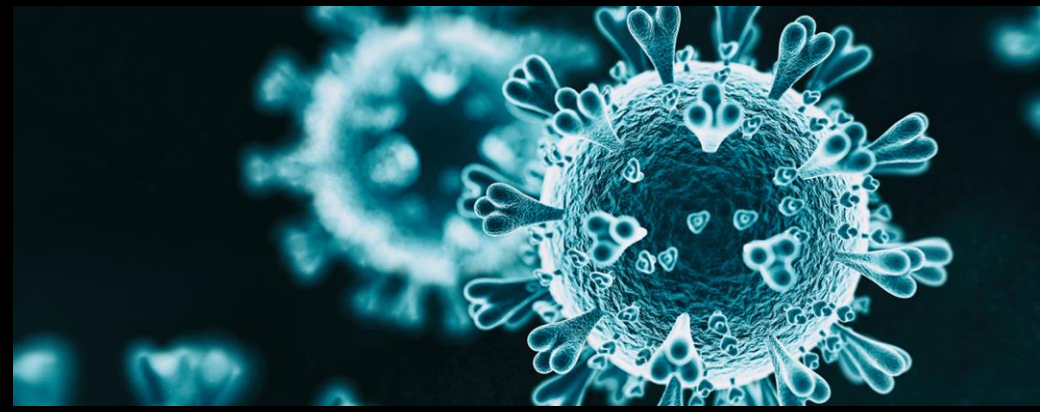
2021 ACOI Annual Convention
And Scientific Sessions
October 27-30



COVID-19 AND SOLID ORGAN TRANSPLANTATION

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- Honoraria: Alexion; CareDx; Mallinckrodt; Thermo Fisher
- Scientific Advisory Board: Alexion; Bristol Myers Squibb; CareDx; Natera; Relypsa; Veloxis
- Research Funding: Gilead
- Some slides have been borrowed from Dr Bem Agegnehu with permission

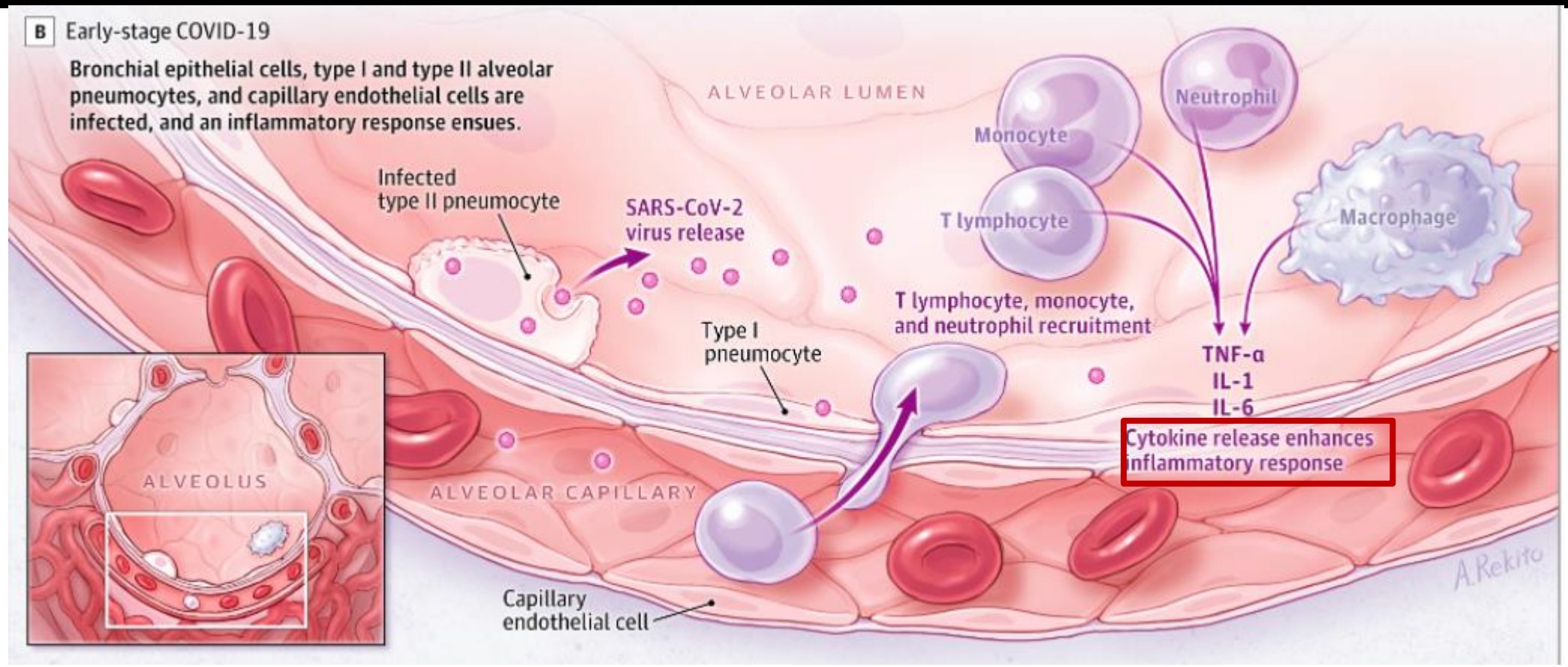
Disclosures

2021 ACOI Annual Convention and Scientific Sessions
October 27-30

OBJECTIVES

- Describe the pathophysiology and epidemiology of coronavirus disease 2019 (COVID-19) from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the context of solid organ transplant (SOT)
- Distinguish immunological responses in SOT patients in comparison to immunocompetent (IC) patients
- Evaluate the evidence regarding effects of immunosuppression (IS) and management of IS in the setting of COVID-19 in SOT patients
- Examine vaccine response rates and real-world application in SOT patients

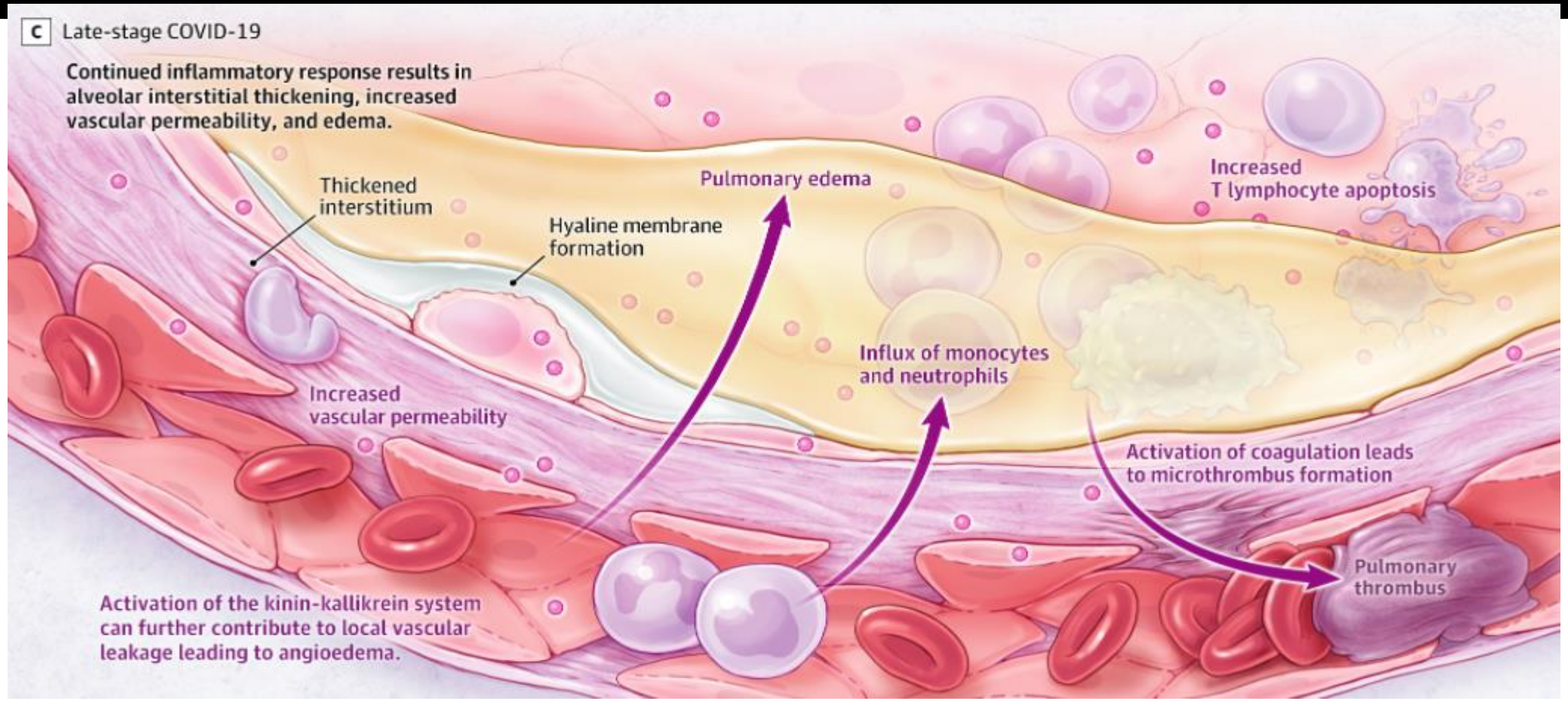
Pathophysiology



Infected bronchial and capillary cells exhibit cytokine mediated inflammatory response

Wiersinga WJ, et al. *JAMA*. 2020;324(8):782-793

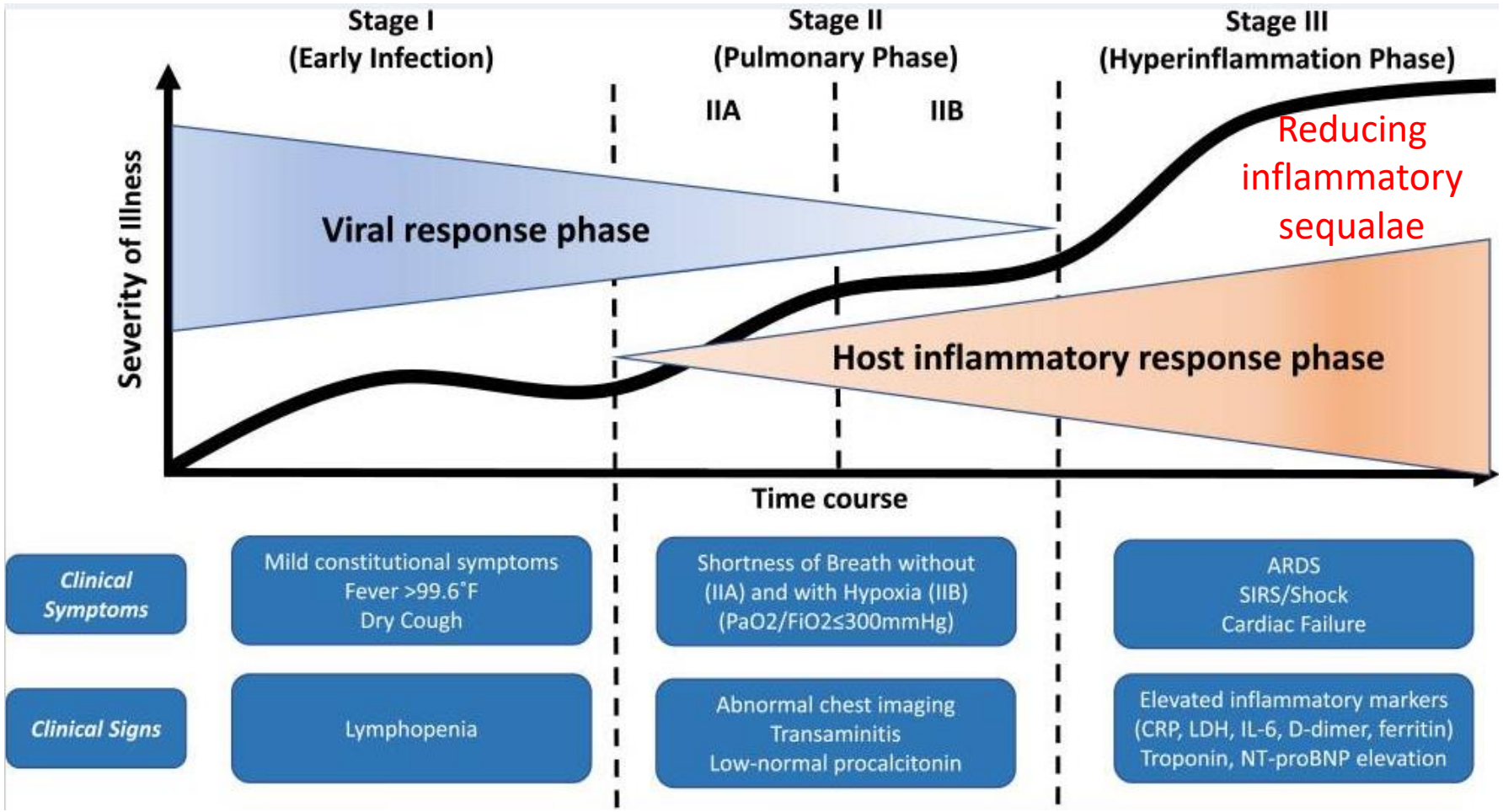
Pathophysiology



Inflammation impairs oxygen exchange, promotes pulmonary edema, and causes coagulopathies

Wiersinga WJ, et al. *JAMA*. 2020;324(8):782-793.

pathophysiology



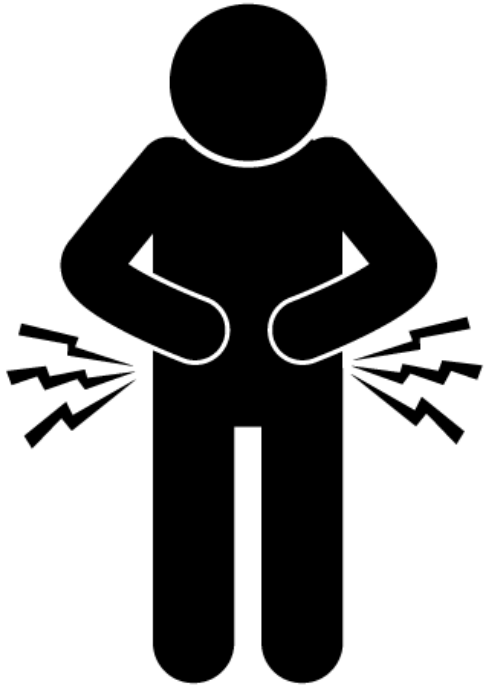
Yi SG, et al. *Transplantation*. 2020;104(11):2208-2214.

Siddiqi HK, et al. *J Heart Lung Transplant*. 2020;39(5):405-407.

Clinical presentation in solid organ transplant (SOT) recipients vs. immunocompetent (IC)

↑ Nasal congestion

↑ Diarrhea

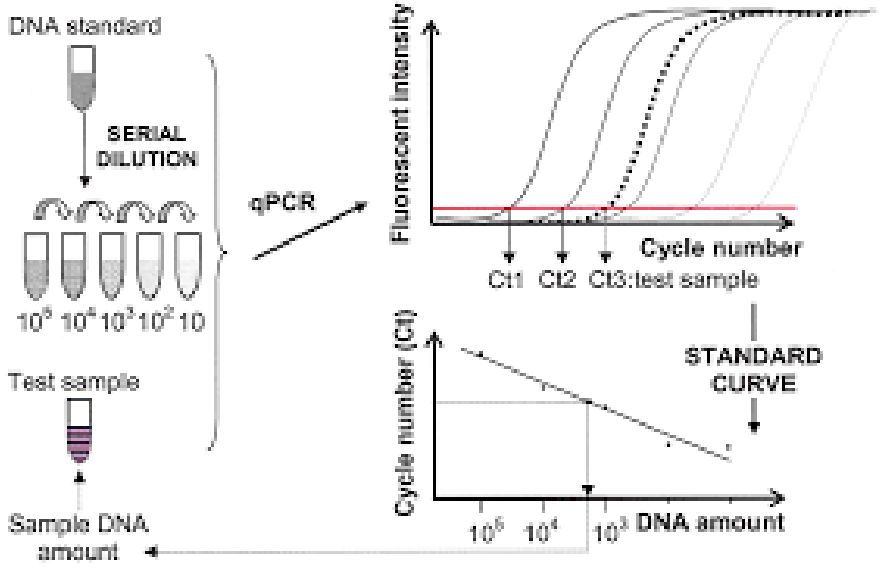


↓ Fever

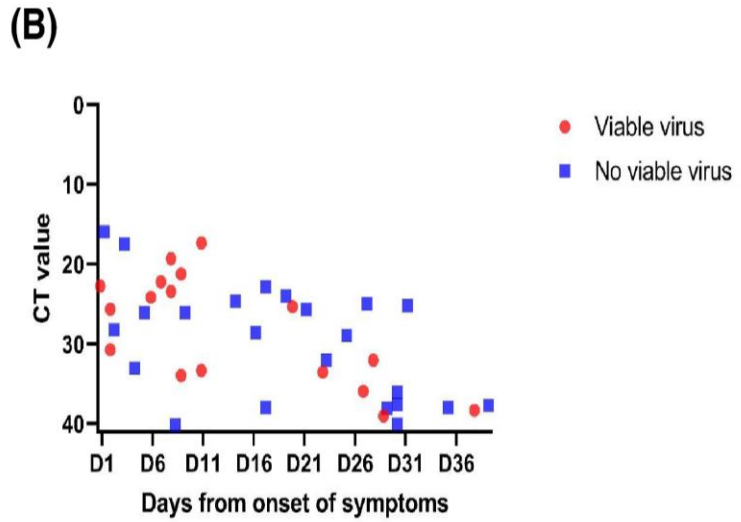
↑ Lymphopenia

Cravedi P, et al. *Am J Transplant.* 2020;20(11):3140–3148.
Pereira MR, et al. *Am J Transplant.* 2020;20(7):1800–1808.
Caillard S, et al. *Kidney Int.* 2020;98(6):1549–1558.

Prolonged Viral Shedding in Transplant Patients



- Cycle Threshold testing
  - Lower CT count demonstrates higher RNA viral loads

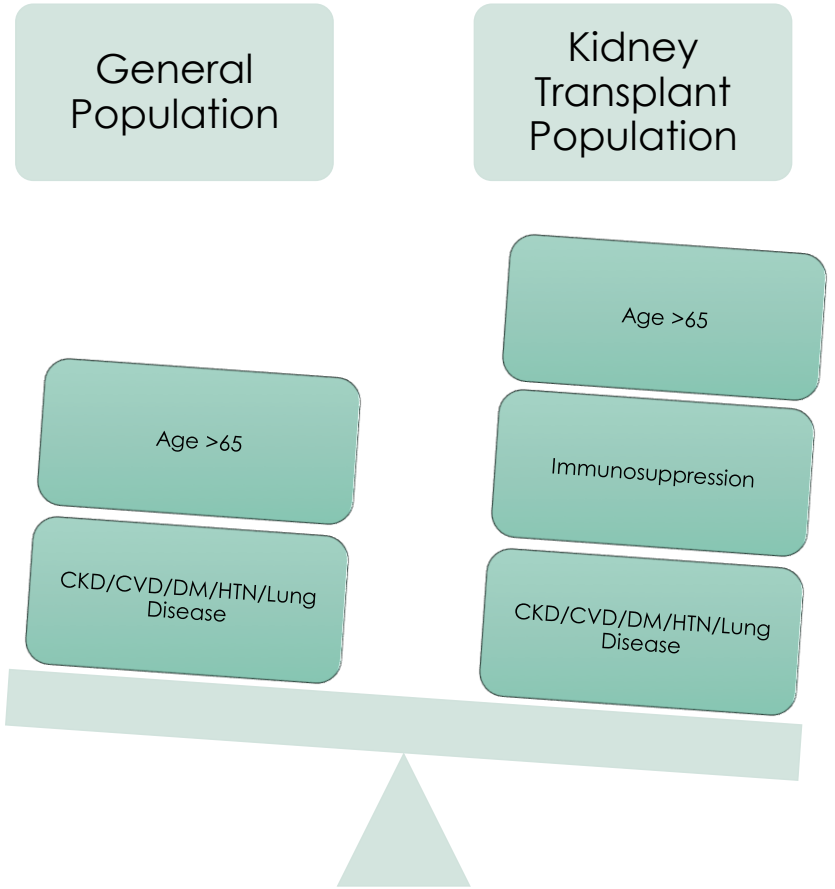


SOT Patients can shed both viable and non-viable virus for up till 30 days post-infection

Benotmane, AJT 2021

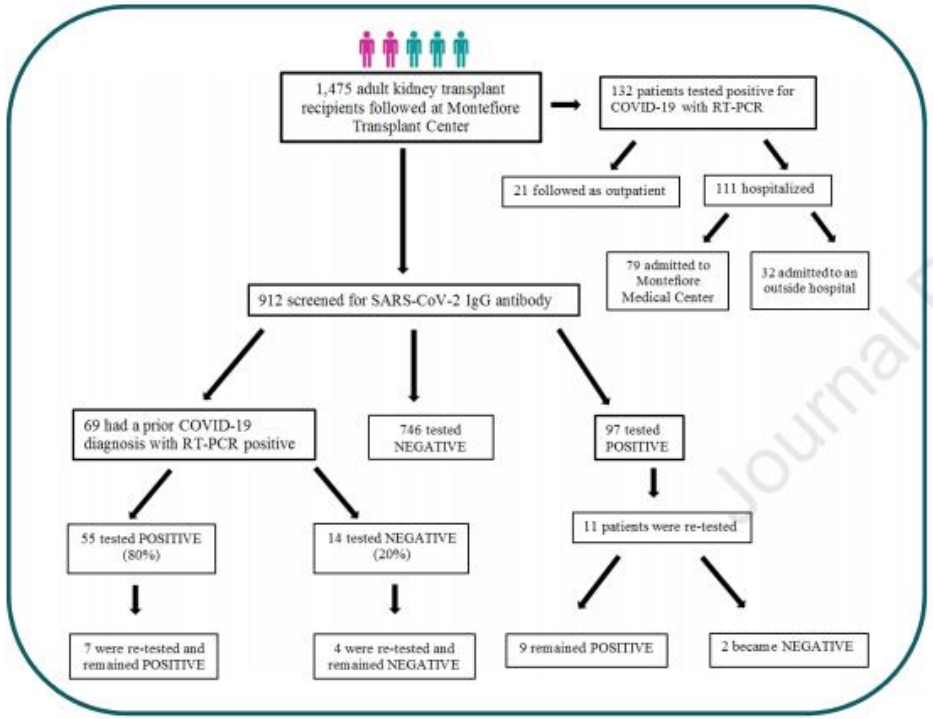
Outcomes: SOT vs. Immunocompetent

- Why does transplant status matter?
  - Increased risk due to:
    - Age
    - Comorbid conditions
    - Immunosuppressive medications
- How does COVID present in transplant?
  - More aggressive?
  - Increased viremia?
  - Longer illness? Longer viral shedding?



COVID in Kidney Transplant at the Epicenter: Montefiore

COVID-19 INFECTION IN KIDNEY TRANSPLANT RECIPIENTS AT THE EPICENTER OF PANDEMICS



The prevalence of SARS-CoV-2 infection was 23.4% in the 975 patients tested by either RT-PCR or SARS-CoV-2 IgG
Older patients and patients with higher serum creatinine levels were more likely diagnosed by RT-PCR compared to SARS-CoV-2 IgG

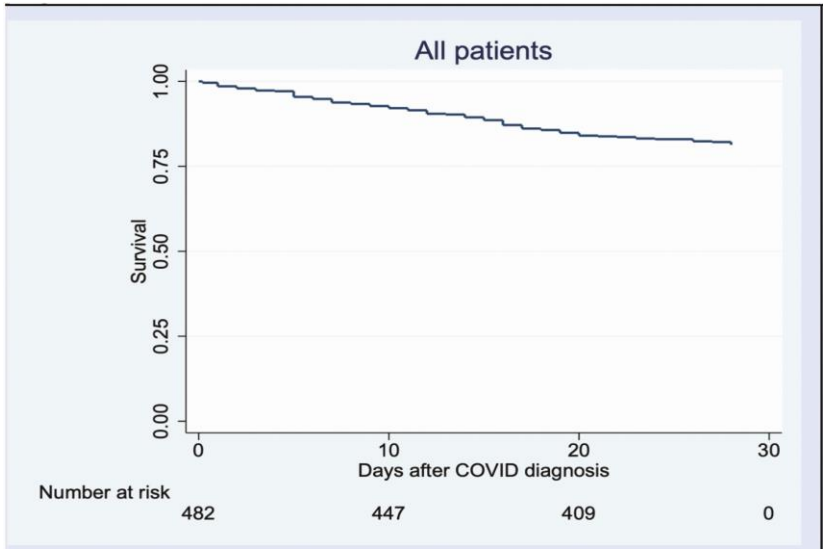
Overall mortality 20.5%
Mortality in hospitalized patients 37.8%
Older age, receipt of deceased-donor transplant, lack of influenza vaccination in the previous year and higher serum IL-6 levels were associated with mortality

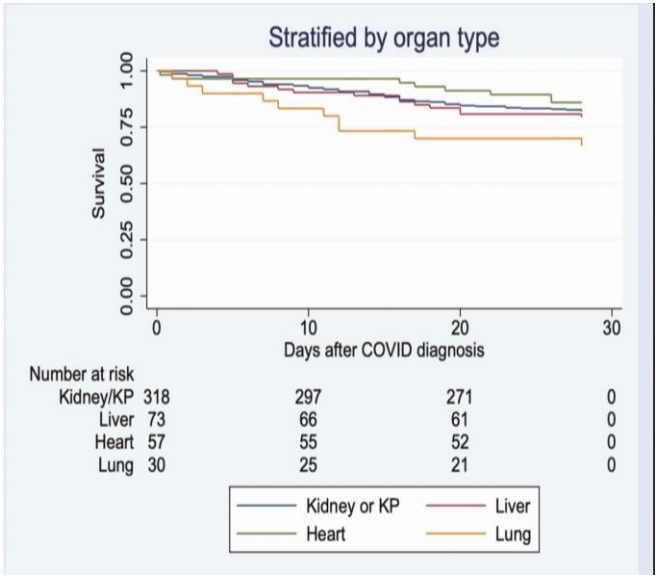
CONCLUSION:
42% of kidney transplant recipients were SARS-CoV-2 IgG positive without significant symptoms and 80% of kidney patients developed an antibody response after confirmed diagnosis by RT-PCR

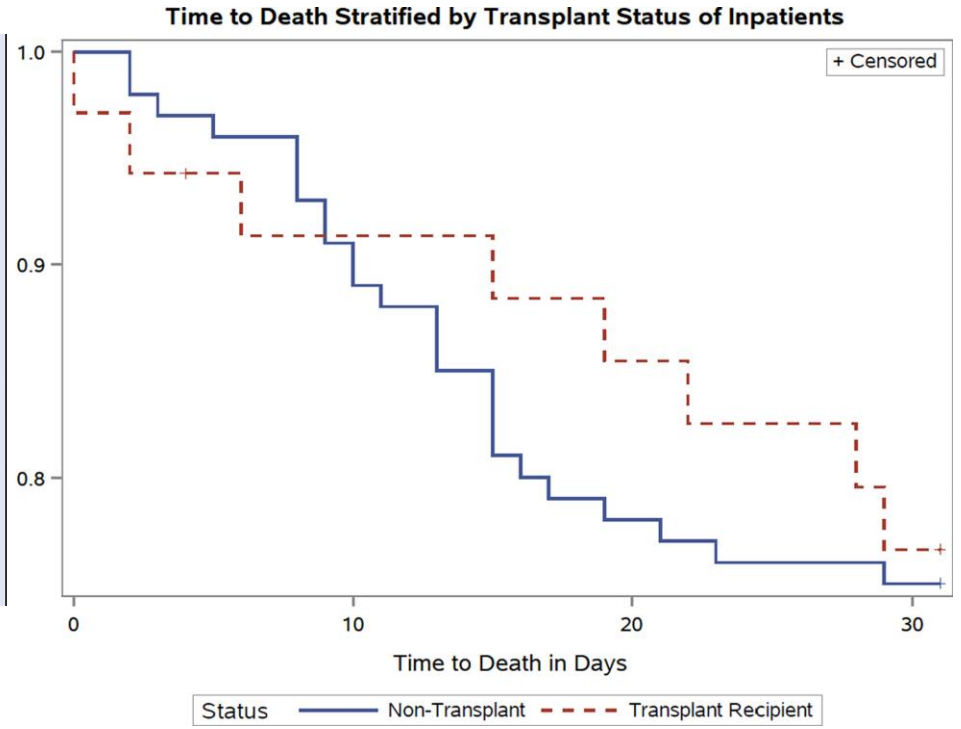
ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Azzi et al, 2020

Mortality outcomes: SOT vs. Immunocompetent



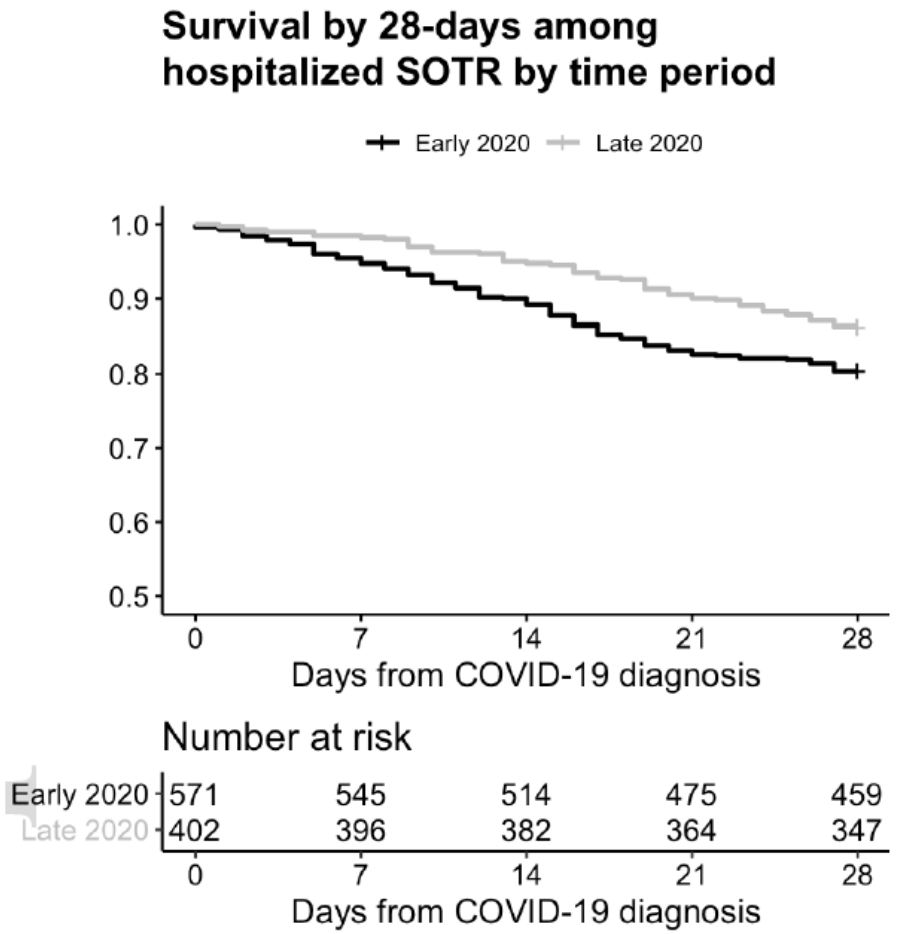




Kates, et al, Clin InfectDis, 2020

Chaudhry, et al. Am J Translplant. 2020. July

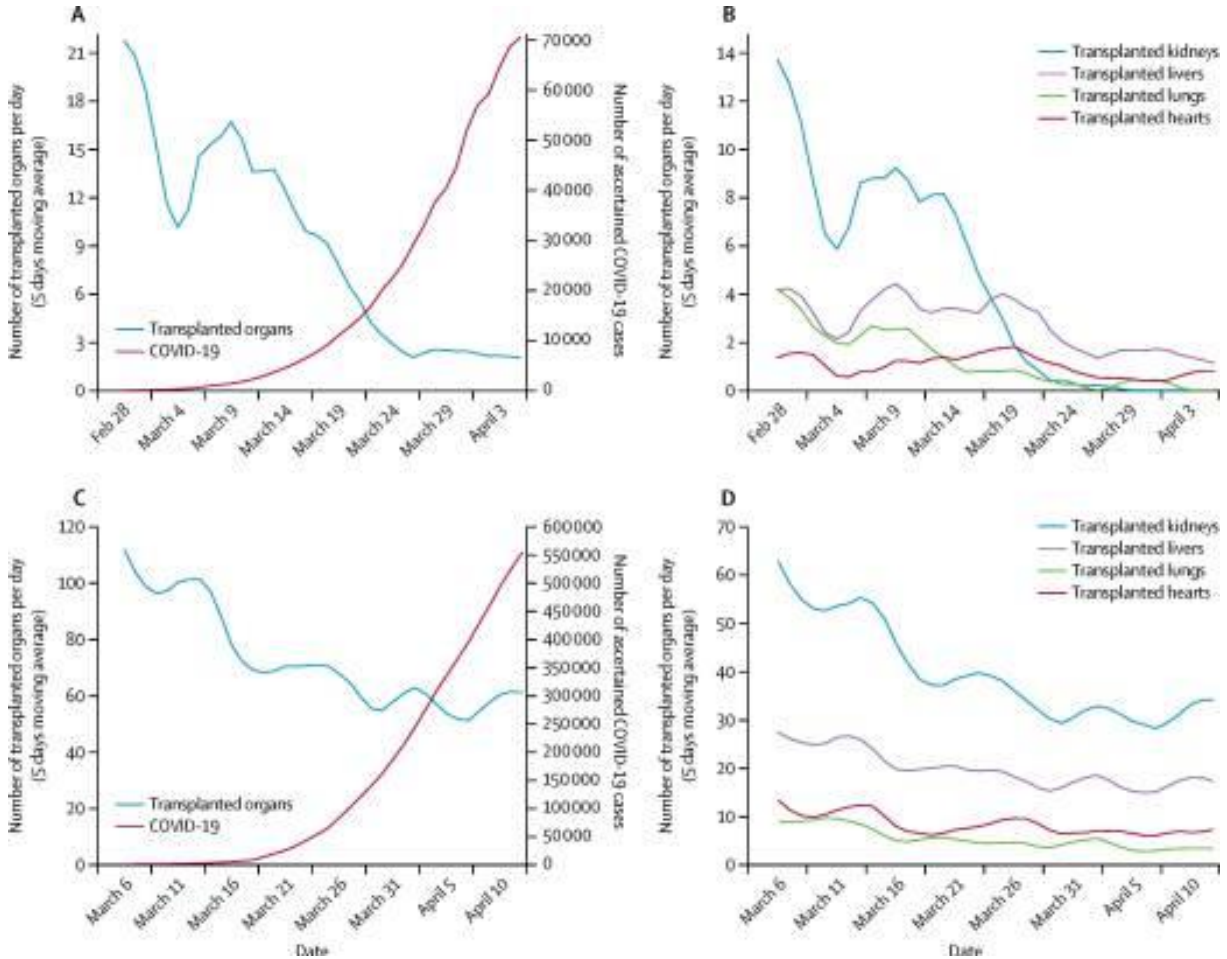
Mortality outcomes: SOT



But what about the Delta Variant?

Heldman, et al. Am J Translplant. 2021. Sep

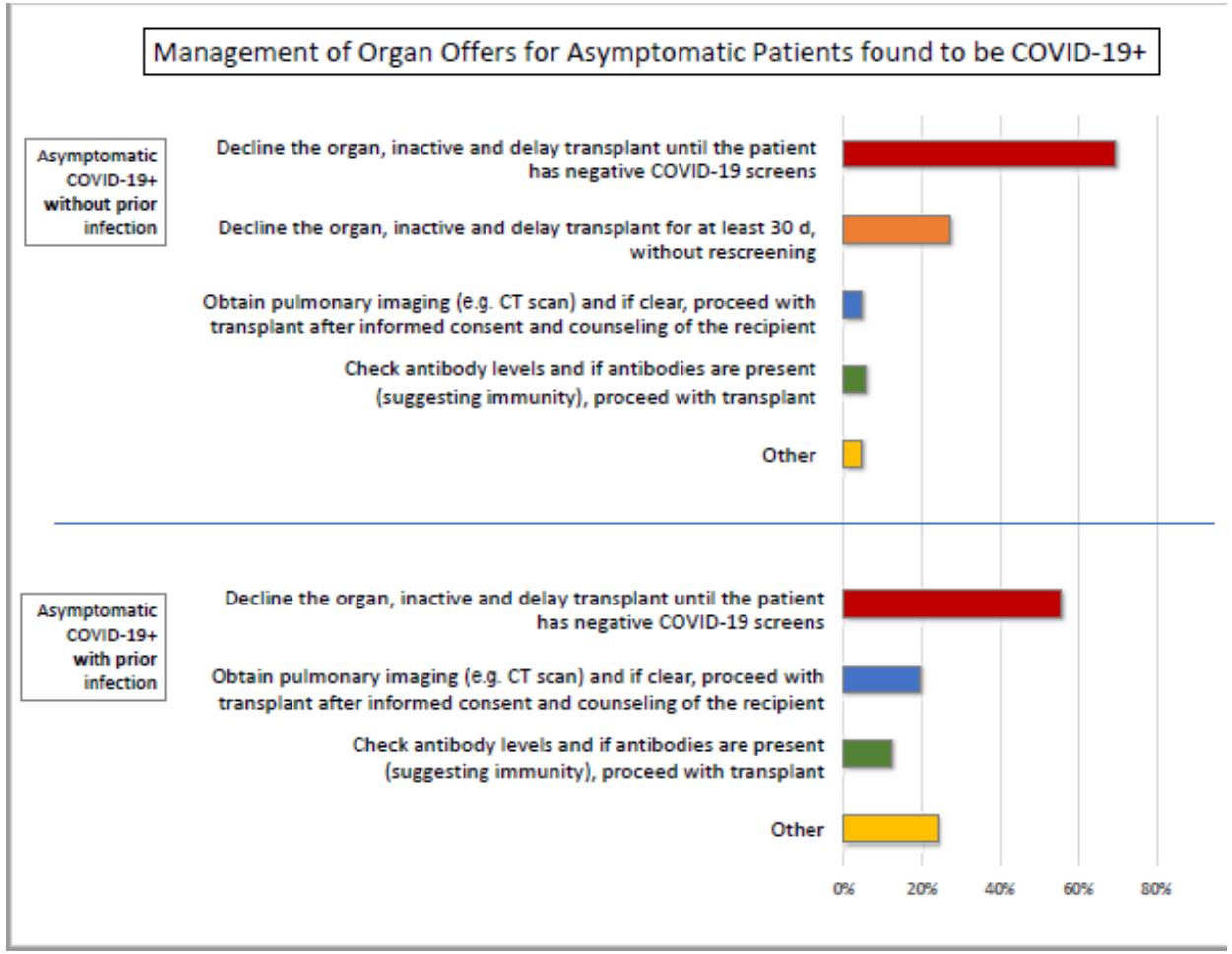
Impact on Transplant Activity



But what about the 4th Wave?

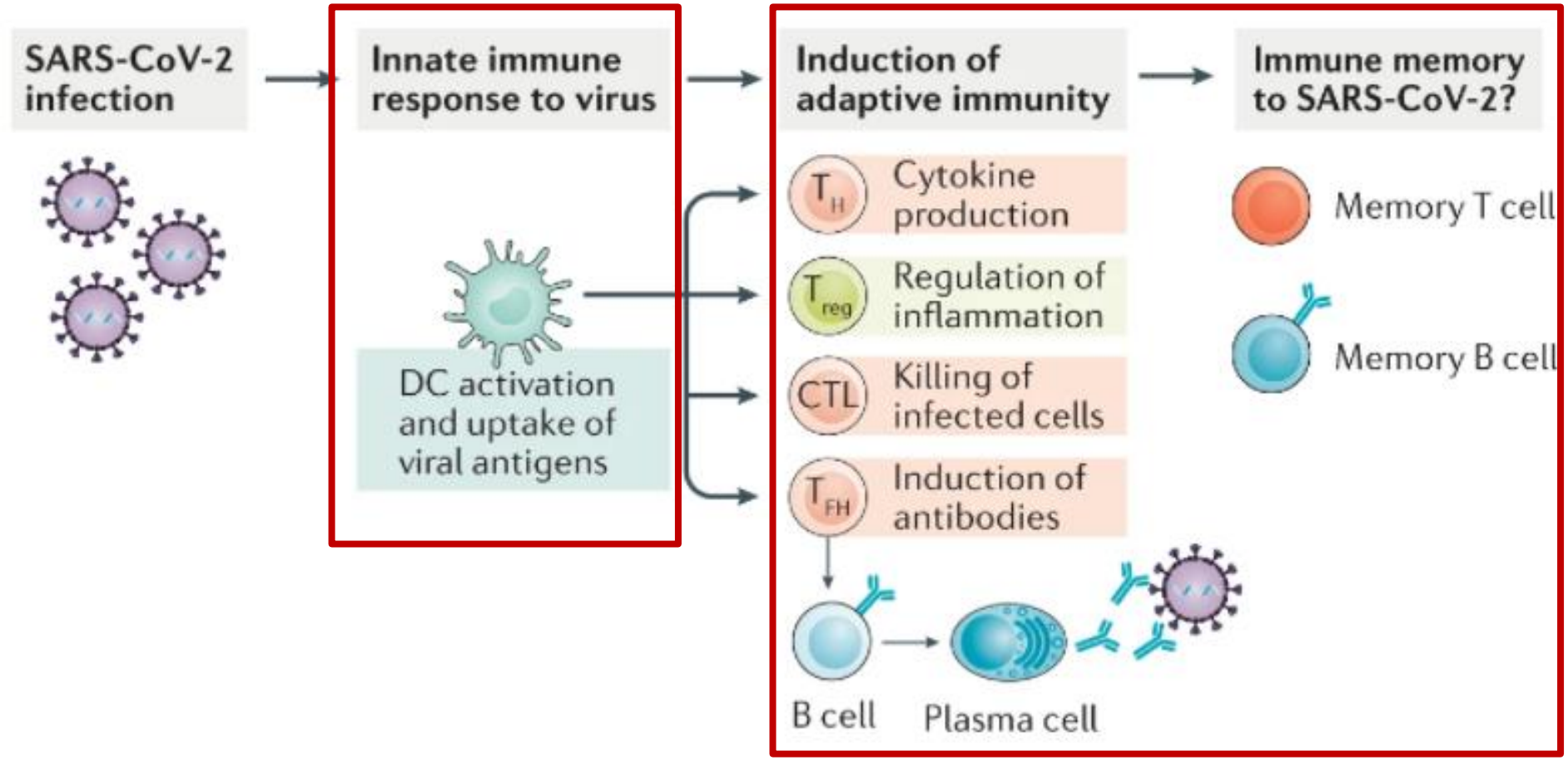
Loupy, et al. Lancet, 2020

Impact on Transplant Activity



Axelrod, Clin Transplant 2021

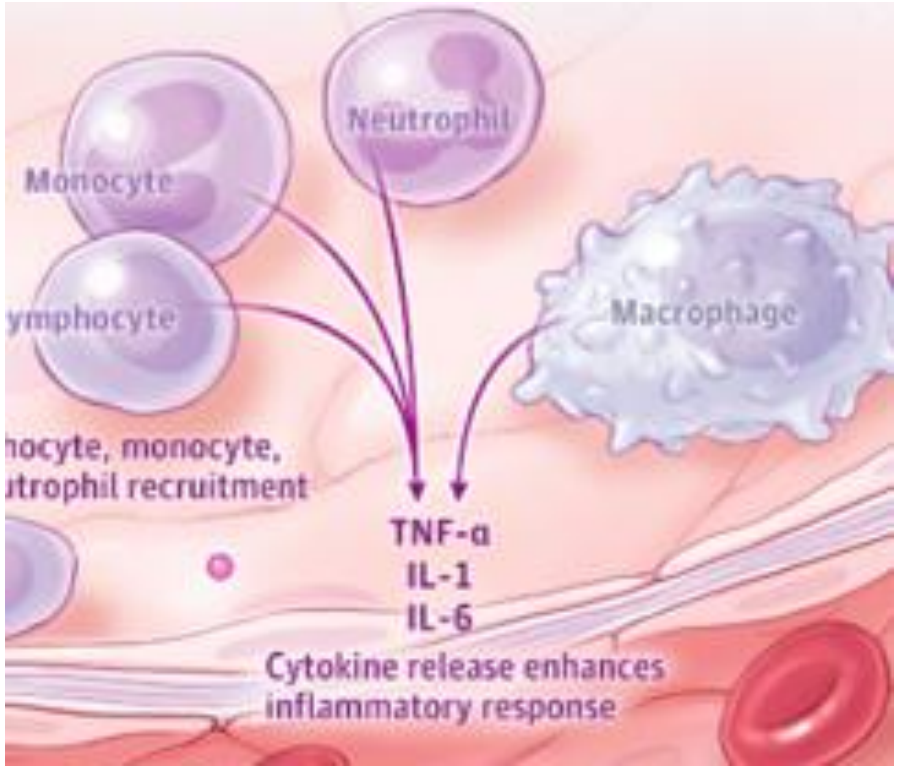
Innate and adaptive immunity to SARS-CoV-2



DC = dendritic cell

Cox RJ, et al. *Nat Rev Immunol*. 2020;20(10):581-582.

Innate COVID immunity



<u>Similar levels between IC and SOT:</u>

- Erythrocyte sedimentation rate
- C-reactive protein
- Ferritin
- D-dimer
- Lactate dehydrogenase
- Procalcitonin
- IL-6 levels

Phadke, et al. *Curr Transplant Rep*. 2021;1-13.

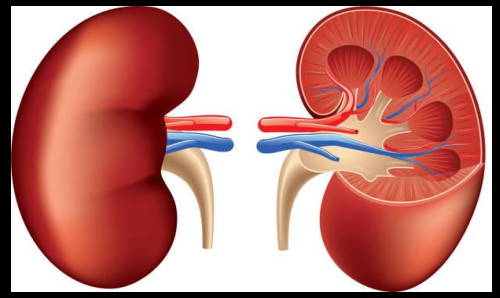
Adaptive immunity to SARS-CoV-2

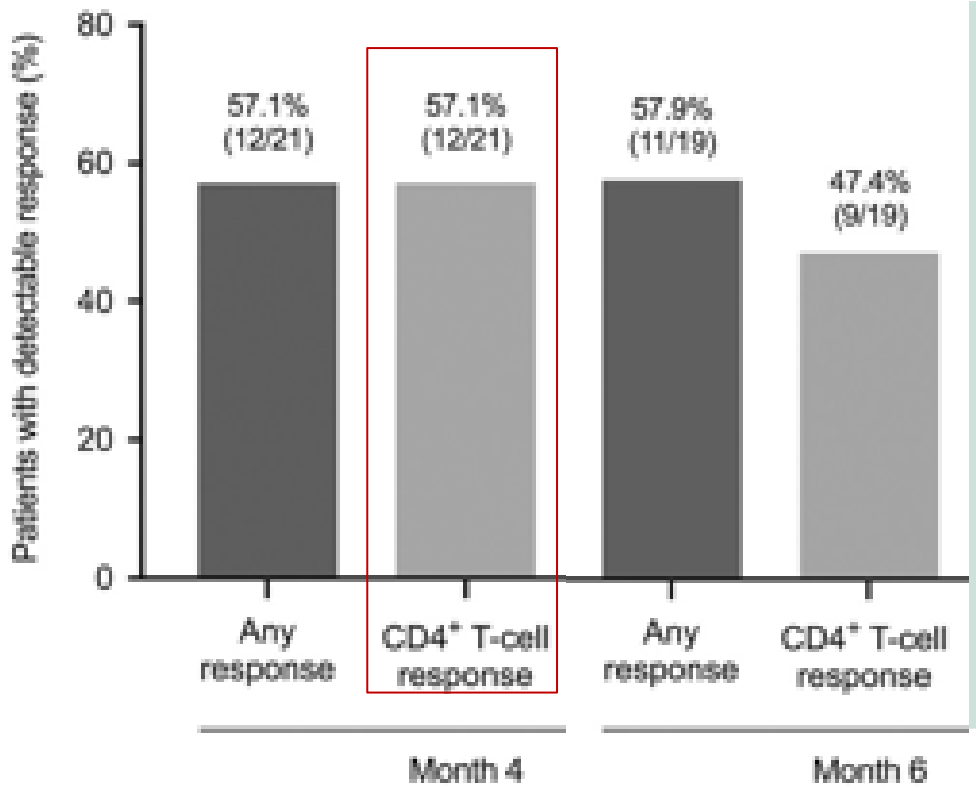
	Cellular responses	Humoral responses
IC	T cell responses: Wide range & displayed in early phase	Antibodies: Sustained **for at least 2 months** and potentially up to 4-6 months post-infection
SOT	T cell responses: Lower and delayed**; Prolonged viral shedding**	Antibodies: **Delayed** seroconversion; **Rapid loss** of antibodies

Fava, et al. *Am J Transplant*. 2021;10.1111/ajt.16570.

After COVID-19 exposure

Cellular Response



Study	Design	Population	Outcome
Fernandez-Ruiz, et al.	21 SOT recipients	KT recipients 86% tac; 67% MMF; 24% mTOR; 81% pred Median time from transplant = 6 years (2-16 years)	

KT = kidney transplant
tac = tacrolimus
MMF = mycophenolate

mTOR = mammalian target of rapamycin
pred = prednisone

Fernández-Ruiz M, et al. *Transplantation*. 2021;105(6):1372-1380.

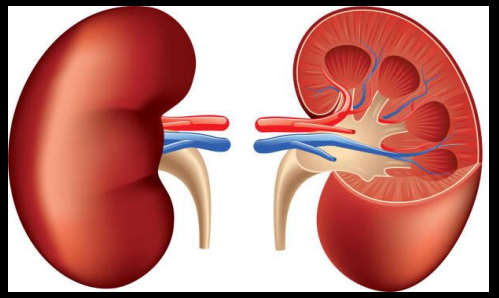
Adaptive COVID Immunity

	Cellular responses	Humoral responses
IC	T cell responses: Wide range & displayed in early phase	Antibodies: **Sustained for at least 2 months and potentially up to 4-6 months post-infection**
SOT	T cell responses: Lower and delayed; Prolonged viral shedding	Antibodies: **Delayed** seroconversion; **Rapid loss** of antibodies

Fava, et al. *Am J Transplant*. 2021;10.1111/ajt.16570.

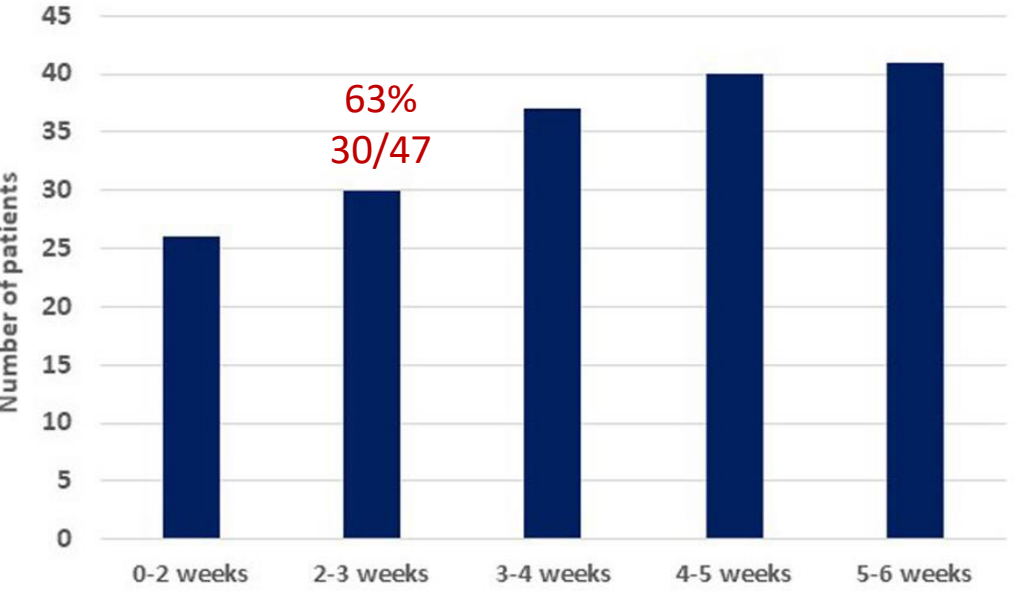
After COVID-19 exposure

Humoral response



(A) Time to seroconversion

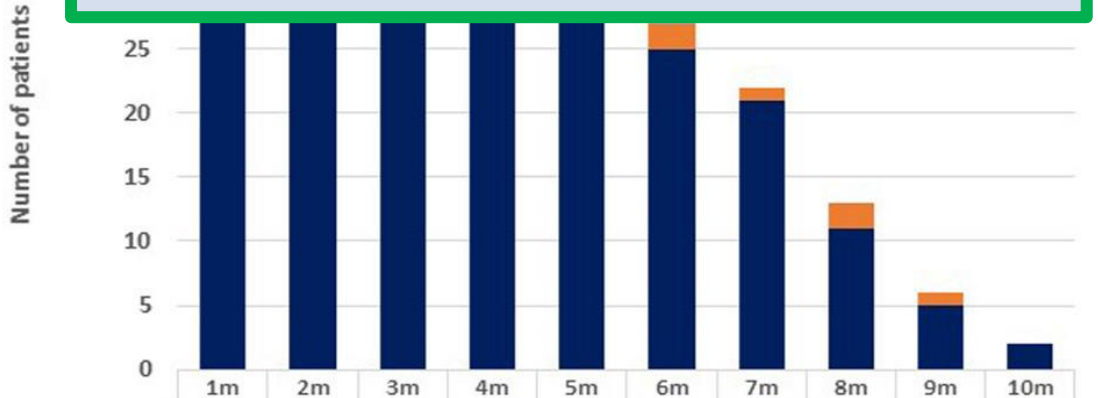
(N=47; 40% severe COVID)



(B)

Trend toward persistence of antibody response (not statistically significant):

- **Severe COVID-19 history**
- Withdrawal of antimetabolite
- Reduction/withdrawal of CNIs



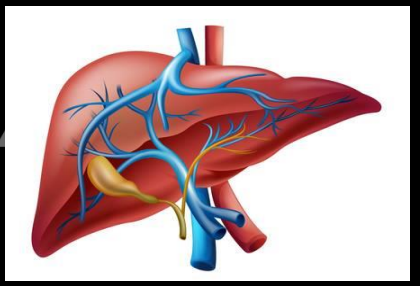
	1m	2m	3m	4m	5m	6m	7m	8m	9m	10m
Always IgG negative (no seroconversion)	6	6	6	4	2	2				
Turned IgG negative over time	0	0	0	0	1	2	1	2	1	
IgG Positive	41	38	37	36	32	25	21	11	5	
Total Patients tested	47	44	43	42	35	29	22	13	6	2

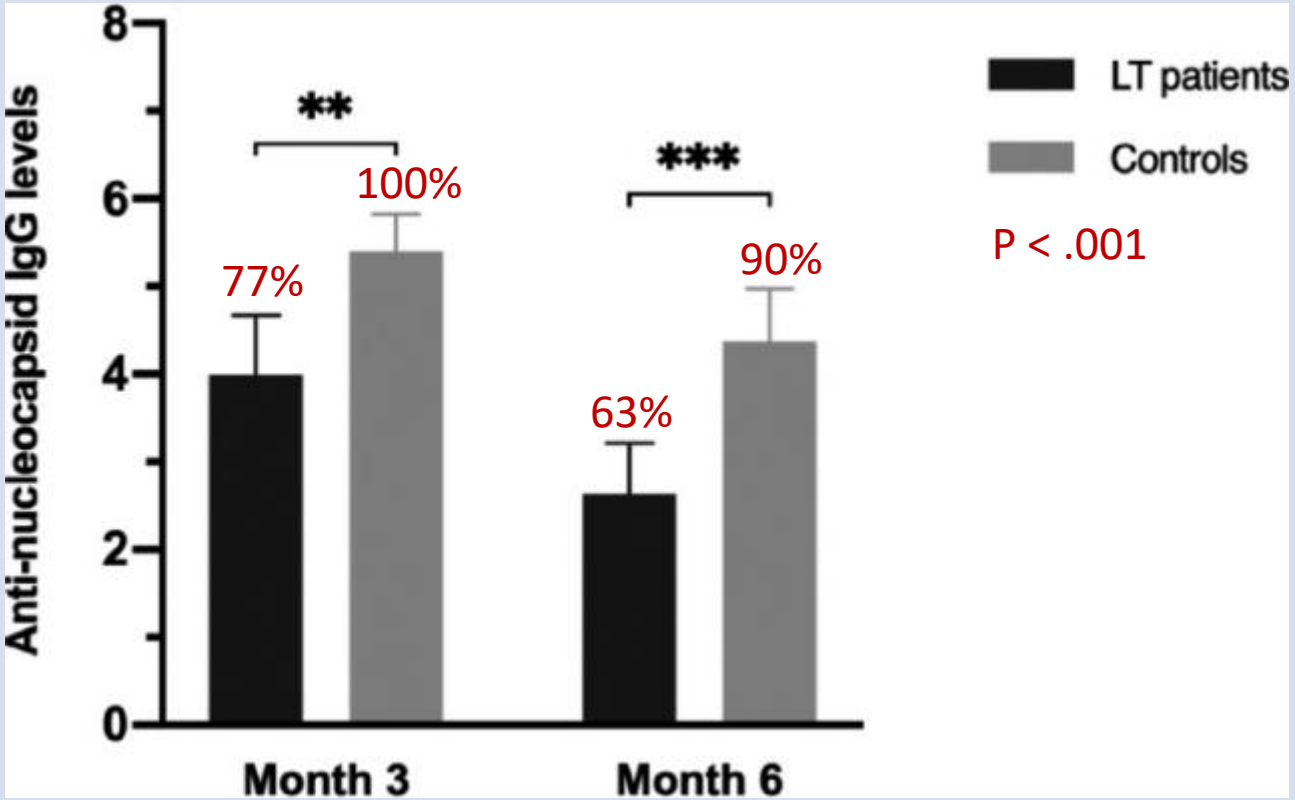
17%
7/41

Bajpai D, et al. *Transpl Infect Dis*. 2021;e13646.

After COVID-19 exposure

Humoral response



Study	Design	Population	Outcome
Caballero-Marcos, et al.	71 SOT patient; prospective multicenter study	LT recipients 62% tac; 49.3% MMF; 21.1% everolimus; 5.6% pred	

LT = liver transplant

Caballero-Marcos A, et al. *Am J Transplant.* 2021;21(8):2876-2884.

Baseline Maintenance immunosuppression

CNIs:
tacrolimus or cyclosporine

T-cell co-stimulation blockers:

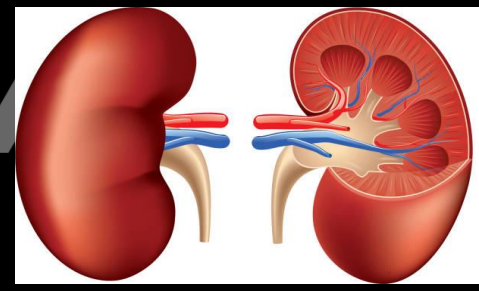
Antimetabolites:
mycophenolate or azathioprine

mTORs:
everolimus or sirolimus

Corticosteroids*:
prednisone

*With steroid: Kidney, lung transplants
Steroid-free protocols: Liver, heart, living donor kidney transplants

Immunosuppression management: Kidney transplant



Maintenance IS	
Hold antimetabolite	347/461 **(75.27%)**
Hold mTOR inhibitor	38/48 **(79.2%)**

Minimal IS management

Asymptomatic — Mild Symptoms

Pneumonia/ new oxygen requirement

Discontinuation or Reduction of CNI (31.9%)

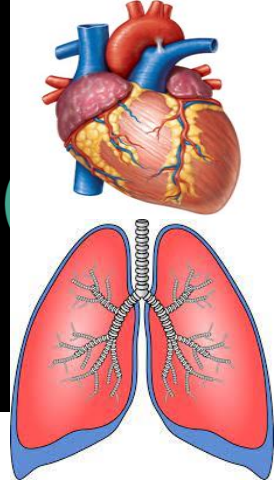
Severely symptomatic

Discontinuation of all IS drugs

Invasive mechanical ventilation

Angelico R, et al. *Medicina (Kaunas)*. 2021;57(5):435.

Immunosuppression management: Heart and lung transplant



ISHLT survey regarding IS strategies in **heart or lung transplant patients with COVID-19 and hypoxemia** (at least moderate-severe disease; n = 465 responders)

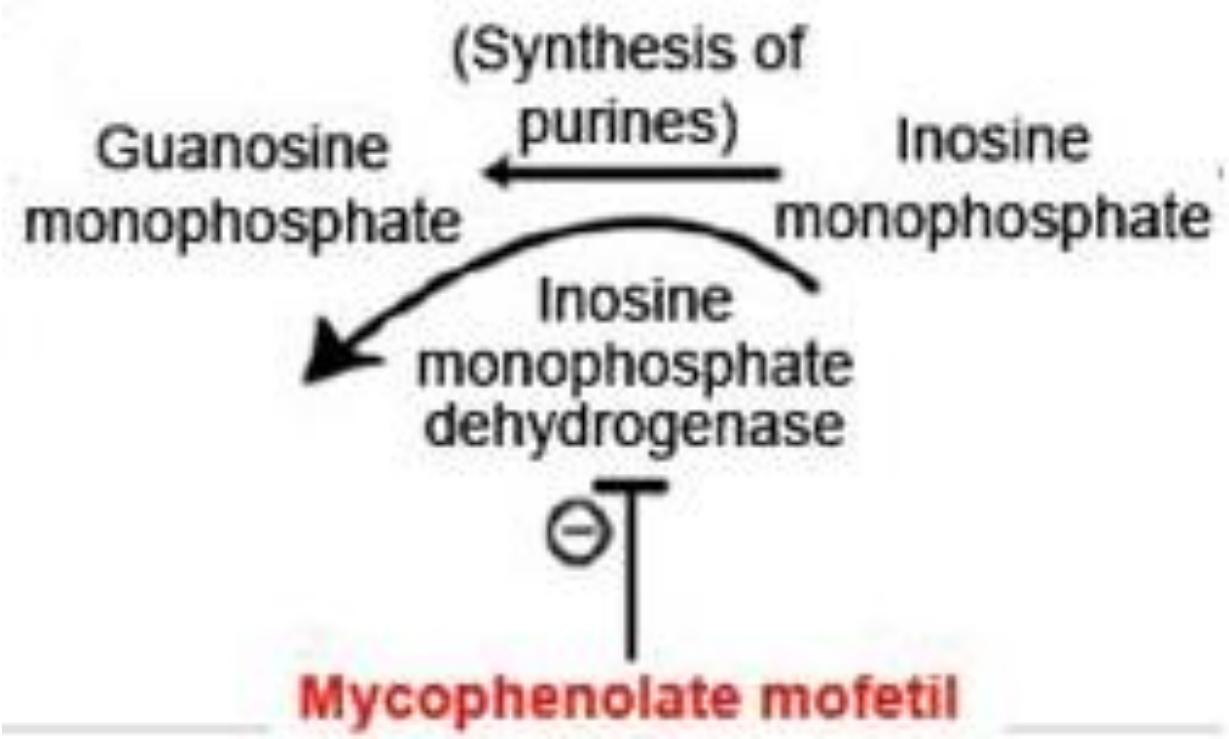
IS adjustment	
No changes in immunosuppression	22%
Reduce MMF and continue tacrolimus	19%
Reduce MMF and tacrolimus	11%
Discontinue MMF only	25%
Discontinue MMF and reduce tacrolimus	18%
Discontinue all immunosuppression	4%

ISHLT = International Society for Heart and Lung Transplantation

Alvarez-Aquino FG, et al. *CCTS*. 2021; 3(1)

Immunosuppression management: Mycophenolate

- MMF inhibits proliferation of B and T cells which may influence antibody response (**i.e. influenza vaccine**) in a dose-dependent manner
- Theoretically impair the ability to develop an adequate immune response to natural infection
- Antimetabolites cause lymphopenia→ **reduce or hold mycophenolate**



Rozen-Zvi B, et al. *Clin Microbiol Infect*. 2021;S1198-743X(21)00216-0.

Immunosuppression management: Corticosteroids

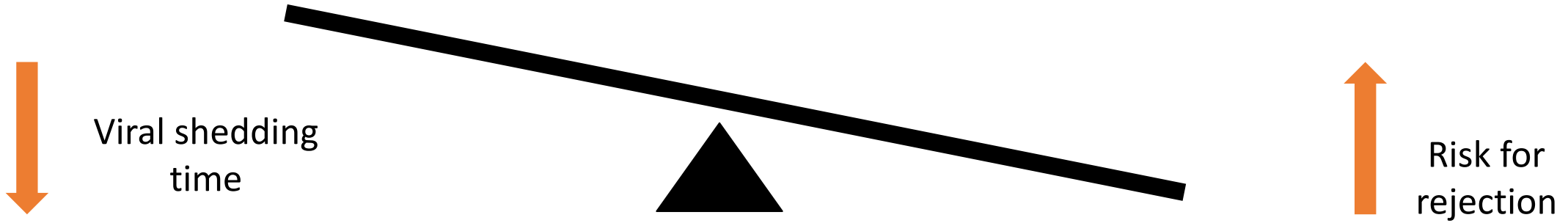
- Role in reducing systemic symptoms and decreasing alveolar exudation that results from cytokine storm
- Improve survival in critically ill patients with COVID-19 requiring supplemental oxygen based on **RECOVERY trial**
  - Substituting dexamethasone for prednisone has become an option in hypoxemic patients (6mg daily for ≤10 days

Steroid	Equivalent dose
Prednisone	5 mg
Dexamethasone	0.75 mg

RECOVERY Collaborative Group, et al. *N Engl J Med*. 2021; 25;384:693–704.

Johnson KM, et al. *Pharmacotherapy*. 2020;40(6):517-524.

Immunosuppression management: SUMMARY



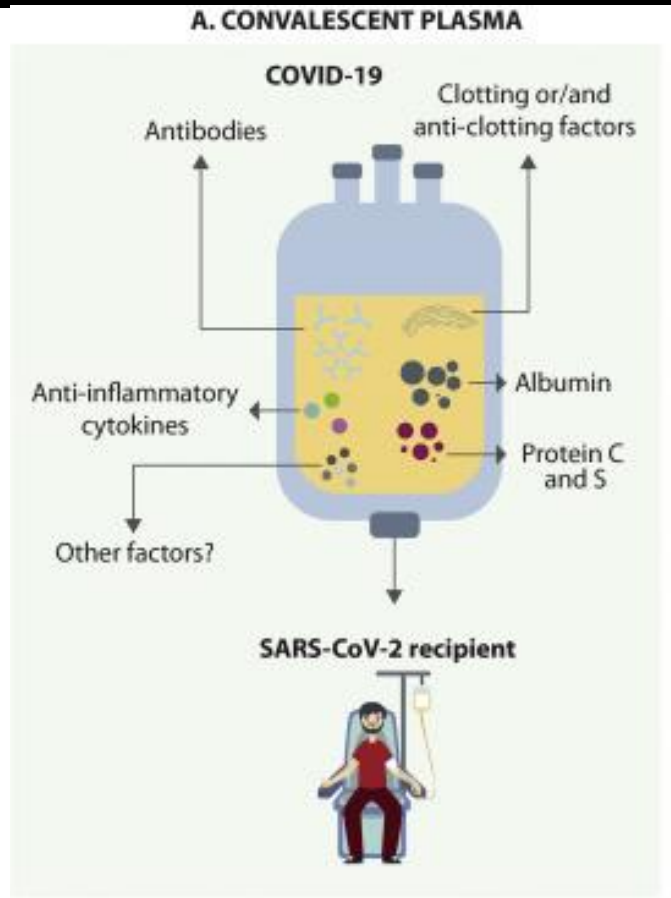
- **Generally, a reduction in immunosuppression is a widely used strategy for the management of viral infections:**
  1) Reduce or hold the antimetabolite particularly for patients with lymphopenia
  2) Continue the calcineurin inhibitor (CNI) **because inhibits IL-6 and IL-1 pathways**
  3) Switch prednisone to dexamethasone

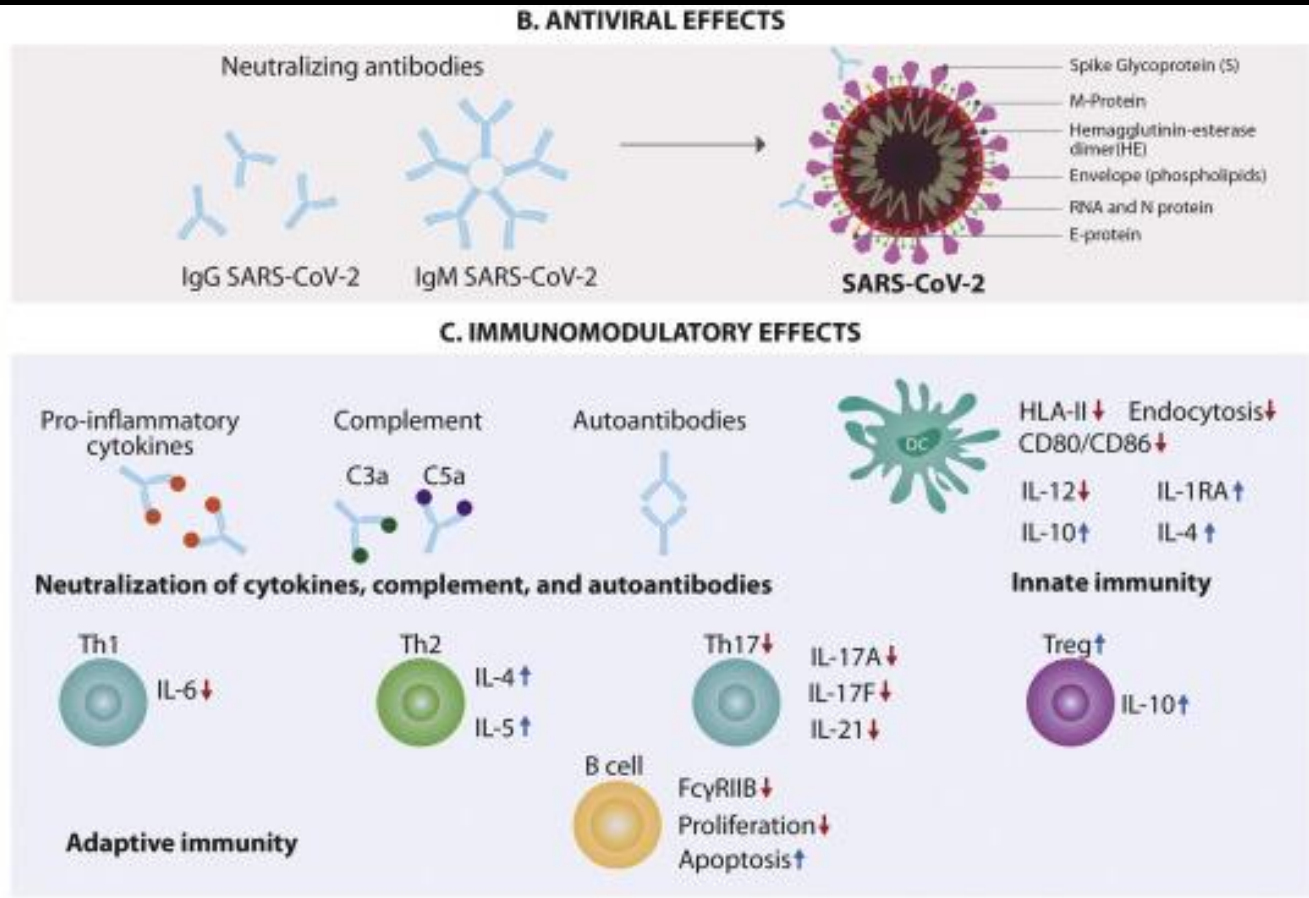
Angelico R, et al. *Medicina (Kaunas)*. 2021;57(5):435.

Early COVID Antibody treatments

Convalescent plasma (Passive immunization)

<u>EUA:</u> Hospitalized patients with COVID-19 when administered early in the course of disease or when administered to patients with impaired humoral immunity





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

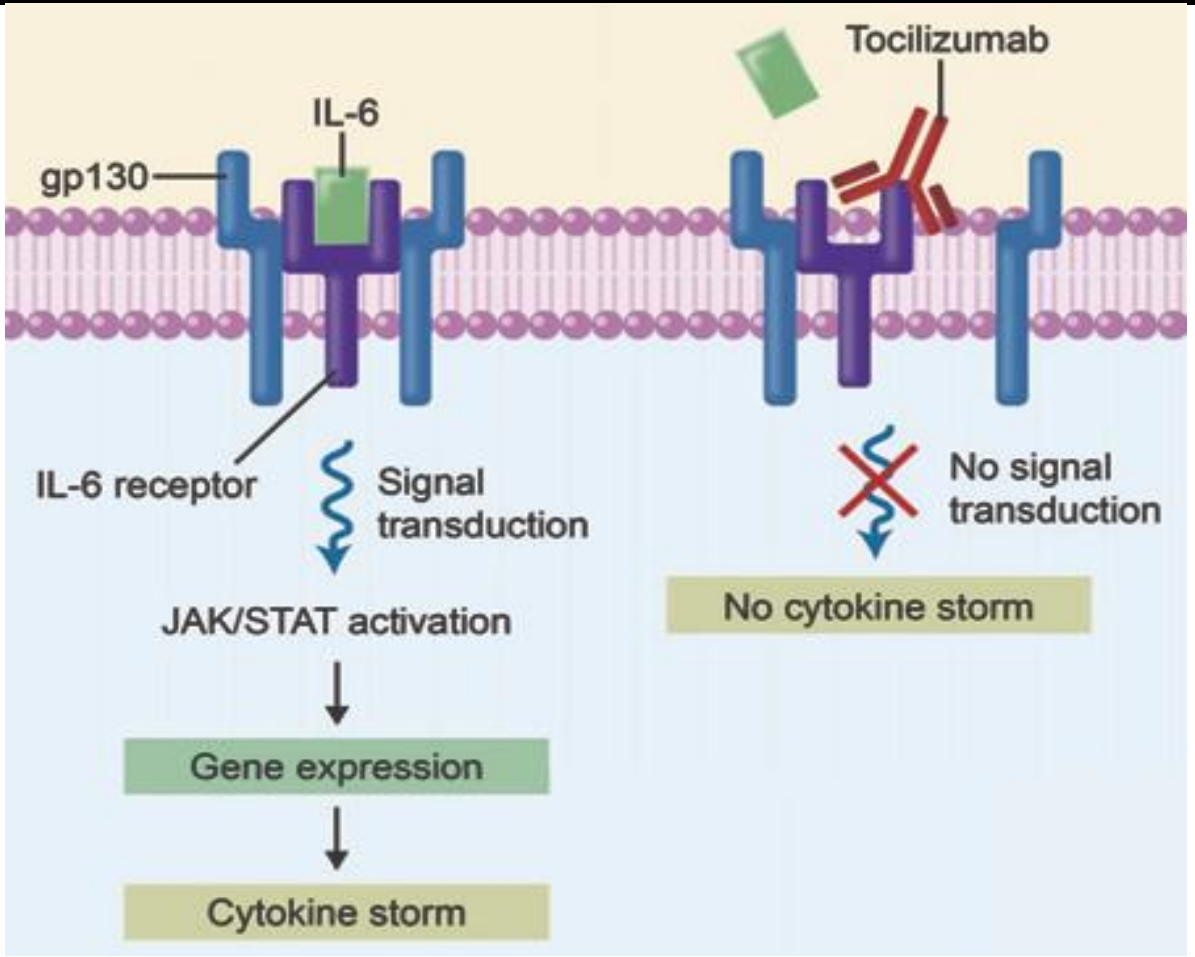
Early COVID Antibody treatment

Tocilizumab

<u>EUA:</u> Hospitalized adults and pediatric patients (<u>≥</u>2) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

<u>RECOVERY trial:</u>

- C-Reactive Protein (CRP) >75 mg/L
- No difference on benefit when comparing patients treated with tocilizumab within <2 days of hospital admission versus >2 days after hospital admission



Emergency Use Authorization (EUA) for use of ACTEMRA for the treatment of COVID-19

Early COVID Antibody treatment

Studies in SOT patients

<table>
<tr><th>Study</th><th>Outcome</th></tr>
<tr><td>Pereira MR, et al

(29 SOT with severe COVID; 45% KT, 26% lung, 17% heart)</td><td>
<table>
<tr><th>N = 58</th><th>SOT with tociluzumab (N = 29)</th><th>Matched SOT control group (N = 29)</th><th>P-value</th></tr>
<tr><td>Mortality</td><td>41%</td><td>28%</td><td>0.27</td></tr>
<tr><td>Hospital discharge</td><td>52%</td><td>72%</td><td>0.26</td></tr>
<tr><td>Secondary infections</td><td>34%</td><td>24%</td><td>0.55</td></tr>
</table>
</td></tr>
<tr><td>Perez MJ, et al

(80 KT with severe COVID)</td><td>CRP levels decreased after tocilizumab, and this decrease positively correlated with survival
(mean 12.3 mg/L in survivors vs. 33 mg/L in non-survivors)</td></tr>
</table>

Pérez-Sáez MJ, *Am J Transplant*. 2020;20(11):3182-3190Pereira MR, et al. *Am J Transplant*. 2020;20(11):3198-3205.

Newer COVID antibody treatments

April 16, 2021 — Bamlanivivumab monotherapy revoked due to resistance

June 25, 2021 — Banlavivimab/etesevimab revoked due to resistance

July 2, 2021 — Casirivimab/imdevimab preferred instead

July 30, 2021 — Casirivimab/imdevimab Post-exposure prophylaxis

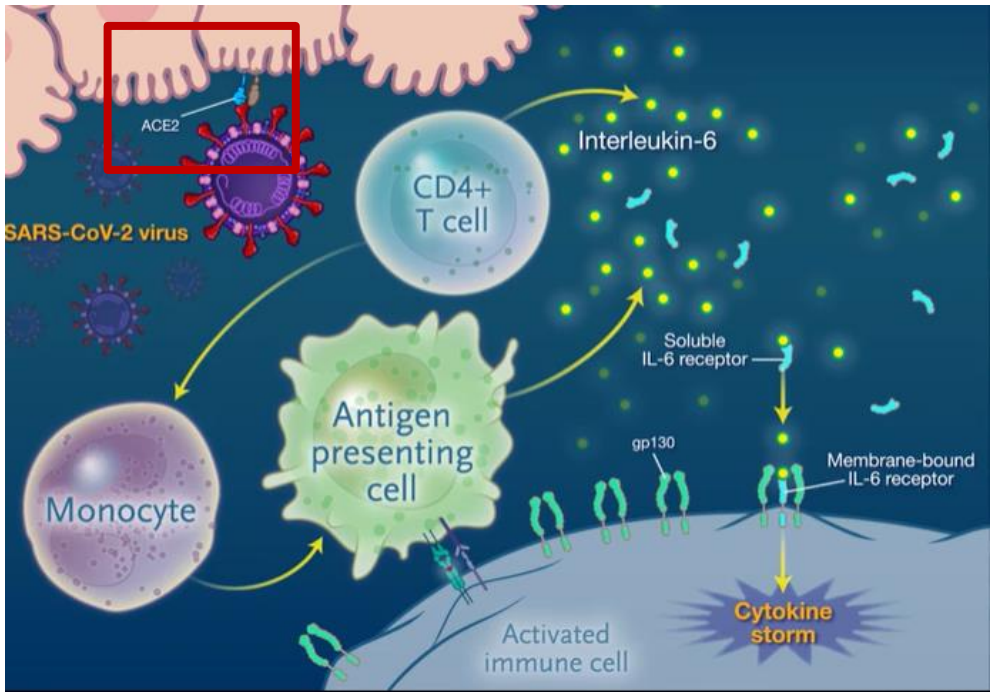
September 2, 2021 — Resumption of Banlavivimab/etesevimab due to Delta variant

September 16, 2021 — Bamlanivivimab/etesevimab Post-exposure prophylaxis

Casirivimab/imdevimab (REGN-COV2/Regeneron):

<u>EUA:</u> Mild to moderate COVID-19 in adults and pediatric patients (≥12 years of age and weighing ≥40 kg) with positive results on direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization

<u>NOT authorized for</u> use in patients who are hospitalized due to COVID **OR** require oxygen therapy due to COVID **OR** increase in baseline oxygen due to COVID



Yetmar ZA, et al. *Open Forum Infect Dis.* 2021;8(6).

Dhand A, et al. *Transplantation.* 2021;105(7):e68-e69.

Newer COVID antibody treatments

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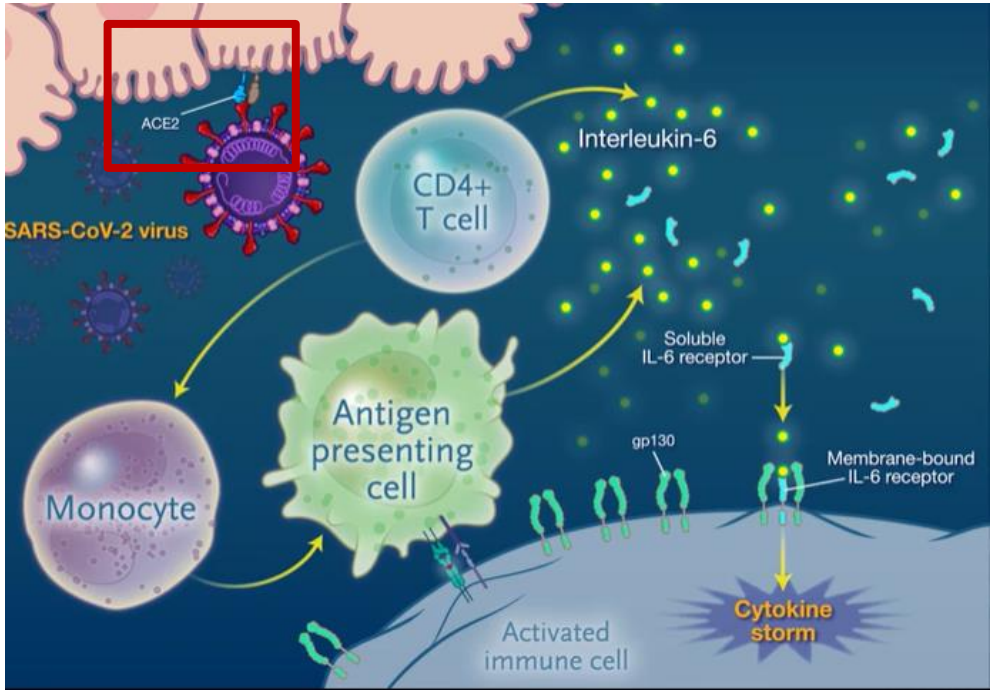
Studies in SOT patients

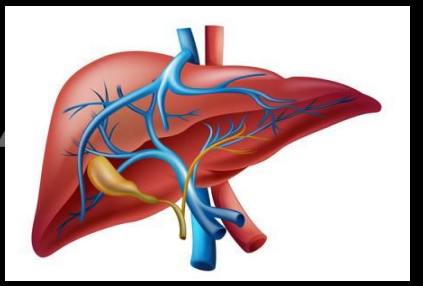
Study	Outcome
Yetmar, et al. (73 SOT with mild-moderate COVID; 56% KT, 18% LT, 15% heart	75% bamlavivimab; 25% REGN-COV2 – No deaths, COVID-19-related ICU admissions, or requirement for advanced respiratory support
Dhand, et al. (25 SOT with mild-moderate COVID; 68% KT, 12% liver, 12% heart)	100% REGN-COV2 – None experienced progression of symptoms or required hospitalization due to COVID-19

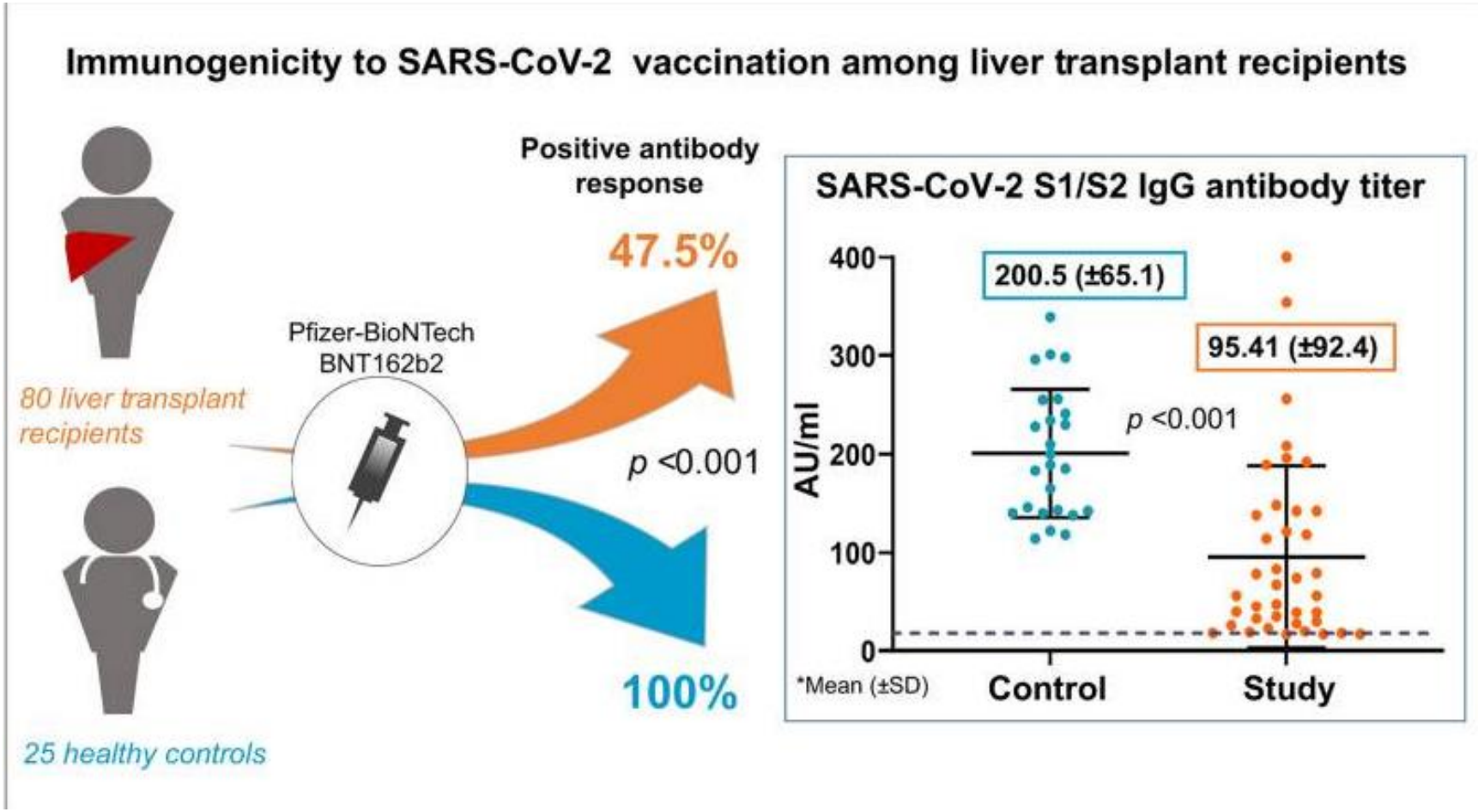
Yetmar ZA, et al. *Open Forum Infect Dis.* 2021;8(6).

Dhand A, et al. *Transplantation.* 2021;105(7):e68-e69.



Vaccination in SOT



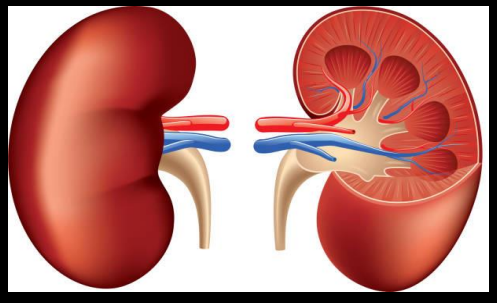


Maintenance IS	
CNIs	94%
MMF	50%
mTOR	22.5%
2 IS	62.5%
3 IS	21.2%

Median of 5 years post-transplant

Rabinowich L, et al. *J Hepatol.* 2021;75(2):435-438.

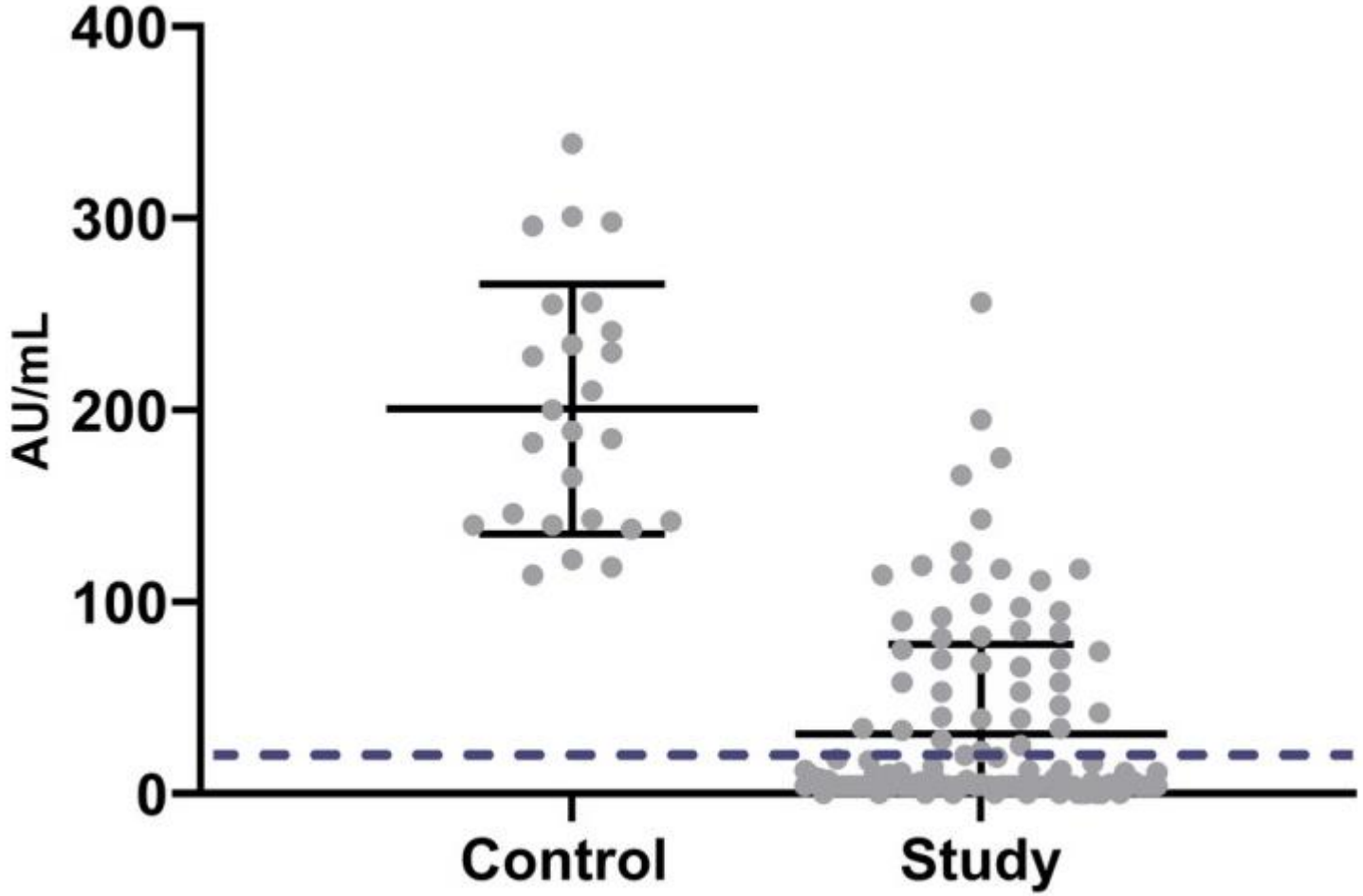
Grupper, et al (2021): Kidney Transplant



Results

Protective levels of SARS-CoV-2 S1/S2 IgG antibodies were detected in all of the controls (25/25)

Only **51/136 KT recipients** (37.5%) had positive serology (p <0.001)



Grupper A, et al. *Am J Transplant*. 2021;10.1111/ajt.16615.

DDKT = deceased donor kidney transplant

Boyarsky, et al (2021)

Purpose

Assess immunogenicity and safety of 2 doses of the **Pfizer-BioNTech BNT162b2 (31%) and Moderna mRNA-1273 (69%) SARS-CoV-2 vaccines**

Population

N = 658 transplant recipients

Maintenance IS	
Antimetabolite containing	72%
No antimetabolite	28%

Study group

49% = kidney
20% = liver
15% = heart
11% = lung
1% = pancreas
4% = multiorgan

Boyarsky BJ, et al. *JAMA.* 2021;325(21):2204–2206

Boyarsky, et al (2021)

N = 658	Dose 1- Dose 2-	Dose 1+ Dose 2+	Dose 1- Dose 2+	P-value
Antibody response				
Receiving MMF	57%	8%	35%	<0.001
Not receiving MMF	18%	32%	50%	
Moderna	40%	**22%**	38%	<0.001
Pfizer	51%	**8%**	40%	
Years since transplant				
<3	63%	7%	**30%**	<0.001
3-6	50%	11%	**39%**	
7-11	38%	18%	**43%**	
≥12	33%	23%	**45%**	

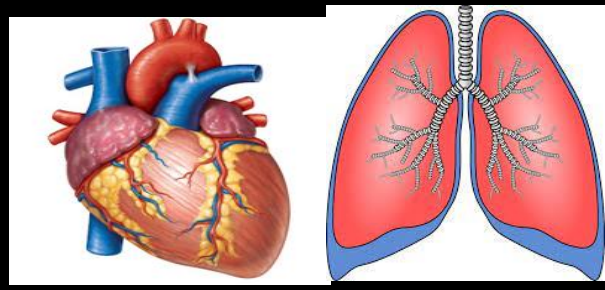
Overall Results

Of the 658 participants:

357 **(54%)** had antibody response after D2

Boyarsky BJ, et al. *JAMA.* 2021;325(21):2204–2206

Schramm R, et al. (2021): T-cell Response?



Purpose

Analyze the antibody as well as the T-cell response after the first and second dose of the Pfizer-BioNTech BNT162b2

Population

N = 100

Maintenance IS	
Tac/MMF	82%
CSA/MMF	10%
Tac/mTOR	8%

2% 1 year from transplant
25% 1-2 years from transplant
24% 2-3 years from transplant

Study group
N = 50

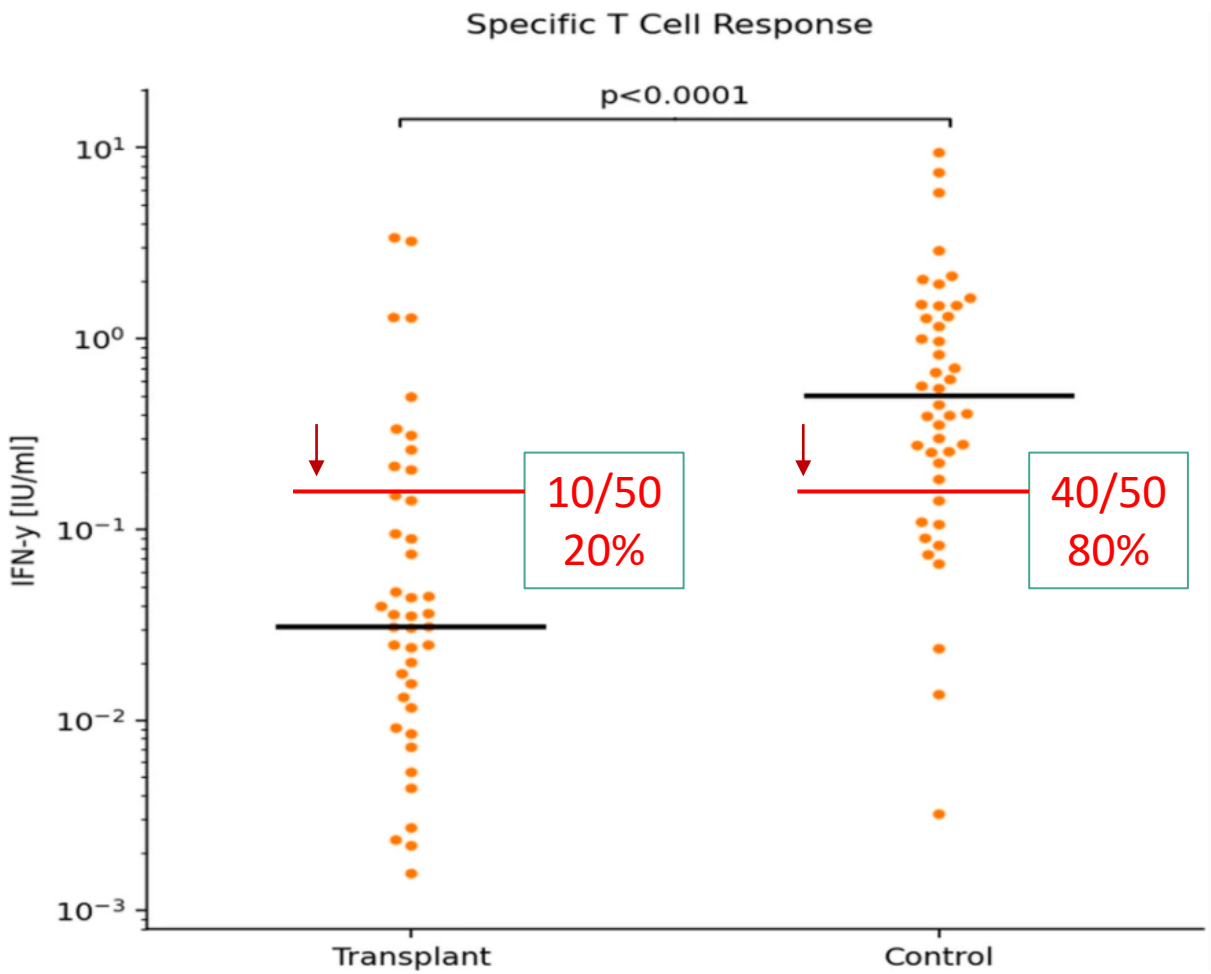
84% = heart
14% = lung
2% = heart-lung

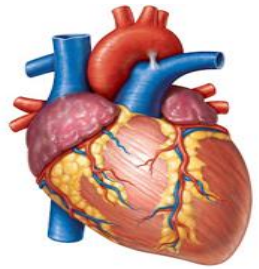
Control group
N = 50

Controls with no major comorbidities

Schramm R, et al. *Clin Res Cardiol*. 2021;1-8.

Schramm R, et al. (2021): T-cell Response?





Red horizontal line: > 0.16 IU/ml = suggested as a cut-off for scoring ; Black horizontal line: Median

Schramm R, et al. *Clin Res Cardiol*. 2021;1

Summary COVID Antibody & Cellular response

Reference	Organ	Vaccine type	Sample size	Antibody response after D2	Cellular response after D2
Rabinowich, et al	Liver	Pfizer	N = 80	47.5%	-
Grupper, et al	Kidney	Pfizer	N = 136	37.5%	-
Cucchiari, et al	Kidney	Moderna	N = 117	30%	65%
Boyarsky, et al	All	Pfizer or Moderna	N = 658	54%	-
Ou MT, et al	Kidney - Belatacept	Pfizer	N= 24	5%	-
Chavarot, et al	Kidney - Belatacept	Pfizer	N = 101	6%	30%
Schramm, et al	Heart / lung	Pfizer	N = 100	10%	20%
Itzhaki, et al	Heart	Pfizer	N = 42	36%	-
Shostak, et al	Lung	Pfizer	N = 168	18%	-

COVID-19 Breakthrough infection

- Wadei et al, reported 7 SOTs with undetectable or low titer antispike antibodies who developed COVID-19 infection after receiving one or two doses of the SARS-CoV-2 mRNA vaccine
  - Clinical presentation and course of these patients comparable to those who have not been vaccinated
  - 4/7 kidney; 3/7 heart transplant recipients
  - 4/7 received ATG for induction therapy
  - Day from last COVID vaccine to diagnosis: Range = 6-44 days
- Chang et al, reported a case of severe COVID-19 despite full vaccination with mRNA-1273 SARS-CoV-2 vaccine (Moderna) in a DDKT from February 10, 2020
  - COVID-19 infection boosted the vaccine-induced anti-spike antibody response in patient but was not able to induce a natural antibody response to nucleocapsid protein

Wadei HM, et al. *Am J Transplant*. 2021.
Chang KM, et al. *Transpl Infect Dis.* 2021;e13710.

Third COVID-19 dose

Effective August 13, 2021, CDC recommends that people who are moderately to severely immunocompromised receive an additional dose of an mRNA COVID-19 Vaccine **(Pfizer-BioNTech or Moderna) at least 28 days** after the completion of the initial mRNA COVID-19 vaccine series

Discussion points:

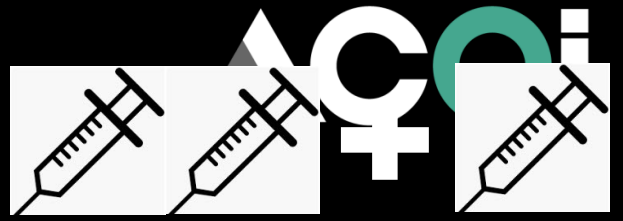
Third dose

Same vaccine product

Janssen additional dose

https://www.cdc.gov/vaccines/covid-19/hcp/immunocompromised-patients.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Fclinical-considerations%2Fimmunocompromised-patients.html

Benotmane, et al (2021)



Purpose

To describe antibody responses and vaccine reactions in recipients of SOT patients who had a suboptimal response to standard vaccination and subsequently received a third dose of **mRNA-1273 (Moderna) vaccine**

Population

77% deceased donor

Maintenance IS	
Tac +MMF + steroid	52.8%

- 60% had no antibody response after D2
- 40% showed a response below the positivity limit

- Patients received the third dose of vaccine a median of 51 days after the second dose of their initial vaccine series

- Median time from transplantation was 5.3 years (IQR, 1.9-11.1 years)

Study group

159 KT recipients

Benotmane I, et al. JAMA. 2021;10.1001/jama.2021.12339.

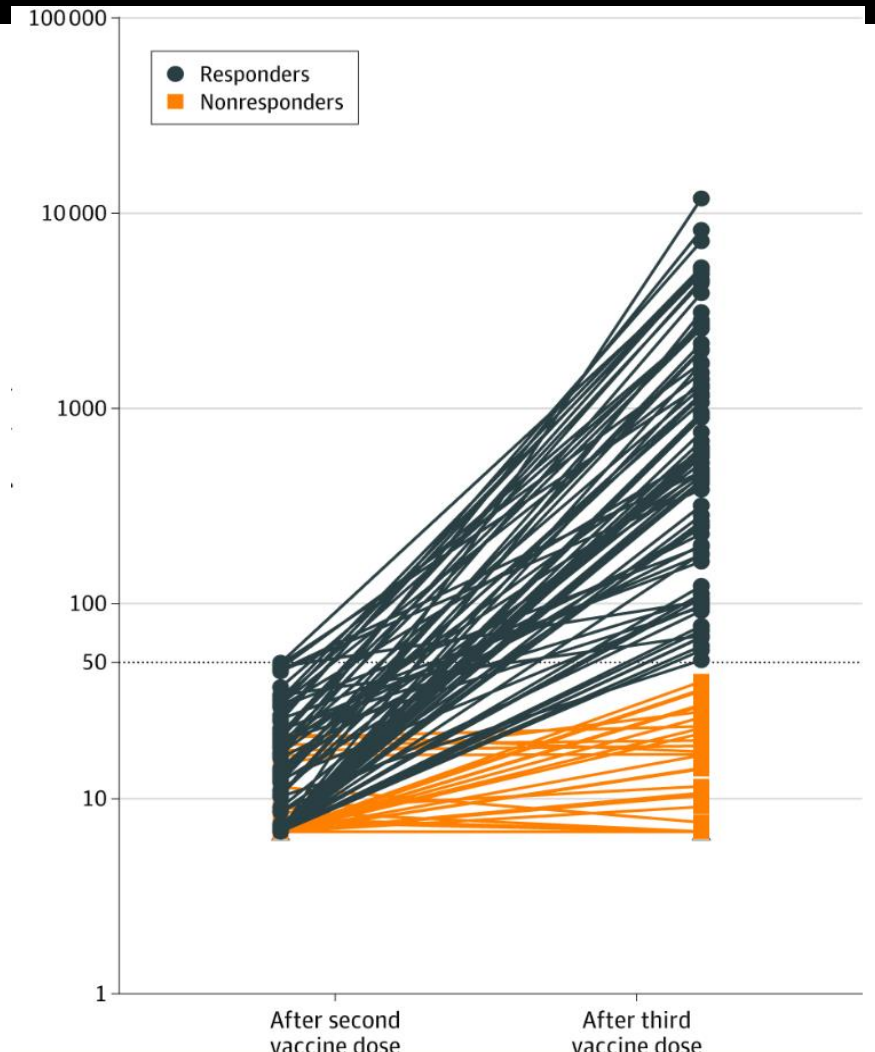
Benotmane, et al (2021)

Results

After the third vaccine injection 78 patients (49%) had a positive antibody response in those who did not respond after D2

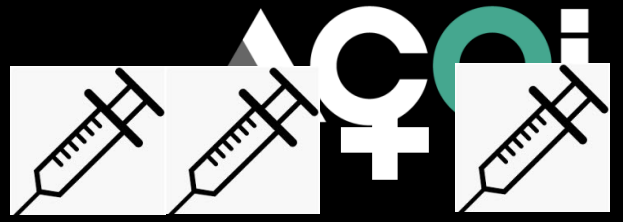
However, 51% of the patients did not develop anti–SARS-CoV-2 antibodies after the third dose, especially those receiving triple immunosuppression

No severe adverse events were observed after the third dose



Benotmane I, et al. JAMA. 2021;10.1001/jama.2021.12339.

Kamar, et al (2021)



Purpose

To describe antibody response in recipients of SOT patients who had a suboptimal response to standard vaccination and subsequently received a third dose of **BNT162b2 (Pfizer–BioNTech) vaccine**

Population

N = 101 transplant recipients

Maintenance IS	
CNI	79%
Belatacept	12%
MMF	63%
mTOR	30%
Steroids	87%

- Patients received the third dose of vaccine a median of 61 days after the second dose of their initial vaccine series

- Median time after transplant: 8±1 year

Study group

77% kidney; 12% liver; 8% lung or heart; 3% pancreas

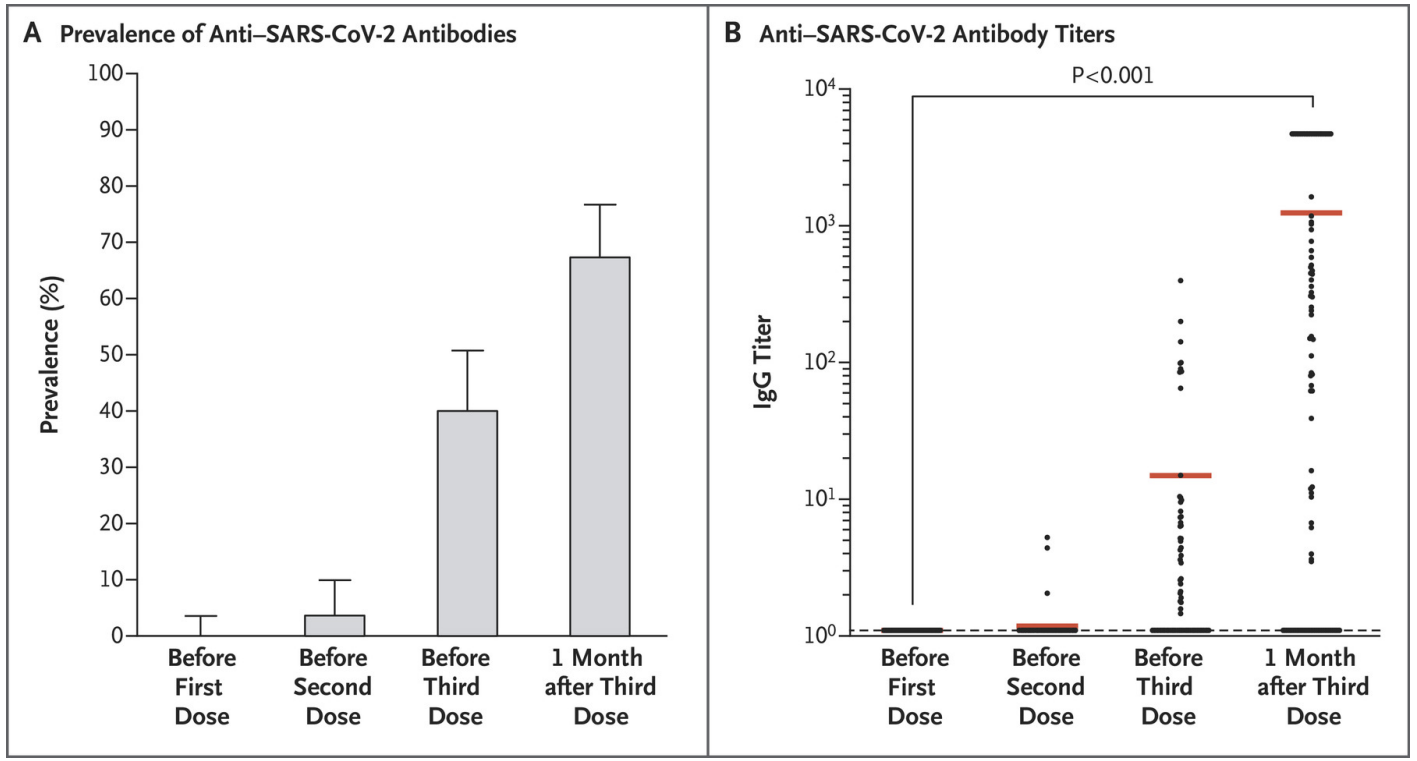
Kamar N, et al. N Engl J Med. 2021;NEJMc2108861.

Kamar, et al (2021)

Results

Among the 59 patients who had been seronegative after D2, 26 **(44%) were** seropositive at 4 weeks **after the third dose**

No severe adverse events were observed after the third dose and no acute rejection episodes occurred



Kamar N, et al. N Engl J Med. 2021;NEJMc2108861.

Conclusions

- Clinical outcomes between solid organ transplant (SOT) recipients are poor with a high morbidity and mortality rate.
- SOT patients demonstrate a delayed T cell response and rapid loss of antibodies to both COVID infection as well as COVID vaccination.
- Immunosuppression management during COVID infection in SOT is patient-specific, but generally involves careful reduction in immunosuppression.
- Roughly 50% in SOT recipients demonstrate an immune response after two doses of the Moderna and/or Pfizer vaccines and a third dose is recommended.

Thank You