58TH ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

Rejection episodes during COVID-19 pandemic:

Who to treat?

How to treat?

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Outlines

- Introduction in COVID-19 in KT patients
- AKI in KT patients with COVID-19.
- Rejection in KT patients with COVID-19
- KT rejection and COVID vaccination
- Summary

Clinical presentation of COVID-19 in KTR

- In immunocompromised hosts, laboratory data — notably biomarkers associated with inflammation and COVID-19 — have less intrinsic value in predicting a patient's clinical course.
- An elevation in the CRP level predicts the need for intensive care.
- **Procalcitonin** levels generally remain low (<0.5-0.8ng/mL)for the first 7 to 10 days of SARSCoV-2 infection and may **subsequently rise**, even **in the absence** of superinfection.
- Case fatality rate: 2%–4%.

Case 29-2020: A 66-Year-Old Man with Fever and Shortness of Breath after Liver Transplantation

Jay A. Fishman, M.D., Matthew B. Roberts, M.B., B.S., Eric W. Zhang, M.D., Deepali Kumar, M.D., Hans H. Hirsch, M.D., and Umberto Maggiore, M.D.

Immunosuppression Management: Data from the first reports of KTRs with COVID-19

Type of anti-rejection treatment change according to different stages

	Asymptomatic	Moderate	Serious	Critically ill
Tacrolimus	↔	↔	↓	stopped
MMF	↔	↓ or stopped	↓ or stopped	stopped
Steroids	↔	↔	↔ or ↑	↑

MMF, mycophenolate mofetil

Akalin *N Engl J Med 2020*

Columbia University Kidney Transplant Program *J Am Soc Nephrol* 2020

Husain Clin *J Am Soc Nephrol* 2020

Alberici *Kidney Int Rep* 2020

Zhu *Eur Urol* 2020

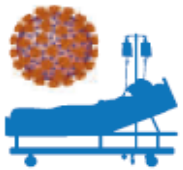
Clinical Kidney Journal

Immunosuppression minimization in kidney transplant recipients hospitalized for COVID-19

Kidney transplant (KT) recipients have an increased mortality risk in the setting of COVID-19.
The role of decreased immunosuppression must be characterized.

Methods

Madrid
+
Barcelona

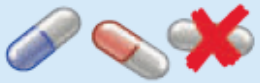


COVID-19 in 74 KTs:
March 12 to June 29 2020

Survived (n = 47)

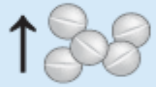
Analysis of COVID-19 survivors = follow-up 3 months after discharge

Results



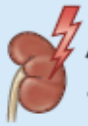
Withdrawal of 1 immunosuppressive drug
83%

Withdrawal of all immunosuppressive drugs
17%



Increased steroids
15%

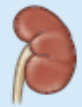
Median time 17 days



AKI
55%

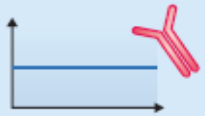
AKIN I 38%
AKIN II 8.5%
AKIN III 4.2%

- Related to tacrolimus levels
- All patients recovered baseline kidney function



No rejection episodes

No de novo DSA



No changes in PRA

Conclusion: Immunosuppression in COVID-19 kidney transplant recipients can be safely minimized.

Anton P., Trujillo H. et al.
Clinical Kidney Journal (2021)
@CKJsocial

- All samples were tested by single-antigen bead assay (SAB; One Lambda) to detect donor-specific anti-HLA IgG by single-antigen Classes I and II flow beads assay kit.
- The test was considered positive if MFI was >500 or if MFI/MFI lowest bead was >5.

Potential risk factors for AKI in COVID-19

- **Demographic risk factors:**
- Older age
- DM
- HTN
- CVD or CHF
- High BMI
- CKD
- Smoking history
- Immunosuppressed state

- **Risk factors for AKI during hospitalization:**
- Nephrotoxins: medications, contrast
- Vasopressors
- Ventilation; high positive end-expiratory pressure.
- Fluid dynamics; fluid overload, hypovolaemia

Potential risk factors for AKI in COVID-19

- **Risk factors for AKI at admission:**
- Severity of COVID-19
- Degree of viremia
- Respiratory status
- Non-respiratory organ involvement: eg. Diarrhea
- Leukocytosis
- Lymphopenia
- Rise in CRP, Ferritin, d-Dimer
- Hypovolemia
- Rhabdomyolysis
- Medication exposure: ACEIs, ARBs, NSAIDs.

Is more rejection in COVID-19 era?

	Total N. of KTR with COVID-19	IS minimization	AKI	Rejection	De novo DSA
Pereira 2020	51	88%	NA	0	NA
Demir 2020	40	100%	NA	0	NA
Zhang 2020	5	80%	20%	?1	NA
Santeusanio 2020	95(38 hospitalized)	100%	59%	0	NA
Pampols 2021	47	83%	55%	0	0
Feldin 2021	31	NA	NA	0	NA
Cubillo 2021	29	100%	48%	0	NA
Fernandez-Ruiz2021	8	100%	NA	0	NA

Is more rejection in COVID-19 era?

- Low rate of rejection despite strong reduction of IS:
  - Too high mortality?
  - Low biopsy number?
- High report of AKI: volume depletion? Hypoperfusion? Drug toxicity?

- Long term consequences are not known: de novo DSA
- No data on subclinical rejection


Perspective

AJKD

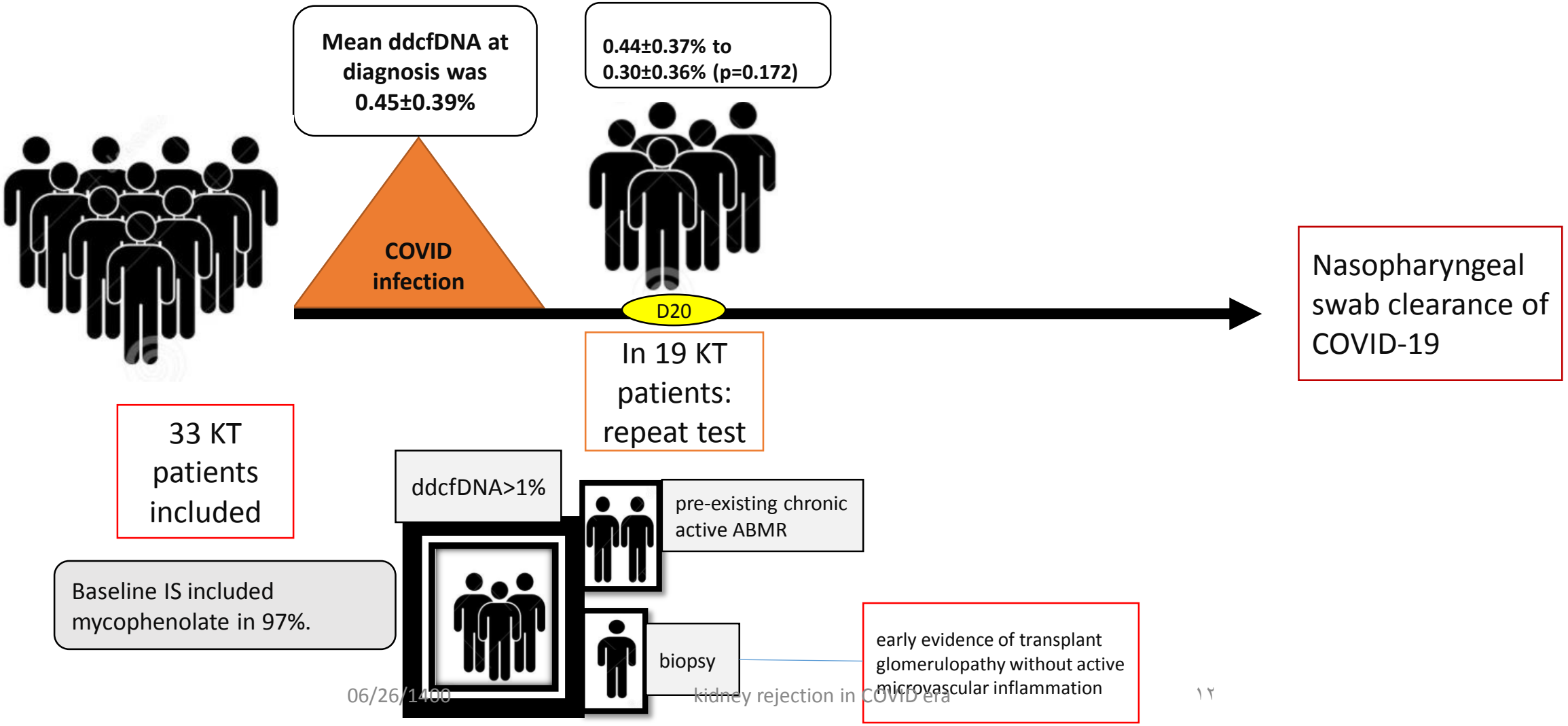
Practicing With Uncertainty: Kidney Transplantation During the COVID-19 Pandemic

Krista L. Lentine, Roslyn B. Mannon, and Michelle A. Josephson

Non invasive biomarkers for Dx:

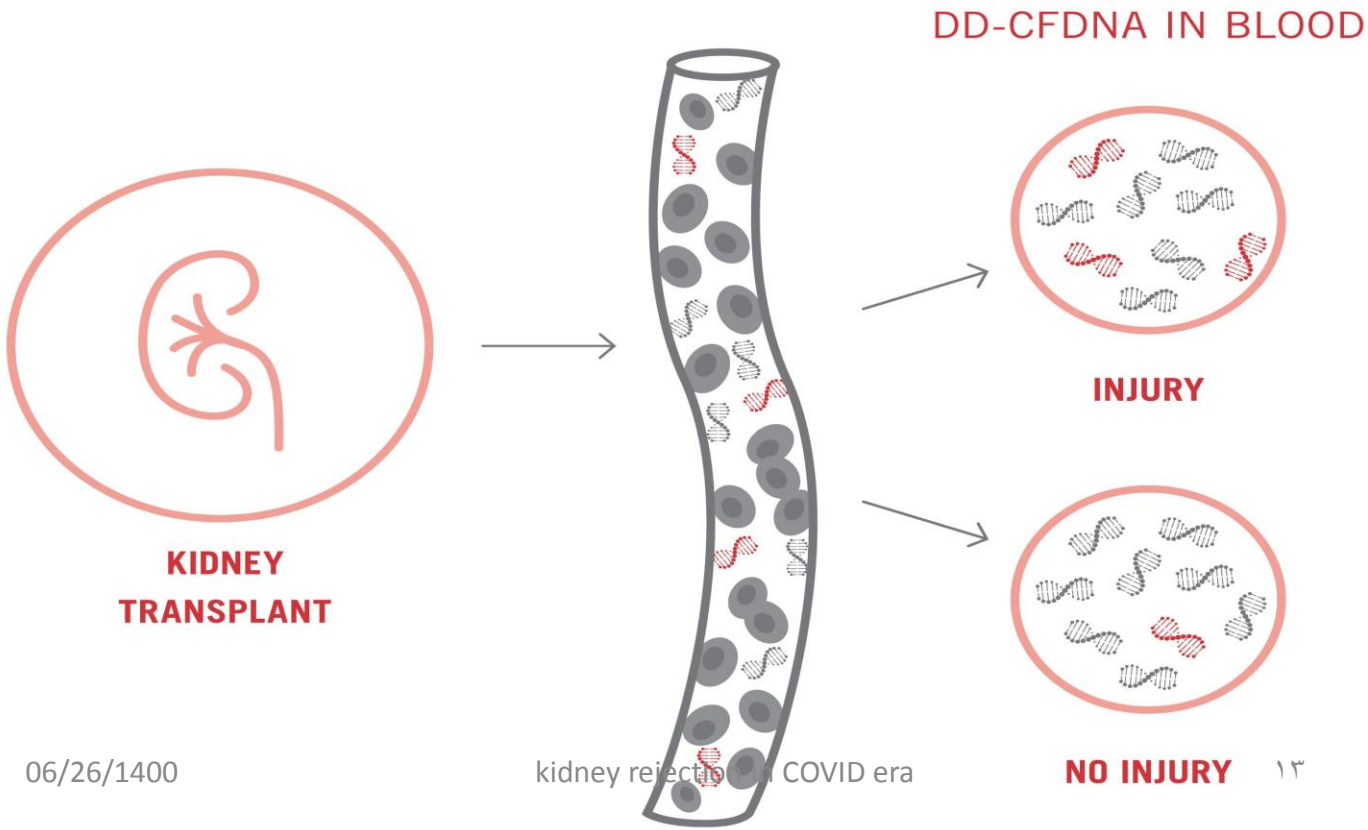
- **Methods:** Since March 2020 we initiated a protocol of measuring donor derived cell free DNA (ddcfDNA) (Allosure, CareDx) and HLA DSA at the time of diagnosis of COVID-19 infection (prior to reduction or cessation of antimetabolite).
- ddcfDNA, HLA DSA and additional clinical markers of allograft function were serially monitored until the point of nasopharyngeal (NP) swab clearance of COVID-19.

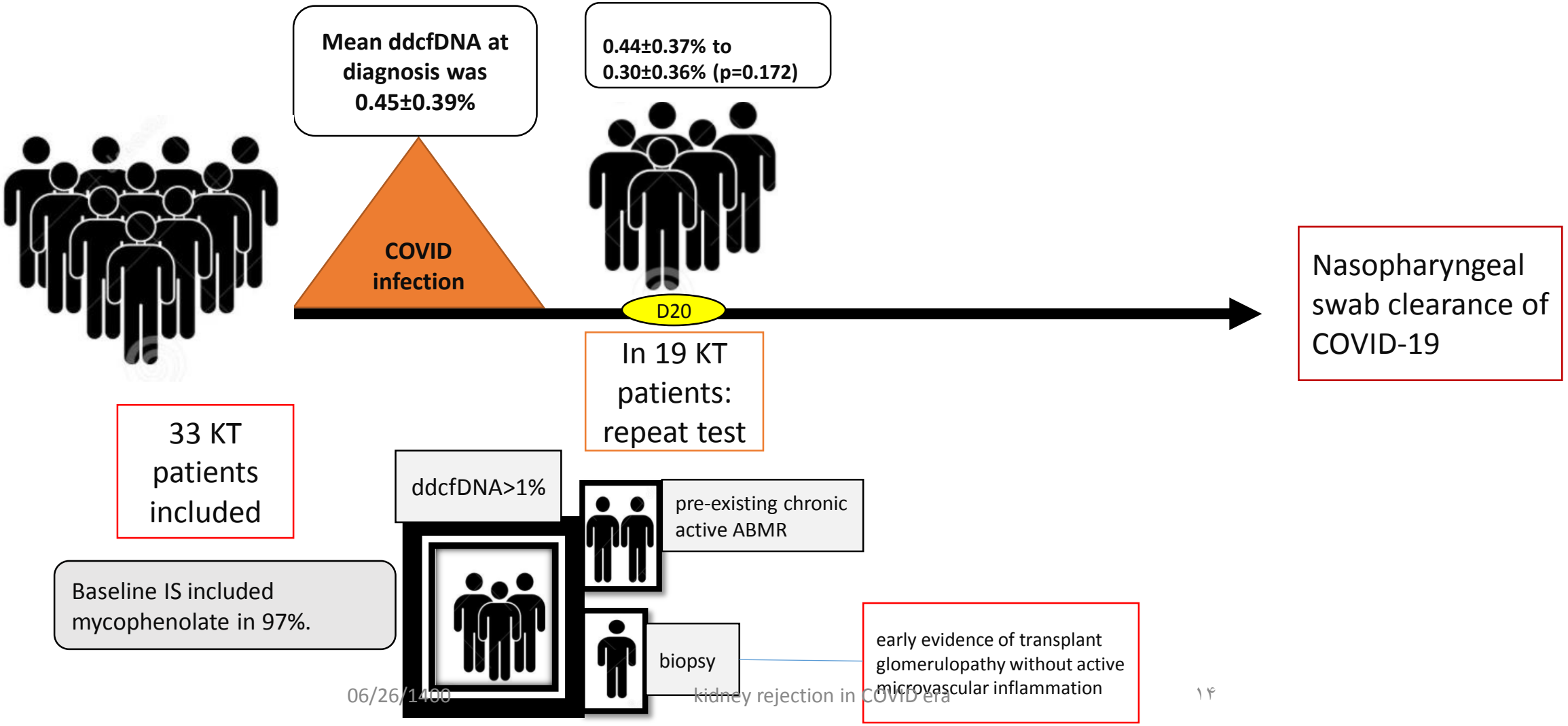
J. Christensen, G. Gupta, A. Bryson, S. Paluri, R. Thompson, S. Sterling, N. Vissichelli, P. Kimball, D. Kumar Utility of Non-Invasive Rejection Biomarkers to Guide Immunomodulation in Kidney Transplant Patients with Active Covid-19 Infection . **Meeting:** 2021 American Transplant Congress


Mean ddcfDNA at diagnosis was 0.45±0.39%
0.44±0.37% to 0.30±0.36% (p=0.172)
COVID infection
D20
Nasopharyngeal swab clearance of COVID-19
33 KT patients included
In 19 KT patients: repeat test
ddcfDNA>1%
pre-existing chronic active ABMR
Baseline IS included mycophenolate in 97%.
biopsy
early evidence of transplant glomerulopathy without active microvascular inflammation

Donor-derived cell-free DNA:ddcfDNA

- Detected in the blood of transplant recipients.
- As a noninvasive marker for diagnosis of graft rejection

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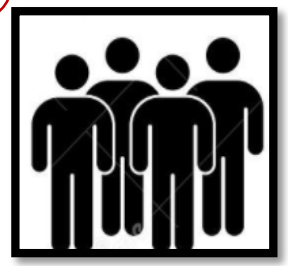
88% did not have any HLA DSA

COVID infection



pre-formed HLA DSA
at the time of diagnosis
and during the infection

Nasopharyngeal swab clearance of COVID-19

33 KT patients included

Baseline IS included mycophenolate in 97%.

In the majority of patients, ddcfDNA was low initially and remained low on subsequent testing arguing against allograft injury.
In addition despite reduced IS, COVID-19 infection did not stimulate alloimmune responses in the short-term as evidenced by a very low rate of de-novo DSA.

Donor-derived cell-free DNA:ddcfDNA

- Stable kidney transplant recipients have a median of 0.21% dd-cfDNA
- The dd-cfDNA levels > 1% strongly correlate with biopsy-proven active rejection.
  - High negative predictive value of 84% and a positive predictive value of 61%

- dd-cfDNA may also be released in response to kidney allograft injury due to ATN and can act as an immunogen stimulating development of DSAs

- .

Donor-specific antibodies: DSA

- **Limitations of DSA testing:**
- High frequency of false positives
- Variability of time between DSA emergence and manifestation of rejection
- False negatives due to sequestered antibodies in the graft or presence of non-HLA DSAs
- Absence of consensus criteria for clinically meaningful antigens or IgG subclasses
- Uncertainty of clinically meaningful quantitative thresholds (mean fluorescence intensity) for clinical decisions
- Fluctuating levels of DSAs
- Lack of assay standardization

KT rejection in COVID-19 era

- In vitro reactivity between spike protein antibodies and human collagen has been demonstrated, but molecular mimicry has not been identified as a primary mechanism of kidney injury in COVID-19.
- Available data suggest acute allograft rejection is uncommon during COVID-19, despite frequent reduction in immunosuppression as a therapeutic strategy.

Clinical Infectious Diseases
MAJOR ARTICLE

Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study

- Available data suggest acute allograft rejection is uncommon during COVID-19, despite frequent reduction in immunosuppression as a therapeutic strategy.

SARS-CoV-2 Vaccines in Kidney Transplant Recipients: Will They Be Safe and Effective and How Will We Know?

Madeleine R. Heldman and Ajit P. Limaye
Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington

JASN 32: 1021–1024, 2021. doi: https://doi.org/10.1681/ASN.2021010023

If I underwent with a KTR rejection, what could I do?

- 53 yo female SPKT with COVID-19 with no need for IS reduction.
- She experienced pancreatic dysfunction resistant to steroids
- Treated with ATG 7.5mg/kg (total) empirically
- Clinically she recovered well without any sign or symptoms of recurrent COVID-19

	Day 0	Day 3	Day 6	Day 23 (First admission)	Day 26	Day 30, 31, 32	Day 33 (Discharge day)	Day 36 (Second admission) rATG given	Day 47	Day 57	Day 78
COVID-19 data											
SARS-CoV-2 PCR	Positive	Positive	Positive	Positive		Inconclusive		Positive	Negative		
SARS-CoV-2 IgG antibody					Detected				Detected		
Clinical data											
Lipase				571 U/L			1067 U/L	1780 U/L	805 U/L	335 U/L	24 U/L
C-peptide								3.8 ng/ml	6.7 ng/ml	2.7 ng/ml	2.3 ng/ml
Hemoglobin A1C				5.4%				6.1%	6.7%	6.5%	
DSA						Negative			Negative		

If I underwent with a KTR rejection, what could I do?

- 46 yo SPKT with asymptomatic COVID-19 developed worsening of kidney graft function (Cr: 1.3 to 8.4mg/dL) and develop de novo DSA.
- Kidney biopsy: TCMR and chronic active ABMR
- Treatment: PEX, IVIG, ATG(5mg/Kg)
- He had no improvement but no sign or symptoms of COVID-19

	Day 0	Day 46	Day 48 (First admission)	Day 50, 51	Day 55	Day 56–62 rATG given	Day 63	Day 75 (Second admission)	Day 77
COVID-19 data									
SARS-CoV-2 PCR	Positive		Positive		Positive				
SARS-CoV-2 IgG antibody				Detected			Negative	Negative	
Clinical data									
Creatinine		8.4 mg/dl		9.5 mg/dl	10.4 mg/dl	9–10 mg/dl		8.6 mg/dl	
Other clinical data		Tacrolimus 5.1 ng/ml		DSA positive[a]	Hemoglobin A1C: 6.5%	Total plasma exchange	Hemoglobin A1C: 6.8%	HD started on day 76	DSA positive[b]
		Sirolimus 2.9 ng/ml		Stent placement		on days 56, 57, 59, 61, 61		Lipase: 75 U/L	
		Lipase 156 U/L				IVIG		C-peptide: 6.5 ng/ml	
		C-peptide: 1.9 ng/ml				rATG			
						Rituximab			

Received: 20 September 2020 | Revised: 27 October 2020 | Accepted: 28 October 2020
DOI: 10.1111/ctr.14149

RESEARCH LETTER TO THE EDITOR

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Rabbit anti-thymocyte globulin administration to treat rejection in simultaneous pancreas and kidney transplant recipients with recent COVID-19 infection

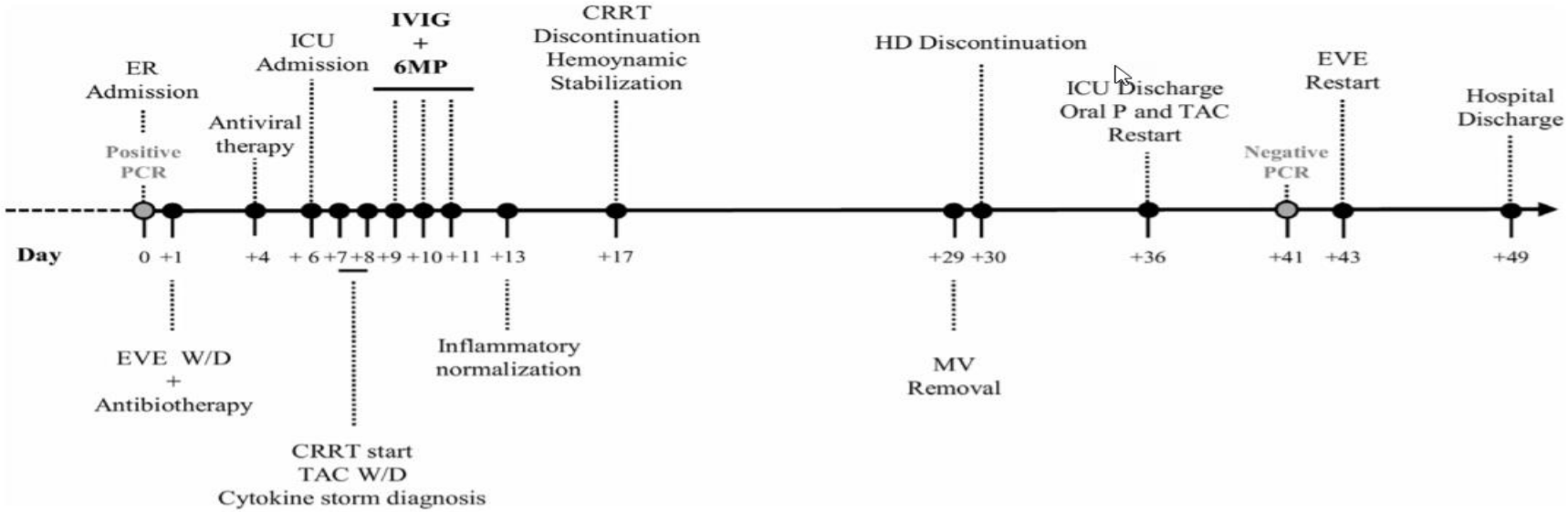
- Our patients continued to have viral shedding when rejection was diagnosed.
- Viral shedding has been detected up to 119 days from symptom initiation and prolonged shedding is not a rare phenomenon.
- However, the duration of infectivity remains unknown.
- The management of rejection in patients with **recent** COVID-19 and positive SARS-CoV-2 PCR should be individualized

TCMR treatment during COVID-19

- Safe to use steroids for TCMR especially in the later “ inflammatory phase”: Dexamethason vs. methylprednisolone pulse.
- Further treatment with ATG should be very carefully considered in steroid resistant rejection.
- **Consider TMP/SMX prophylaxis** & **CMV monitoring.**

Ideal treatment of acute ABMR during COVID-19 infection

- Increased steroid in acute worsening graft function
- Optimization of maintenance therapy when feasible
- PEX: could be useful not to over immunosuppressed pts, can be logistically difficult.



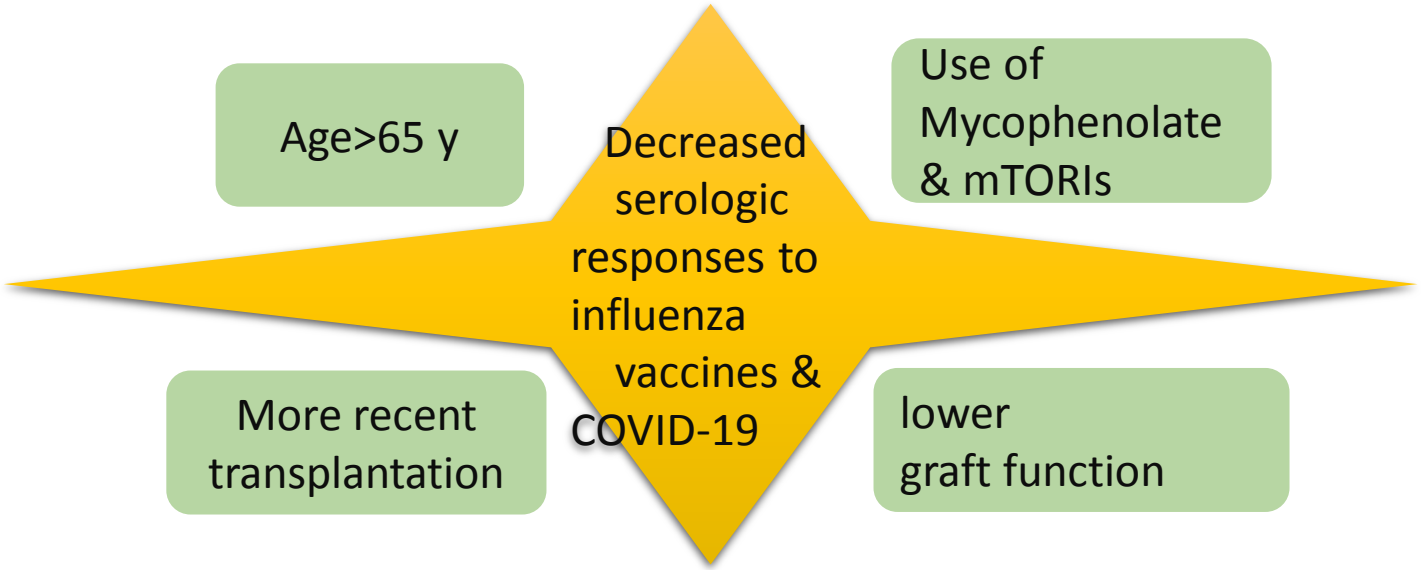
Ideal treatment of acute ABMR during COVID-19 infection

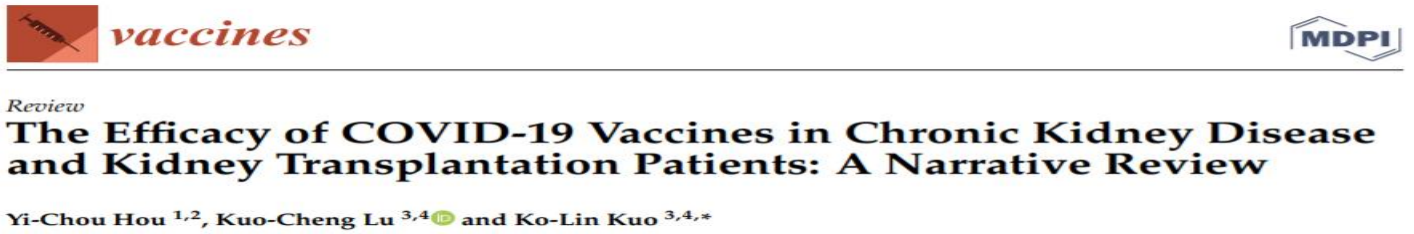
- High dose IVIg : immunomodulatory role (potentially reduced superinfectious risk, potentially increased thrombotic risk)
- Rituximab: should be carefully considered after COVID-19 resolution
- Eculizumab: role as rescue therapy

Vaccine and KT rejection risk

Reduce the immunogenicity of SARS-CoV-2 vaccines by IS

- Relative humoral response rates that are approximately 50%–70% of those seen in non-transplant populations.





vaccines

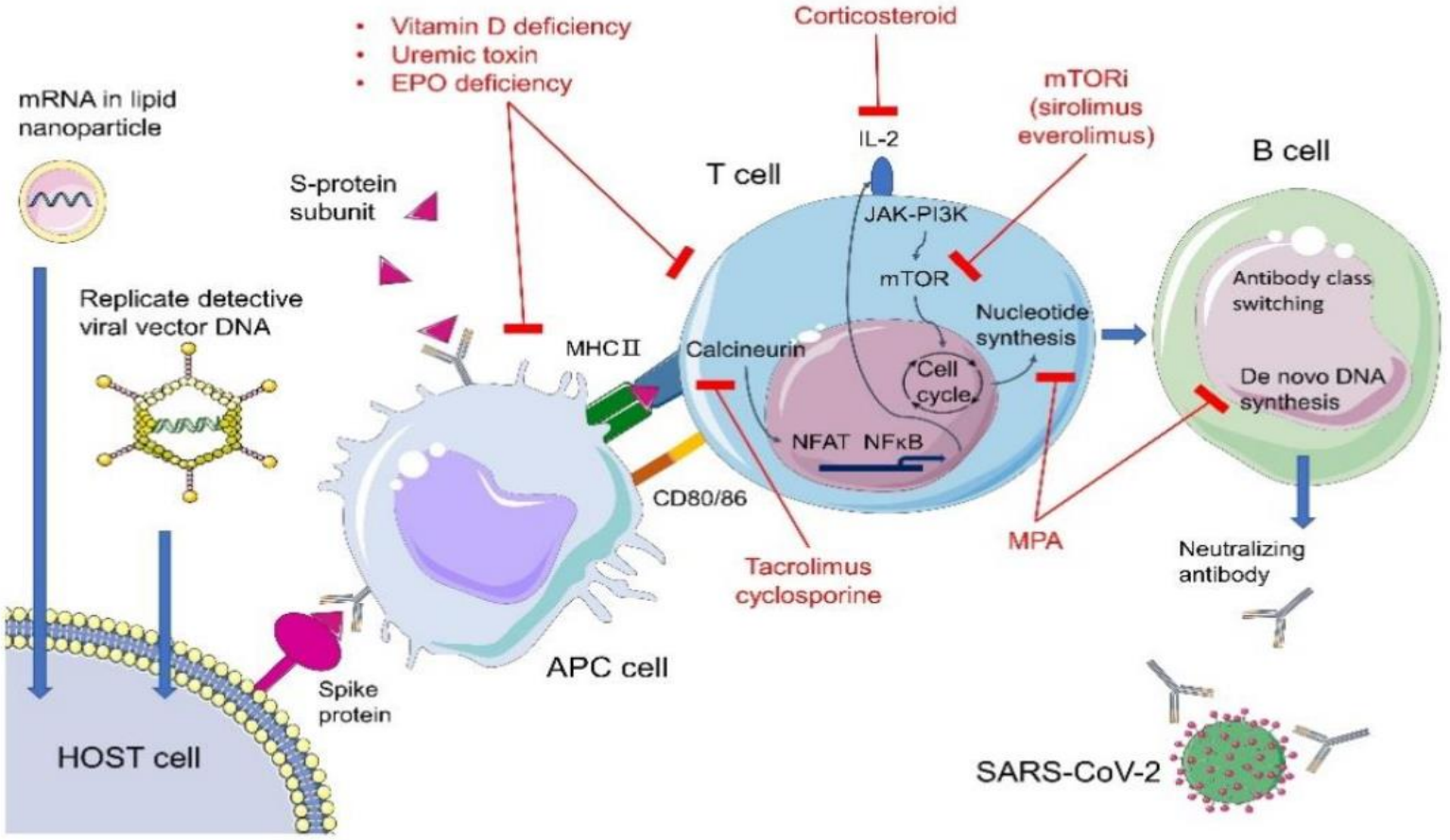
MDPI

Review

The Efficacy of COVID-19 Vaccines in Chronic Kidney Disease and Kidney Transplantation Patients: A Narrative Review

Yi-Chou Hou [1,2], Kuo-Cheng Lu [3,4] and Ko-Lin Kuo [3,4,*]

The mechanism of the impaired generation of neutralizing antibody after SARS-CoV-2 vaccine injection in CKD and KT patients



Clinical TRANSPLANTATION
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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice

Lara Danziger-Isakov, Deepali Kumar, On Behalf of The AST ID Community of Practice,

- Adjuvants(used to enhance vaccine immunogenicity) → nonspecific inflammatory responses → potential to induce acute allograft rejection

Adjuvant safety in organ transplant recipients

- An unusually high incidence of anti-HLA antibodies in KT who received the H1Na1 pdm09 vaccine: contained the squalene-based **AS03** adjuvant system
- Only a fraction of these anti-HLA antibodies were donor specific.
- The **AS01B** adjuvant used in the recombinant varicella zoster virus vaccine
- This adjuvant induces a potent innate immune response and associated concerns for precipitating acute allograft rejection in KT recipients

Adjuvant safety in organ transplant recipients

- Several **recombinant spike protein SARS-CoV-2 vaccines** contain adjuvants, such as **AS03** and the novel Matrix M1 adjuvant, which contains the same QS21 saponin found in the recombinant varicella zoster vaccine.
- **Viral-vectored and mRNA vaccines** do **not** generally contain **adjuvants**, although lipid nanoparticle delivery devices used in the mRNA vaccines have natural adjuvant activity.

SARS-CoV-2 Vaccines in Kidney Transplant Recipients: Will They Be Safe and Effective and How Will We Know?

Madeleine R. Heldman and Ajit P. Limaye

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- **No definitive association between any vaccine or adjuvant and allograft rejection has been identified to date.**

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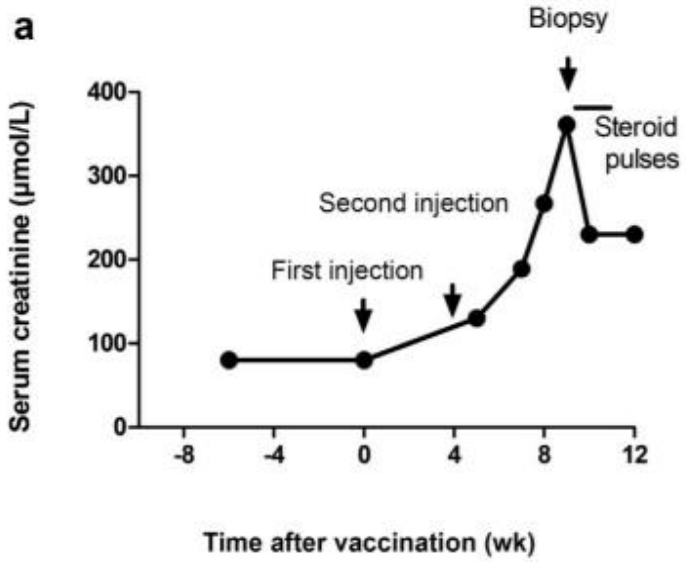
KT rejection after COVID-19 vaccination

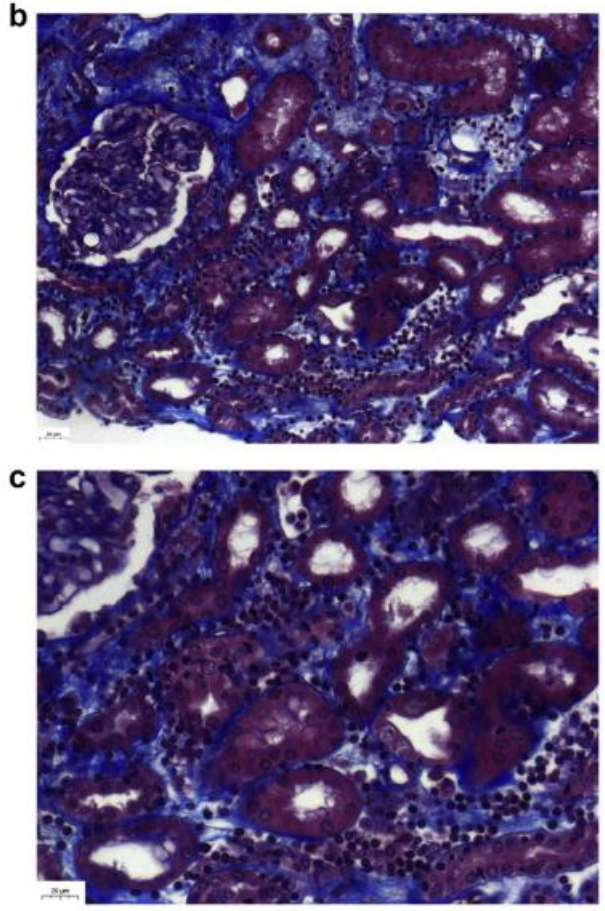
- A 23 Y/O female, KT 18 months ago, received BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech) .
- Her graft: deceased donor kidney.
- The post-transplant period was uneventful.
- Her maintenance therapy was based on tacrolimus (target trough level, 5-7 ng/ml), mycophenolic acid, and low-dose steroid.

letters to the editor www.kidney-international.org

Acute rejection after anti–SARS-CoV-2 mRNA vaccination in a patient who underwent a kidney transplant,
Arnaud Del Bello, Olivier Marion, Audrey Delas , Nicolas Congy-Jolivet , Magali Colombat and Nassim Kamar
Kidney International (2021) 100, 238–242

KT rejection after COVID-19 vaccination





-Inflammatory infiltration
-Tubulitis
-Edema
-Peritubular capillaritis:

Acute Cellular Rejection

KT rejection after COVID-19 vaccination

- Donor-specific anti-HLA antibodies became detectable with a weak intensity, targeting donor HLA class II antigens.

- This report suggests that kidney function should be carefully monitored in kidney transplantation undergoing anti–SARS-CoV-2 vaccination, especially if a third boost dose is performed.

Take home message

- Acute rejection episodes during COVID-19 are rare, they are mainly chronic active ABMR in high risk patients (proteinuria and DSA)
- When treating for rejection always rule out persistent of COVID-19 infection or superinfection and consider the activity/chronicity score ratio.
- Always balance the risk between a life-threatening disease and graft survival

Thanks for your attention