
NATIONAL INISTITUTE OF UROLOGY & NEPHROLOGY
المعهد القومي للكلى
والمسالك البولية

Immunosupressive Management In Covid 19 Infected Kidney Transplant Patients

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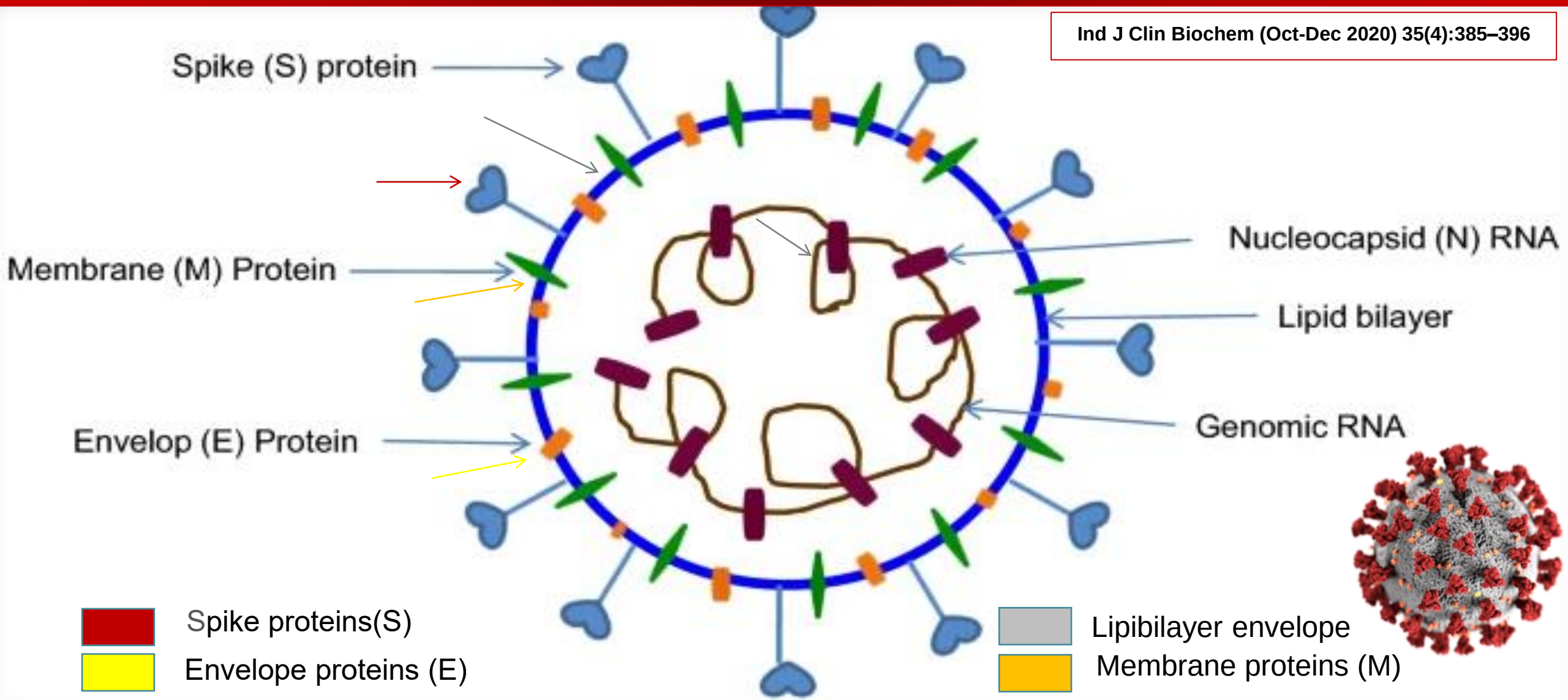
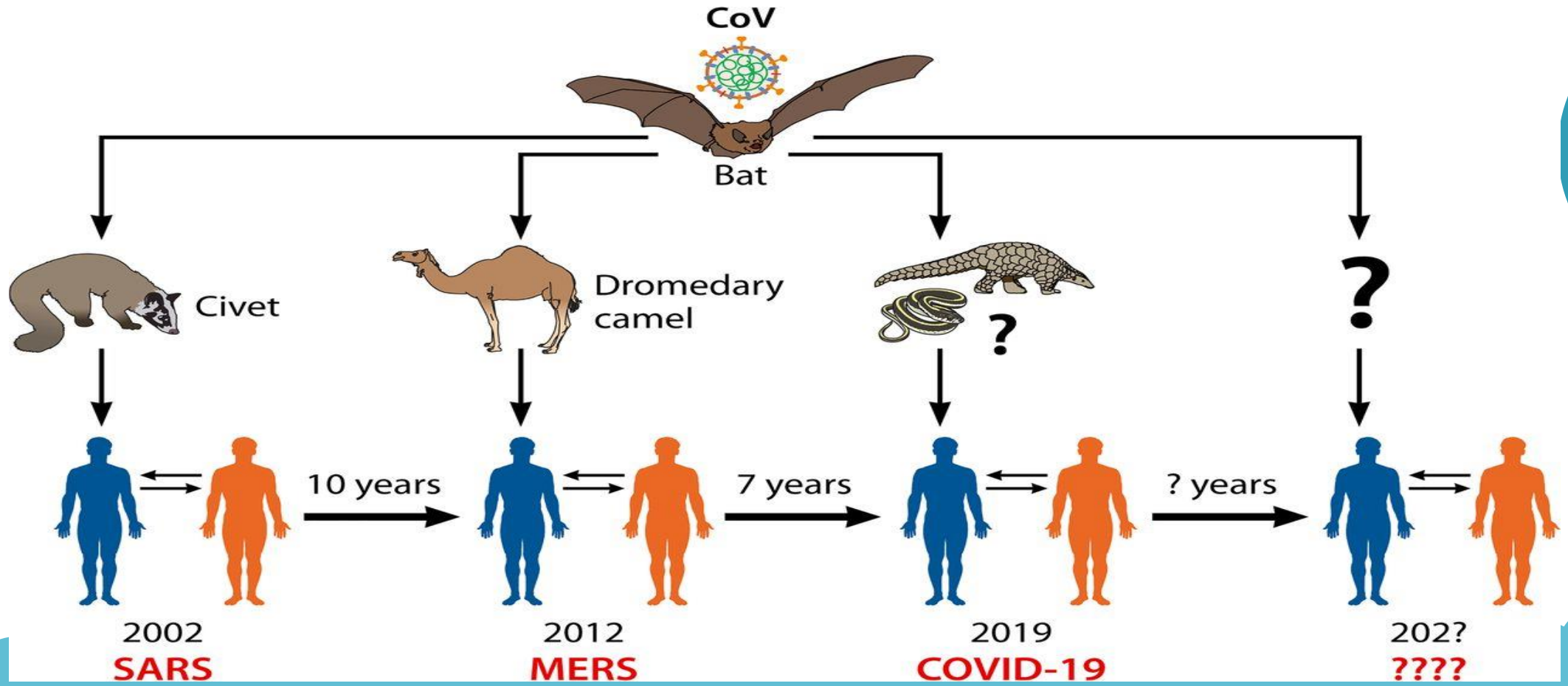
1. Identify the causative organism and its major structures proteins
2. Enumerate its mode of transmission
3. Clarify its clinical manifestation, precautions, diagnosis and prevention
4. Explain proper vaccines for renal transplant recipient, timing, doses and efficacy
5. Define immunosuppressive management in COVID-19 infected kidney transplant patients

Our Agenda

Schematic Structure Of Virion (Sars-cov2) and Its Major Structural Proteins

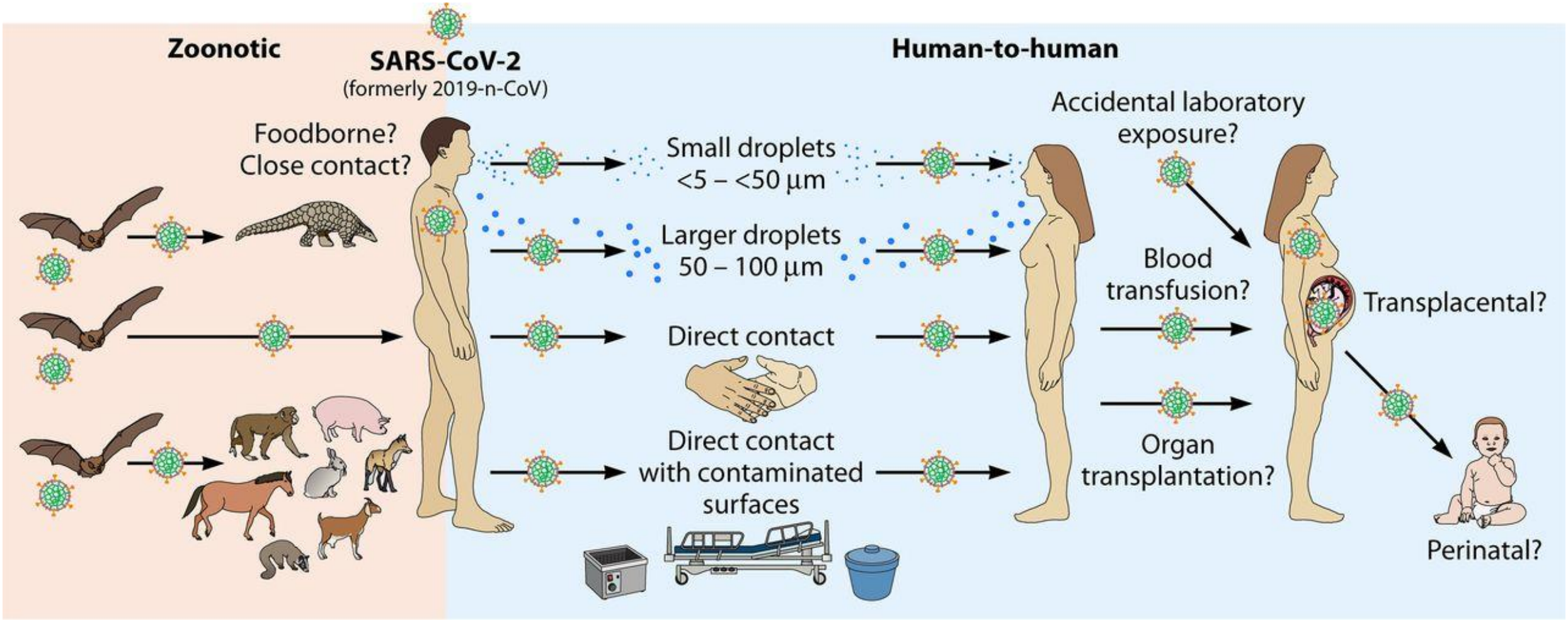
Ind J Clin Biochem (Oct-Dec 2020) 35(4):385–396



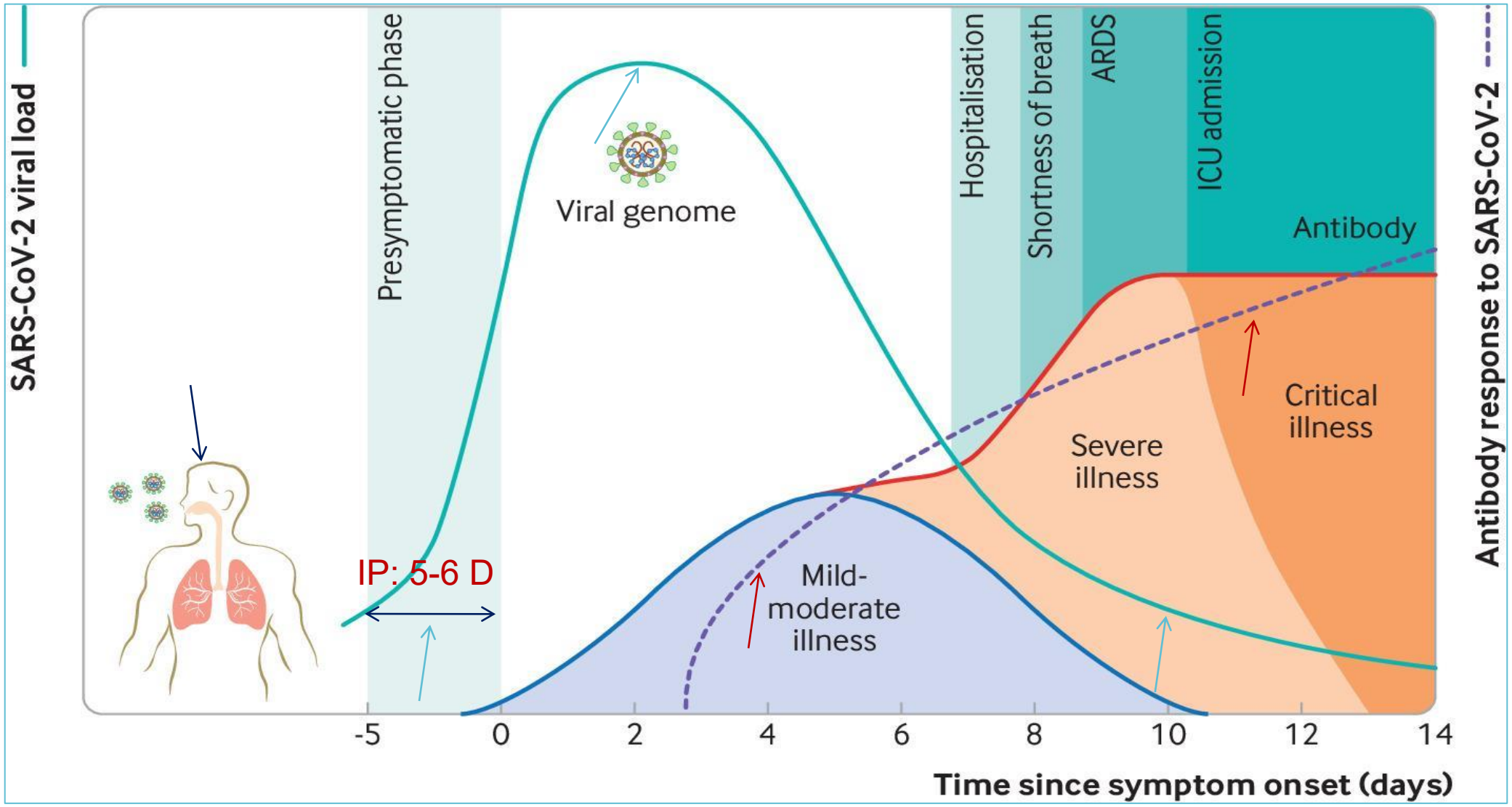


Coronavirus origins. Coronavirus is the most prominent example of an emerging virus that has crossed the species barrier from wild animals to humans, like SARS and MERS. The origin of SARS-CoV-2 is also suspected to be from an intermediate animal host.

Potential Transmission routes For Sars-cov-2.

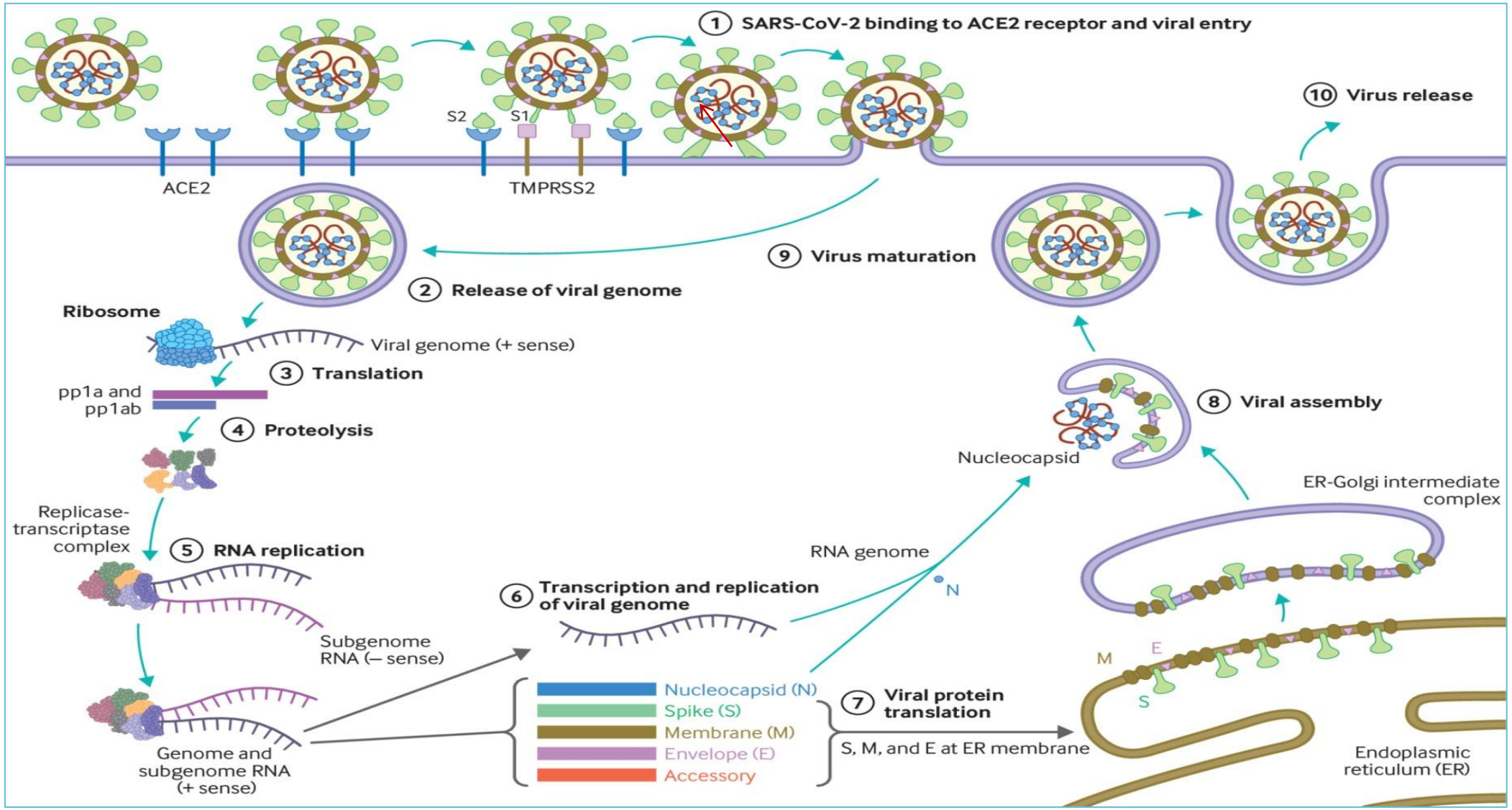


The viral load peaks in the 1st week of infection, declines thereafter gradually, while the antibody response gradually increases & is often detectable by day 14



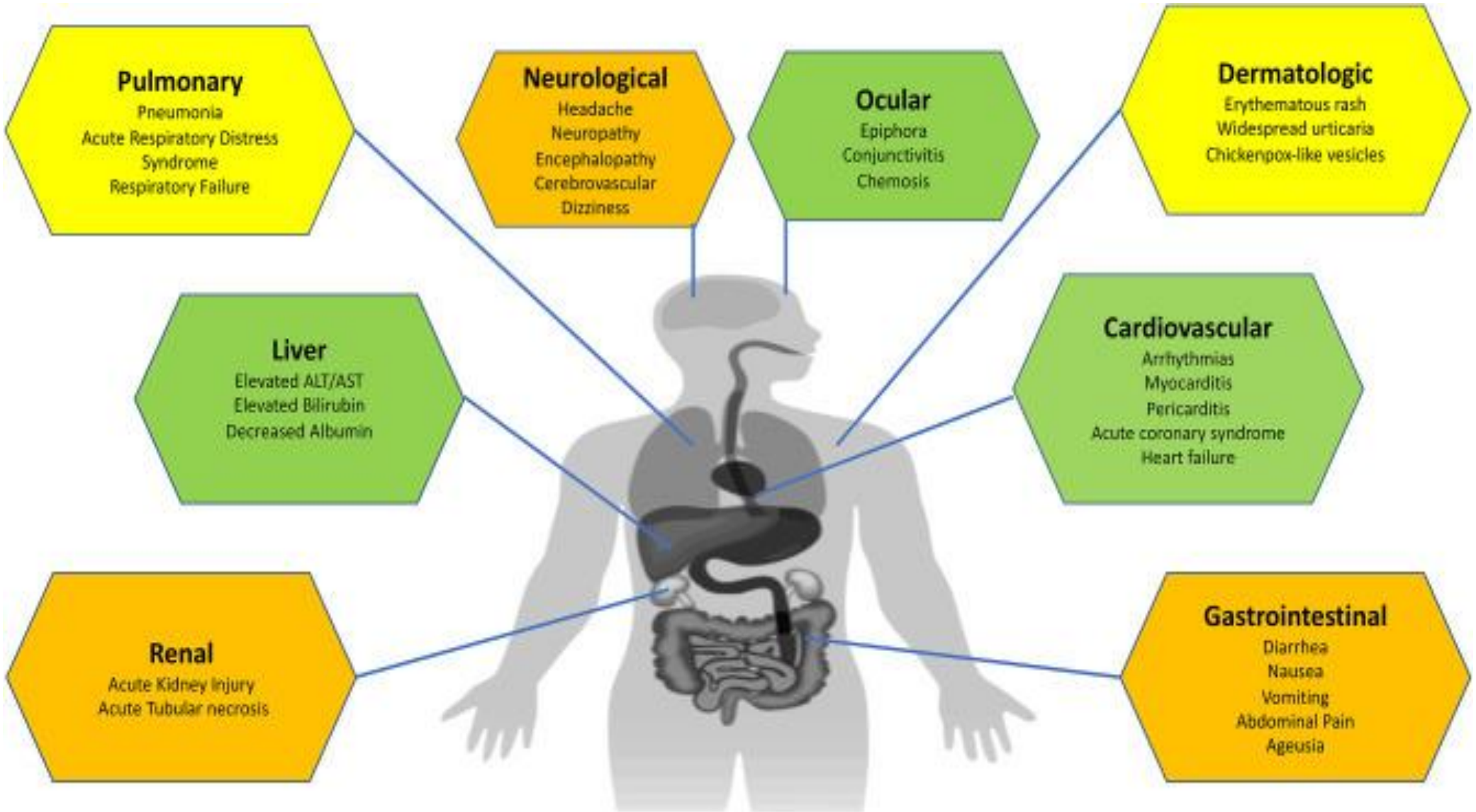
BMJ 2020;371:m3862

The Virus Binds To ACE 2 In Synergy With Trans-membrane Serine Protease 2 (Cell Surface Protein)



BMJ 2020;371:m3862

Pulmonary and Extra-pulmonary Clinical Manifestations Of COVID-19



Front Med (Lausanne). 2020; 7: 526

Risk Factors Associated With Severe Disease, Admission To ICU & Mortality

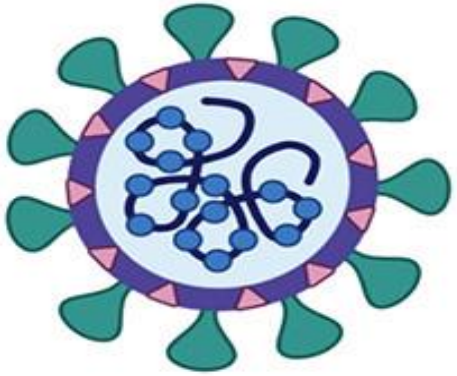
Underlying Condition

- Older age
- Hypertension
- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Diabetes
- Obesity
- Malignancy

Presentation & Laboratory Markers

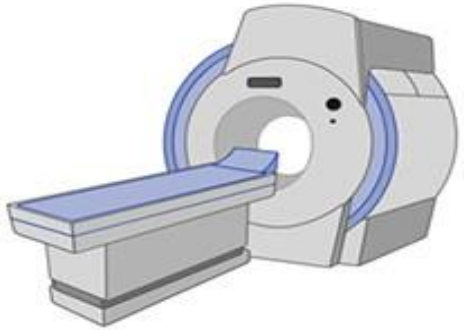
- Higher fever ($\geq 39^{\circ}C$)
- Dyspnoea on admission
- Neutrophilia / lymphopenia
- Raised lactate & LDH
- Raised C reactive protein
- Raised ferritin
- Raised IL-6
- Raised ACE2
- D-dimer >1 μg/m

Diagnosis

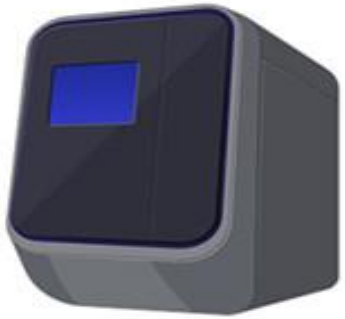


SARS-CoV-2
Diagnosis

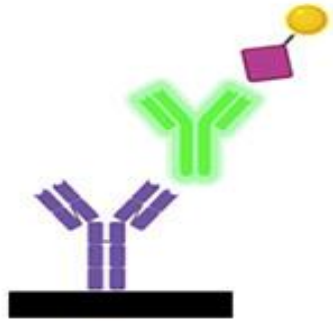
Symptoms



Imaging findings

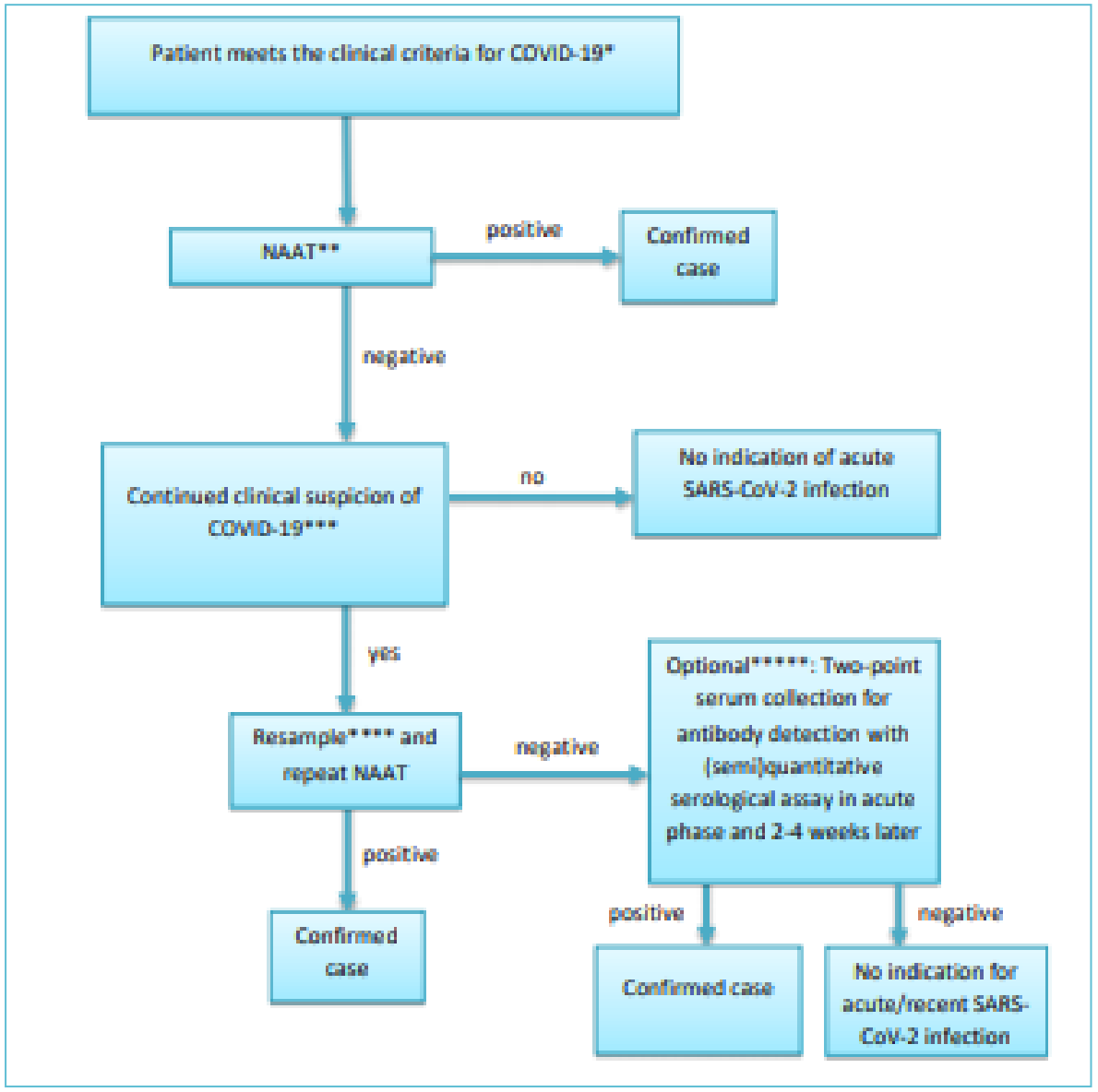


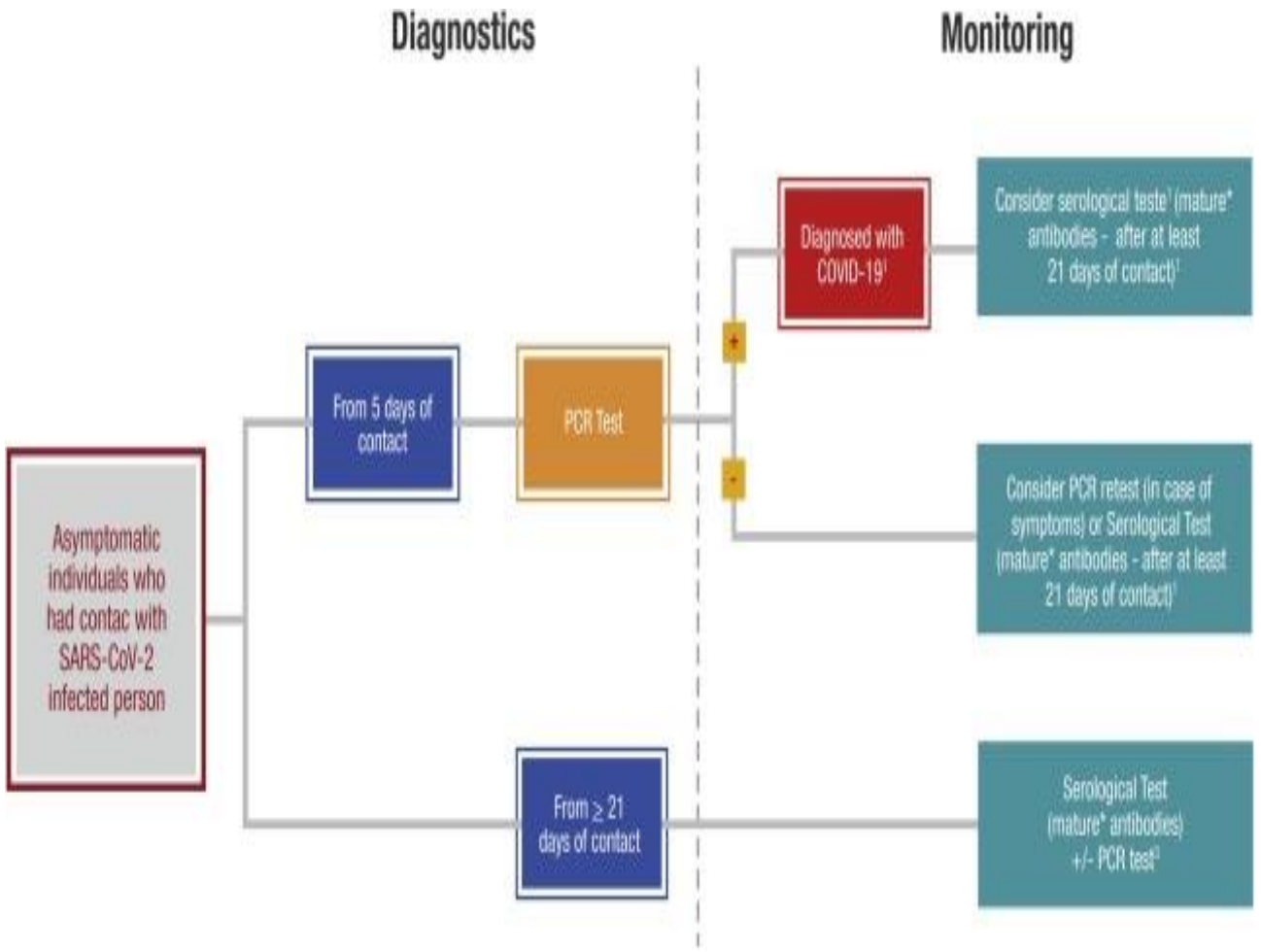
RT-qPCR



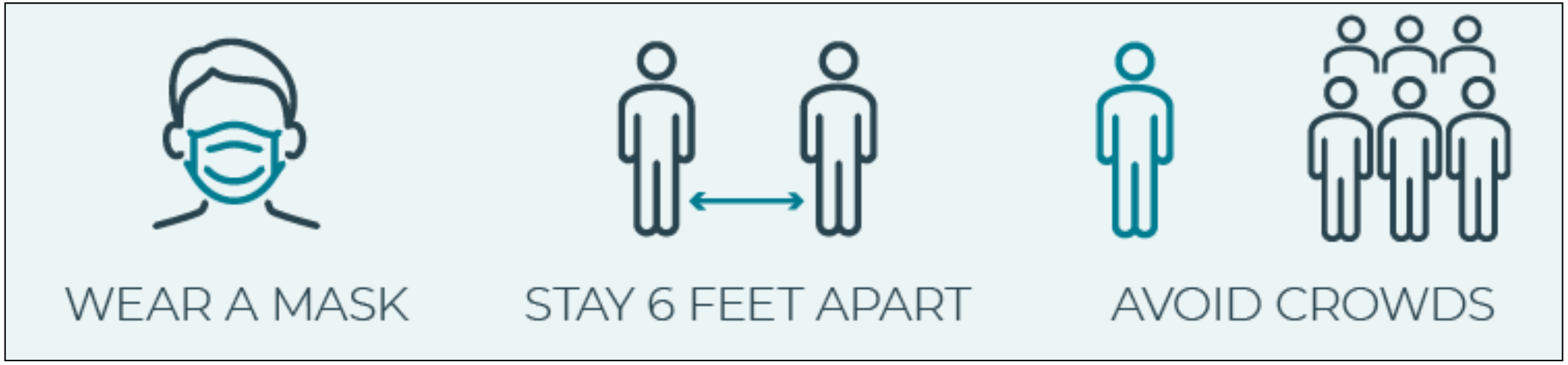
Immunoassays

Diagnostic Diagram For The Detection Of Acute Sars-cov-2 Infection In Individuals With Clinical Suspicion For COVID-19 & Asymptomatic one





Preventive Measures



- Personal protective equipment (PPE): wearing of face masks, respiratory etiquette, hand and environmental hygiene are a vital elements
- Distace:2 meters
- Avoid crowdness

	Pfizer-BioNTech	Moderna	Janssen
Vaccine type	mRNA	mRNA	Replication-incompetent adenovirus type 26 vector
Authorized age groups	≥16 years	≥18 years	≥18 years
Dose	30 µg	100 µg	5×1010 viral particles
Dose volume	0.3 ml	0.5 ml	0.5 ml
Number of doses in series	2	2	1
Interval between doses	3 weeks (21 days)	1 month (28 days)	N/A

Pfizer-BioNTech vaccine	Moderna vaccine	Janssen
✓ Needs to be stored at -70° C (-94F)	✓ Needs to be stored at -20° C (-4F)	✓ Fridge (2-8 oC)
✓ Injection site pain , redness & swelling ✓ Tiredness, Headache, Muscle pain, Joint pain, ✓ Chills, Fever, Swollen lymph nodes ✓ Bell's palsy (4 cases) ✓ Nausea, Feeling unwell, ✓ Severe allergic reactions (6 cases).	✓ Injection site pain, ✓ Fatigue, Headache, Muscle pain, Joint pain , ✓ Chills, Swollen lymph nodes ✓ Bell's palsy (3 cases).	✓ Pain or tenderness at injection sites ✓ Redness ✓ Swelling ✓ Fever ✓ Fatique ✓ Headache and muscle pain
Food & Drug adminstration approval 11 Dec. 2020	Food and Drug Administration approval On December 18, 2020	Food and Drug Administration approval On February 27, 2021

Oxford University-AstraZeneca vaccine	Sinovac & Sino-pharm Vaccine	Sputnik vaccine
✓ Two doses 4-12wks apart	✓ Two doses 3 weeks apart	✓ Two doses
✓ Suitable for peiople ≥ 18 yrs	✓ Cover people 18 to 59	✓ > 18 years
✓ Storage it does not need to be stored at very cold temperatures.	✓ Can be stored in a standard refrigerator at 2–8 °c.	✓ Fridge (at 2–8 °c).
✓ Made from a weakened version of a common cold virus from chimpanzees, that has been modified to not grow in humans.	✓ Inactivated coronavirus that cannot replicate in human cells to trigger an immune response.	✓ Adeno virus vector based plateform the technology deliver the genetic instruction of SARS COVID 2 antigens to patients cells trigerring immune response
✓ Well tolerated , a physical reaction to a medication, one case of hemolytic anemia and a three cases of transverse myelitis	✓ Local reaction: lush, swelling, scleroma, rash, and itching (common), Erythema (uncommon). ✓ Systemic headache (very common), fever, fatigue, muscle ache, joint pain, cough, difficulty breathing, nausea, diarrhea, and itchy skin, (common).	✓ Pain or , Redness and Swelling at injection sites ✓ Asthenia ✓ Body and muscle pain ✓ Fever and chills ✓ Diarrhea , nausea and vomitting ✓ Headache and runny nose

Summary Results On Sars-cov2 Vaccine Trial Efficacy

Vaccine (Company)	Preexisting Variants		
	Sample Size	Efficacy in Preventing Clinical Covid-19	Efficacy in Preventing Severe Covid-19
	no.	*% (no. of events with vaccine vs. placebo)*	
Ad26.COV2.S (Johnson & Johnson)	43,783	66 (NA)	85 (NA)
BNT162b2 (Pfizer)	34,922	95 (8 vs. 162)	90 (1 vs. 9)
mRNA-1273 (Moderna)	28,207	94 (11 vs. 185)	100 (0 vs. 30)
Sputnik V (Gamaleya)	19,866	92 (16 vs. 62)	100 (0 vs. 20)
AZD1222 (AstraZeneca)	17,177	67 (84 vs. 248)	100 (0 vs. 3)
NVX-CoV2373 (Novavax)	15,000	89 (6 vs. 56)	100 (0 vs. 1)
CoronaVac (Sinovac)¶			
Brazil	12,396	51 (NA)	100 (NA)
Turkey	7,371	91 (3 vs. 26)	NA
BBIBP-CorV (Sinopharm)	NA	79 (NA)	NA

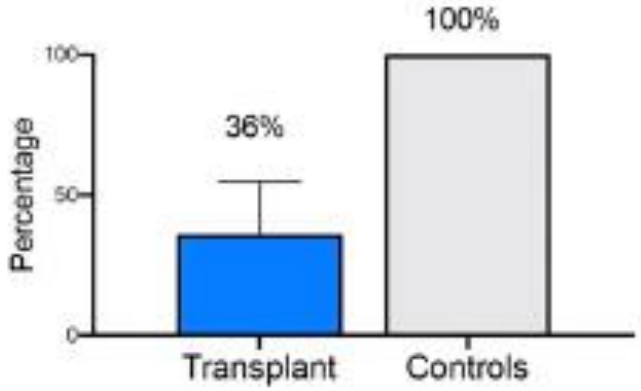
SS Abdool Karim, T de Oliveira. N Engl J Med 2021. DOI: 10.1056/NEJMc2100362

American Society Of Nephrology Recommendations Of Post Organ Donation Vaccination

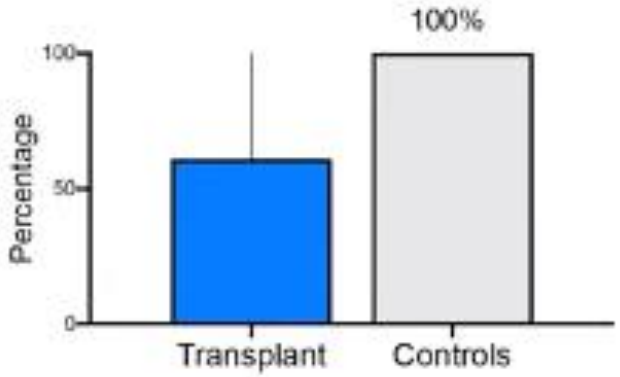
- ✓ SARS-CoV-2 vaccination in all solid organ transplant (SOT) recipients (12 years and older) is recommended.
- ✓ mRNA vaccination in SOT recipients is preferable
- ✓ Protective measures is recommended regardless of vaccination status.
- ✓ Vaccination for SARS-CoV-2 in patients who have recovered from COVID-19, after all symptoms have resolved and the period of isolation has ended are recommended
- ✓ We do not recommend routinely checking antibody responses to the vaccine.

Transplant Patients Have A Weaker Response To COVID- 19 mRNA Vaccines

- **Antibody response:**
  - After 1st dose: 2-15%
  - After 2nd dose: 6-54%

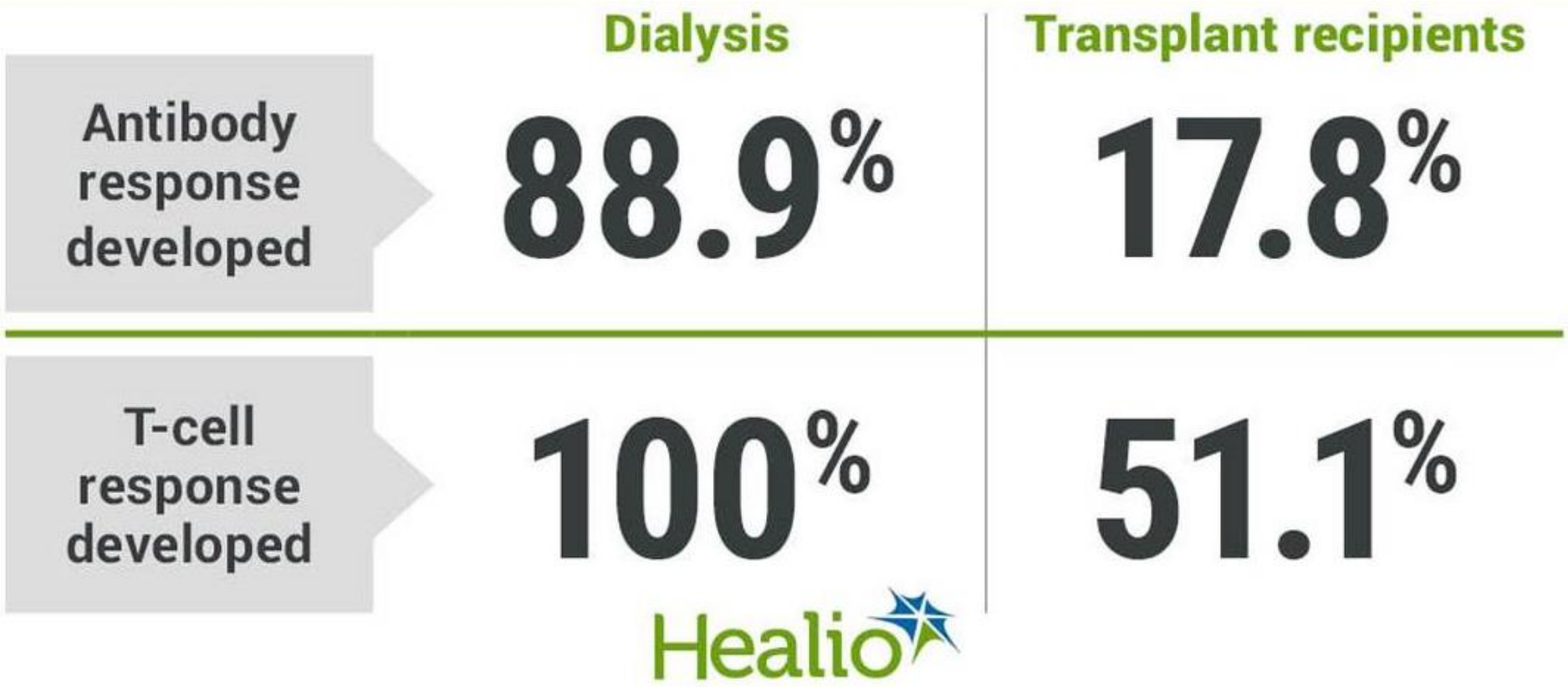


- **Cellular response:**
  - After 2nd dose: 30%-92%

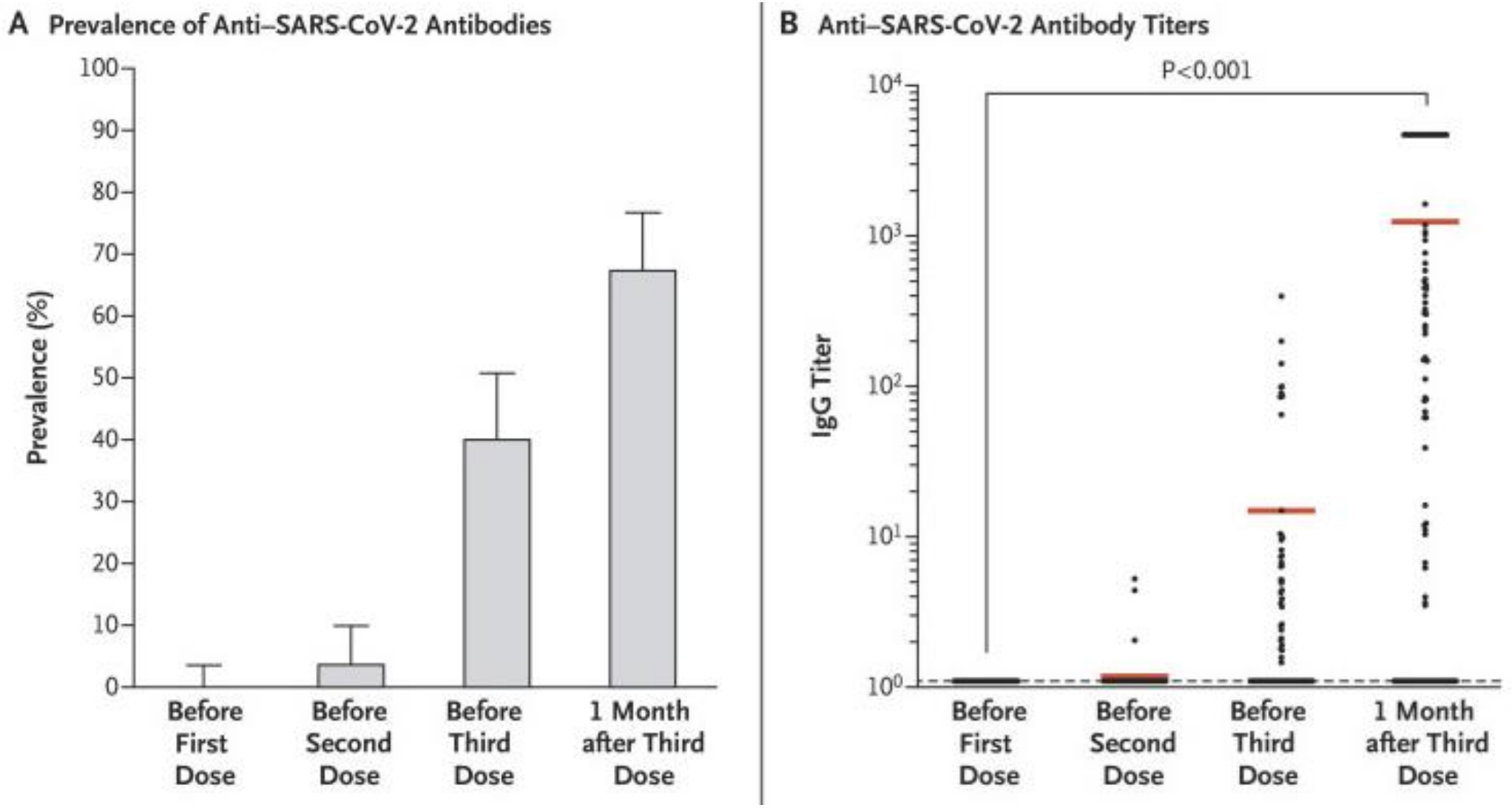


Sattler et al. *MedRxiv*. 2021
Chavarot et al. *Transplantation*. 2021
Benotmane et al. *Kidney Int*. 2021
Boyarsky et al. *JAMA*. 2021

Vaccine From Pfizer- Biontech Leads To Varying Protection For Patients With Kidney Failure



Prevalence Of COVID 19 Antibodies (Panel A) And Antibodies Titre Before And After Vaccinations



American Society Of Nephrology Recommendations Of Post Organ Donation Vaccination

- ✓ For pre-transplant patients, vaccination completion at least 2 weeks prior to transplantation if possible.
- ✓ For post-transplant patients, administering vaccination beginning as early as 1-3 months after transplantation.
- ✓ A third dose of mRNA vaccine in patients who have received two previous doses of mRNA vaccine, as approved by the FDA.
- ✓ Routine adjustment of immunosuppressive medications prior to vaccination outside of clinical trials are not recommended.

Elevations Of Biomarkers Predicted Mortality For Transplant

Procalcitonin: greater than 0.3 mg/L

hs-troponin I/ greater than 20 ng/L

D-dimer greater than 1,500 UI/L.

Serum creatinine: greater than 150 µmol/L
CRP: greater than 50 mg/L
Procalcitonin: greater than 0.3 mg/L
hs-troponin I/ greater than 20 ng/L
D-dimer greater than 1,500 UI/L.

Caillard S, et al. *Kidney Int Rep.* 2021;doi:10.1016/j.ekir.2021.06.034

Therapeutics Currently Under Investigation

Entry to the cell	Viral replication	Host immune response
ACE receptor inhibitors	**RNA polymerase inhibitors**	Immunomodulators
Angiotensin II receptor blockers	Remdesivir	Tocilizumab
Fusion inhibitors	Ribavirin	Sarilumab
Umifenovir	Favipiravir	Adalimumab (TNF inhibitor)
Baricitinib	**Protease inhibitors**	IFN
Monoclonal antibodies	Lopinavir	Corticosteroids
	Darunavir	

BMJ 2020;371:m3862

Treatment

1-Monoclonal Antibodies : Casirivimab / Imdevimab Or Sotrovimab

2-Antiviral therapies

3-Steroids

4-Convalescent Plasma

- ✓ For ttt of hospitalized patients
- ✓ Data remain limited in transplant recipients

5-Tocilizumab or sarilumab

6-Not recommended :

- ➢ **Chloroquine And Hydroxychloroquine** by The FDA EUA
- ✓ Known side effects.
- ✓ Careful monitoring of QTc interval and drug interactions (hydroxychloroquine).
- ➢ **Colchicine And Ivermectin**

Immunosuppressant, Their Mode Of Action And Immunological Outcomes In COVID-19

Immunosuppressant class	Examples	Mode of action	Immunological outcomes in COVID-19	Reference
Corticosteroids	Dexamethasone, prednisone	Inhibition of lymphocyte gene expression	Suppressing cytokine storm prohibition of proinflammatory cytokine production, preserving the permeability and integrity of endothelium	[74]
Antimetabolites	Mycophenolic acid, azathioprine	Blocking DNA replication	Diminished immune response in vitro	[75]
Calcinurine inhibitors	Cyclosporine, tacrolimus	Inhibition of lymphocyte signalling	Selective inhibition of cytokine production and function	[57]
mTOR inhibitors	Sirolimus, everolimus	Inhibition of mammalian target of rapamycin (mTOR)	Inducing and cell cycle arrest in lymphocytes	[76]
Biologics	IL-2 inhibitors (daclizumab), IL-6 inhibitors(tocilizumab)	Act as anticytokine antibodies	Inhibiting the production of cytokines and thus alleviation of cytokine storm	[77]

doi: 10.3389/fimmu.2019.01744 (74)
doi: 10.1007/978-981-10-3332-2_18 (75)
doi: 10.3390/transplantology1020007 (57)
doi: 10.1016/j.canlet.2017.08.038 (76)
doi: 10.1002/jmv.26365 (77)

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Review

The Management of Immunosuppression in Kidney Transplant Recipients with COVID-19 Disease: An Update and Systematic Review of the Literature

Roberta Angelico [1,†], Francesca Blasi [1,†], Tommaso Maria Manzia [1,*], Luca Toti [1], Giuseppe Tisone [1] and Roberto Cacciola [1,2]

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Case Reports Of Kidney Transplant Recipients Infected With Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-cov-2) Included In The Analysis

Authors	Region/Country	N° pts	Type of Study	IS Modifications	Outcomes	HD Necessity	Graft Loss
[11] **Akdur et al.**	Ankara, Turkey	1	Case Report	Withdrawal (AD+Tac)	Alive	No	No
[12] **Allam et al.**	Fort Worth, TX, USA	1	Case Report	AD withdrawal, Tac reduction	Alive	No	No
[13] **Bartiromo et al.**	Florence, Italy	1	Case Report	Tac withdrawal	Alive	No	No
[14] **Billah et al.**	New York, NT, USA	1	Case Report	Tac reduction (AD stable)	Alive	Yes	Yes
[15] **Bussalino et al.**	Genova, Italy	1	Case Report	None (Tac+AD stable)	Alive	No	No
[16] **Chen et al.**	Wuhan, China	1	Case Report	Withdrawal (Tac+AD)	Alive	No	No
[17] **Cheng et al.**	Nanjiing, China	2	Case Report	Withdrawal (Tac+AD)	Alive	No	No
[18] **Chenna et al.**	Albany, NY, USA	1	Case Report	Withdrawal (Tac+AD)	Died	No	DwGF
[19] **Dahl et al**	Aarhus N, Denmark	1	Case Report	None (Tac stable)	Alive	No	No
[20] **Dirim et al.**	Istanbul, Turkey	1	Case Report	AD withdrawal, Tac reduction	Died	Yes	Yes
[21] **Fontana et al.**	Modena, Italy	1	Case Report	CyA withdrawal	Alive	No	No
[22] **Gandolfini et al.**	Parma, Italy	2	Case Report	Withdrawal (Tac+AD)	Alive (1)/ Died (1)	No	DwGF (1) No (1)
[23] Guillen et al.	Barcelona, Spain	1	Case Report	Withdrawal (Tac+mTOR)	Alive	No	No
[24] **Hasan Ahmad et al.**	Ipswich, UK	1	Case Report	Withdrawal (AD+BELAT)	Alive	No	No
[25] **Hsu et al.**	Los Angeles, CA, USA	1	Case Report	AD withdrawal, Tac stable	Alive	No	No
[26] **Huang et al.**	Fuzhou, China	1	Case Report	Withdrawal (AD)	Died	Yes	Yes
[27] **Jiang et al.**	Wuhan, China	1	Case Report	CyA Withdrawal, AD reduction	Alive	NA	NA
[28] **Kates et al.**	Seattle, WA, USA	1	Case Report	AD withdrawal, Tac reduction	Alive	No	No
[29] **Kemmner et al.**	Munich, Germany	1	Case Report	AD withdrawal, CyA introduction	Alive	No	No
[30] **Kim et al.**	Daegu, Korea	2	Case Report	Tac withdrawal (1)/Tac stable (1), AD withdrawal (2)	Alive	No	No
[31] **Kocak et al.**	Istanbul, Turkey	2	Case Report	AD withdrawal (2), Tac reduced (1)/ Tac withdrawal (1)	Alive	No	No
[32] **Kolonko et al.**	Katowice, Poland	3	Case Report	AD withdrawal (1)/AD reduction (2), Tac stable (2)/Tac reduction (1)	Died (1)/ Alive (2)	No	No (2) DwGF (1)
[33] **Kumar et al.**	Chicago, IL, USA	1	Case Report	Reduction (Tac+AD)	Alive	No	No
[34] **Lauterio et al.**	Milan, Italy	1	Case Report	Withdrawal (CyA+mTORi)	Alive	No	No
[35] **Li.Q**	Peking, China	2	Case Report	CyA withdrawal (1) Tac withdrawal (1), AD withdrawal (1)	Died (1)	No	Worsening (1)
[36] **Ma et al.**	Hong Kong	1	Case Report	Tac withdrawal, AD reduction	Alive	No	No
[37] **Machado et al.**	Sao Paulo, Brazil	1	Case Report	Withdrawal (Tac+AD)	Alive	No	No
[38] **Man et al.**	Wuhan, China	1	Case Report	Withdrawal (Tac+AD)	Alive	No	No
[39] **Marx et al.**	Strasbourg, France	1	Case Report	Withdrawal (AD+BELAC)	Alive	No	No
[40] **Meziyerh et al.**	Leiden, the Netherlands	1	Case Report	Withdrawal (mTORi)	Alive	No	Worsening
[41] **Namazee et al.**	Semnan, Iran	1	Case Report	Withdrawal (CyA+AD)	Died	No	Yes
[42] **Ning et al.**	Hefei, China	1	Case Report	Stable (CyA+AD)	Alive	No	No
[43] **Sakulkonkij et al.**	Lampang, Thailand	1	Case Report	Tac reduction, AD withdrawal	Alive	No	No
[44] **Seminari et al.**	Pavia, Italy	1	Case Report	Stable (Tac+AD)	Alive	No	No
[45] **Shingare et al.**	Mumbai, India	2	Case Report	Reduction (Tac+AD)	Alive	No	No
[46] **Sj Antony et al.**	El Paso, TX, USA	1	Case Report	Withdrawal (Tac+AD)	Alive	No	No
[47] **Suwanwongse et al.**	New York, NY, USA	1	Case Report	Tac withdrawal, AD stable	Died	Yes	Yes
[48] **Tanaka et al**	Osaka, Japan	1	Case Report	Tac stable, AD withdrawal, mTORi withdrawal	Alive	No	No
[49] **Tantisattamo et al.**	Orange, CA, USA	1	Case Report	AD withdrawal, Tac stable	Alive	No	No
[50] **Thammathiwat et al.**	Bangkok, Thailand	1	Case Report	Withdrawal (Tac+AD)	Alive	No	No
[51] **Tzukert T. et al.**	Jerusalem, Israel	2	Case Report	Tac stable (2), AD withdrawal (1)/AD stable (1)	Alive	No	No
[52] **Velioglu et al.**	Istanbul, Turkey	1	Case Report	AD withdrawal, Tac stable	Alive	No	No
[53] **Wang et al.**	Zhengzhou, China	1	Case Report	Stable (CyA+AD)	Alive	No	No
[54] **Wang et al.**	Stanford, CA, USA	2	Case Report	Tac stable (2), AD withdrawal (2)	Alive	No	No
[55] **Xu et al.**	Ottawa, Canada	1	Case Report	Tac withdrawal, AD stable	Alive	No	No
[56] **Zhong et al.**	Wuhan, China	1	Case Report	Reduction (Tac+AD)	Alive	No	No
[57] **Zhu et al.**	Wuhan, China	1	Case Report	Tac reduction, AD withdrawal	Alive	No	No
[58] **Zhu et al.**	Wuhan, China	1	Case Report	Tac withdrawal, AD withdrawal	Alive	No	No

Abbreviations: AD = antimetabolite drug, BELAT = belatacept, CyA = cyclosporine A, DwGF = death with graft functioning, IS = immunosuppressive, mTORi = mammalian target of rapamycin inhibitors, n = number, NA = not available, pts = patients, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, Tac = tacrolimus.

Case Series And Prospective Studies Of Kidney Transplant Recipients Infected With Sars-cov-2 Included In The Analysis.

Authors	Region/Country	N° pts	Type of Study	IS Modifications	Mortality Rate (%)	HD Necessity (%)	Graft Loss (%)	DwFG (%)
[59] **Akalin et al.**	Bronx, NY, USA	36	Case series	AD withdrawal (24)/stable (7), Tac withdrawal (6)/stable (29)	27.7%	NA	NA	NA
[60] **Alberici et al.**	Brescia, Italy	20	Case series	IS Withdrawal [Tac (19), AD (14), mTOR (2)]	25%	5%	25%	20%
[61] **Banerjee et al.**	London, UK.	7	Case series	AD withdrawal (5)/stable (2), Tac stable (4)/reduction (1)/withdrawal (1)	14.3%	42.9%	42.9%	–
[62] **Bosch et al.**	Munich, Germany	3	Case series	AD withdrawal (3), Tac withdrawal (1), Cya started (2)	33.3%	33.3%	33.3%	–
[63] **Chen et al.**	Brooklyn, NY, USA	30	Case series	AD Withdrawal (12), Tac withdrawal (26), CyA withdrawal (3)	20%	13.3%	20%	6.7%
[64] **Columbia University**	New York, NY, USA	15	Case series	AD withdrawal (12), Tac stable (11)/reduction (2)/withdrawal (1)	6.7%	13.3%	13.3%	–
[65] **Crespo et al.**	Barcelona, Spain	16	Case series	AD withdrawal (8), mTORi withdrawal (4)/stable (1), Tac withdrawal (8)/stable (6)	50%	18.8%	18.8%	–
[66] **Devresse et al.**	Brussels, Belgium	22	Case series	AD withdrawal (18)/stable (1), Tac reduction (9)/stable (1), CyA withdrawal (2)/stable (3), mTORi withdrawal (1)/reduction (2)	9.1%	–	9.1%	9.1%
[67] Elias et al.	Paris, France	66	Prospective study	AD withdrawal (39)/stable (22), Tac withdrawal (3)/stable (54), BELAT postponed (1)/regular (5)	24.2%	10.6%	24.2%	13.6%
[68] **Fernandez-Riuz et al.**	Madrid, Spain	8	Case series	AD withdrawal (5)/reduction (1), Tac reduction (6)/stable (1), mTORi withdrawal (1)	25%	NA	NA	NA
[69] **Fung et al.**	San Francisco, CA, USA	7	Case series	AD reduction (1), Tac reduction (2)	0%	14.3%	–	–
[70] **Hartzell et al.**	New York, NY, USA	18	Case series	AD withdrawal (5)/reduction (13), Tac withdrawal (1)/stable (17)	38.9%	–	38.9%	38.9%
[71] **Lubetzky et al.**	New York, NY, USA	54	Case series	AD withdrawal (24)/reduction (15), Tac reduction (17)/stable (35)	12.96%	7.4%	5.55%	NA
[72] **Maritati et al.**	Ancona, Italy	5	Case series	AD withdrawal (4), Tac withdrawal (5), mTORi withdrawal (1)	40%	20%	40%	20%
[73] **Mehta et al.**	New York, NY, USA	34	Case series	AD withdrawal (26)/reduction (6)/stable (1), Tac stable (29), Cya stable (1), mTOR stable (1)	17.6%	–	17.6%	17.6%
[74] **Mella et al.**	Turin, Italy	6	Case series	AD withdrawal (3), Tac withdrawal (6)	66.7%	33.3%	66.7%	33.3%
[75] **Monfaret et al.**	Rasht Iran	22	Case Series	CNI withdrawal (5)/reduction (13)/stable (3), AD withdrawal (21)/stable (1), mTOR withdrawal (1)	27.3%	NA	NA	NA
[76] **Nair et al.**	New York, USA	10	Case Series	Tac stable (7)/withdrawal (2), AD stable (1)/withdrawal (8), mTORi stable (1)/withdrawal (19)	30%	10%	30%	20%
[77] **Pierotti et al.**	Sao Paulo, Brazil	51	Case series	Tac reduction (32)/withdrawal (12), AD withdrawal (32)/stable (14), mTORi withdrawal (4), CyA withdrawal (7)	25.5%	25.5%	25.5%	–
[78] **Rodriguez-Cubillo et al.**	Madrid, Spain	29	Case series	AD withdrawal (22), Tac reduction (1)/withdrawal (15), CyA start (23)/stable (6)	20.7%	10.3%	20.7%	10.3%
[79] **Silva et al.**	Porto, Portugal	5	Case series	AD withdrawal (5), Tac reduction (3)/stable (1), Cya withdrawal (1)	20%	–	20%	20%
[80] **Trujillo et al.**	Madrid, Spain	26	Case series	AD withdrawal (13)/stable (1), Tac withdrawal (4)/stable (20), mTORi withdrawal (2)/stable (5)	23.1%	–	23.1%	23.1%
[81] **Zhu et al.**	Wuhan, China	10	Case–control study	AD withdrawal (9)/stable (1), Tac withdrawal (7)/reduction (1)/stable (2)	10%	–	–	Worsening of graft function (10%)

Abbreviations: AD = antimetabolite drug, BELAT = belatacept, CNI = calcineurin inhibitors (used when the difference between Tac and Cya was not specified), CyA = cyclosporine A, DwGF = death with graft functioning, IS = immunosuppressive, mTORi = mammalian target of rapamycin inhibitors, n = number, NA = not available, pts = patients, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, Tac = tacrolimus.

Management Of Immunosuppressive Drugs In Kidney Transplant Recipients With Coronavirus Disease 2019 (COVID-19)

The most frequently used approach for the management of IS therapy is, nowadays, the discontinuation of ADs (MMF, MPA, or azathioprine) and mTOR inhibitors in all patients. In contrast, CNIs are maintained stable, or dose-reduced, in asymptomatic or mildly symptomatic patients, while complete withdrawal of CNIs is considered in symptomatic patients. A total discontinuation of all IS drugs is commonly used only in patients with severe symptomatic COVID-19 infection requiring invasive mechanical ventilation.

Currently available data suggest that, in KT recipients with COVID-19, any modification of IS therapy should be individualized and careful monitoring of IS drugs serum levels is advisable

transplantology

MDPI

Review

SARS-CoV-2 in Kidney Transplant Recipients: A Systematic Review

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Clinical Presentation, Treatments And Outcomes Of COVID-19 In Ktx Recipients.

Study	Place	Sample Size (N) *	Clinical Presentation #	Treatments #	Immunosuppression Adjustment #	Mortality
Abreshami et al., 2020 [28]	Iran	12	fever, cough, myalgia, headache, shortness of breath, gastrointestinal symptoms	HCQ, LR, AB, Ig	Decrease in MMF/AZT, MMF and CNI	8
Akalin et al., 2020 [26]	USA	36	fever, cough, myalgia, diarrhea, shortness of breath	HCQ, AZ, TL, LL	Withdrawal of F and AMB	10
Azzi et al., 2020 [41]	USA	229	-	HCQ, AB, RD, TL, CP, AK, Ig, LL, SL, AC	Withdrawal of AMB, CNI	47
Banerjee et al., 2020 [38]	UK	7	fever, cough, diarrhea, emesis, shortness of breath	-	Withdrawal of MMF and FK	1
Caillard et al., 2021 [31]	France	273	fever, cough, diarrhea, headache, shortness of breath, loss of smell/taste	HCQ, AZ, LR, OR, TL, RD, AB, AF	Withdrawal of CNI, mTOR, AMB and BC	-
Chavarot et al., 2021 [30]	France	100	fever, cough, myalgia, diarrhea, shortness of breath, loss of smell/taste	HCQ, AZ, TL	Withdrawal of CNI, AMB and BC	26
Coll et al., 2021 [42]	Spain	375		HCQ, AZ, AK, AV	CNI, AMB and mTOR adjustments	103
Cravedi et al., 2020 [36]	USA	144	fever, myalgia, diarrhea, shortness of breath,	HCQ, AB, TL, RD, LR, DC, DR	Withdrawal of FK, MMF	46
Cucchiari et al., 2020 [33]	Spain	28	fever, cough, shortness of breath, gastrointestinal symptoms, loss of smell/taste	HCQ, AZ, LR, TL, Steroids	Withdrawal of MPA/mTOR and CNI	5
Dheir et al., 2021 [39]	Turkey	20	fever, cough, shortness of breath, myalgia, diarrhea	HCQ, FR, DX, ORCP, AB	Withdrawal of AMB, CNI, mTOR	2
Elhadedy et al., 2020 [35]	UK	8	fever, cough, shortness of breath	-	Discontinued MMF, increase/decrease in FK	No death
Elias et al., 2020 [14]	France	66	fever, cough, diarrhea, shortness of breath, loss of smell/taste	HCQ, TL, EL	Withdrawal of MMF/MPA/AZ, CNI	16
Fung et al., 2021 [43]	USA	4	fever, cough, diarrhea, fatigue, shortness of breath	HCQ, LR, TL, AB, RD, CP, Steroids	Withdrawal of MPA, FK, MPA	No death
Gandolfini et al., 2020 [24]	Italy	2	fever, myalgia, diarrhea, shortness of breath	HCQ, AB, LR, DC, RD	Withdrawal of Tac and MMF	1
Giorgakis et al., 2020 [37]	USA	4	fever, cough, loss of smell/taste, emesis, throat pain, fatigue, headache, loss of appetite, rhinorrhea	HCQ, AZ, TL	Decrease in FK, MMF, MPA, CNI	1
Kute et al., 2021 [32]	India	250	fever, cough, myalgia, fatigue, headache, emesis, diarrhea, shortness of breath, gastrointestinal symptoms, loss of smell/taste, throat pain, Z, rhinorrhea, loss of appetite, altered mental state	HCQ, AZ, FR, RD, CP, Ig	Withdrawal of and decrease in AMB, decrease in CNI and increase in PS	29
Mamode et al., 2021 [25]	UK	KTx = 121, W/L = 52	fever, cough, myalgia, fatigue, headache, emesis, diarrhea, shortness of breath,	-	-	KTx-36 W/L-12
Naeem et al., 2020 [44]	USA	3	fever, chills, fatigue, diarrhea, shortness of breath, emesis, gastrointestinal symptoms	CP, CFT, AZ, VM, PT, RD	Withdrawal of MMF, AZT	No deaths
Nair et al., 2020 [19]	USA	10	fever, cough, chills, myalgia, nasal congestion, fatigue, headache, emesis, diarrhea, shortness of breath	HCQ, AZ	Decrease in MPA, MMF and FK	3
Oto et al., 2021 [23]	Turkey	109	fever, cough, myalgia, fatigue, headache, diarrhea, shortness of breath, throat pain	HCQ, OR, LR, FR, GC, TL, AK, AP	-	14
Rinaldi et al., 2020 [27]	Italy	24 (22 KTx)	fever, cough, diarrhea, shortness of breath	HCQ, AZ, DC, TL, Steroids		4 (30 days)
Schapiro et al., 2021 [40]	USA	KTx = 80 W/L = 56	fever, cough, diarrhea, emesis, headache, fatigue, myalgia, shortness of breath,	HCQ, AZ, RD, TL, SX, CP, DY	Withdrawal of, increase or decrease in MMF	KTx = 13 W/L = 19
Shrivastava et al., 2021 [34]	USA	39	fever, cough, diarrhea, headache, altered mental state, hypoxia	HCQ, TL	Withdrawal of or decrease in AMB and CNI	9
Zhang et al., 2020 [29]	China	5	fever, cough, myalgia, fatigue	OR, AB, Ig	Decrease in GC, MMF and CNI	No deaths

KTx, kidney transplant; W/L, waiting list. TREATMENTS—AB, antibiotics; AC, anticoagulation; AF, antifungal; AK, anakinra; AP, apheresis; AV, antiretroviral; AZ, azithromycin; CFT, ceftriaxone; CP, convalescent plasma; DC, darunavir-cobicistat; DR, darunavir-ritonavir; DX, dexamethasone; DY, doxycycline; EL, eculizumab; FR, favipiravir; GC, glucocorticoids; HCQ, hydroxychloroquine; Ig, immunoglobulin; LL, leronlimab; LR, lopinavir-ritonavir; OR, oseltamivir; PT, pipperomycin; RD, remdesivir; SL, sarilumab; SX, Selinexor; TL, tocilizumab; VM, vancomycin. I\MMUNOSUPPRESSIONS—AMB, antimetabolite; AZT, azathioprine; BC, belatacept; CNI, calcinerium inhibitor; FK, tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolate acid; PS, predeminisolane. The number of KTx patients admitted to ICUs varied greatly from 20.2% of the patient

Clinical Presentation, Treatments And Outcomes Of Vaccinated COVID-19 In Ktx Recipients.

Patient	Age (Years)	Time from Tx	Vaccine	No. of Doses	Time from Vaccine (Days)	Clinical Presentation	Severity of COVID-19	Treatments	Outcomes	Reference
I.	71	192	Oxford-AstraZeneca	2	20	Fever, cough, shortness of breath	-	TF, DX, RD, MV	Died	[95]
II.	51	18	Oxford-AstraZeneca	2	13	Fever, cough, diarrhea	-	AZ, DX, CP, MV	Ventilator	[95]
III.	46	108	Oxford-AstraZeneca	2	23	Fever, cough, shortness of breath, weakness	-	AZ, DX, RD	Ventilator, dialysis dependent	[95]
IV.	67	72	Oxford-AstraZeneca	2	8	cough	-	AZ	Recovered	[95]
V.	67	72	BNT162b2	2	72	Diarrhea	Moderate	RD	Recovered	[96]
VI.	44	16	BNT162b2	2	11	Fever, cough, shortness of breath	Severe	RD, DX	Recovered	[97]
VII.	68	16	mRNA-1273	2	4	Cough, weakness	Mild	None	Recovered	[97]
VIII.	58	19	Ad26.COV2.S	2	19	Diarrhea	Mild	MAB, RD	Inpatient	[97]
IX.	72	2.5	BNT162b2	2	20	Fever, cough, diarrhea	Mild–moderate	MAB	Recovered	[97]
X.	27	11	BNT162b2	2	43	Cough	Mild	MAB	Recovered	[97]
XI.	69	18	BNT162b2	2	25	Fever, shortness of breath	Severe	RD, DX	Inpatient	[97]
XII.	71	24	mRNA-1273	2	18	Fever, diarrhea, vomiting	Severe	RD, DX, MAB, CP	Recovered	[97]
XIII.	59	47	mRNA-1273	2	36	Headache, body ache, weakness	Mild	None	Recovered	[97]
XIV.	54	48	BNT162b2	2	45	Weakness	Mild	None	Recovered	[97]
XV.	52	53	BNT162b2	2	40	Cough, body aches	Mild–moderate	MAB	Recovered	[97]
XVI.	55	83	BNT162b2	1	7	-	-	None	Recovered	[98]
XVII.	58	38	BNT162b2	1	14	-	-	None	Recovered	[98]
XVIII.	55	58	BNT162b2	1	14	-	Critical	RD, DX	Died	[98]
XIX.	60	48	BNT162b2	1	18	-	-	None	Recovered	[98]
XX.	51	5	BNT162b2	1	21	-	Critical	RD, DX, CP	Died	[98]

Patient	Age (Years)	Time from Tx	Vaccine	No. of Doses	Time from Vaccine (Days)	Clinical Presentation	Severity of COVID-19	Treatments	Outcomes	Reference
XXI.	57	49	BNT162b2	1	22	-	-	None	Recovered	[98]
XXII.	42	64	BNT162b2	1	24	-	Critical	DX, CP	Died	[98]
XXIII.	51	23	BNT162b2	2	4	-	Mild	BAM	Recovered	[98]
XXIV.	35	27	BNT162b2	2	9	-	Severe	None	Recovered	[98]
XXV.	34	13	BNT162b2	2	12	-	Mild	None	Recovered	[98]
XXVI.	34	16	BNT162b2	2	12	-	Mild	None	Recovered with elevated creatinine	[98]
XXVII.	62	246	BNT162b2	2	25	-	Critical	RD, DX, CP	Died	[98]
XXVIII.	64	25	BNT162b2	2	33	-	Severe	RD, DX, CP	Recovered	[98]
XXIX.	49	7	BNT162b2	2	35	-	Severe	DX, CP	Recovered	[98]
XXX.	65	41	BNT162b2	2	36	-	Critical	RD, DX	Died	[98]
XXXI.	26	154	BNT162b2	2	38	-	-	None	Recovered	[98]
XXXII.	40	237	BNT162b2	2	43	-	-	None	Recovered	[98]
XXXIII.	77	9	BNT162b2	2	46	-	Severe	DX	Recovered	[98]
XXXIV.	78	59	BNT162b2	2	52	-	Mild	DX	Recovered	[98]
XXXV.	72	94	BNT162b2	2	53	-	Critical	RD, DX, CP	Died	[98]
XXXVI.	68	23	BNT162b2	2	53	-	-	None	Recovered	[98]
XXXVII.	57	121	BNT162b2	2	54	-	-	None	Recovered	[98]
XXXVIII.	63	69	BNT162b2	2	73	-	Severe	-	In hospital	[98]
XXXIX.	26	250	BNT162b2	2	85	-	-	None	Recovered	[98]
XL.	70	45	BNT162b2	2	-	-	Critical	RD, CP	Died	[98]

Treatments—AZ, azithromycin; BAM, bamlanivimab; CP, convalescent plasma; DX, dexamethasone; FR, favipiravir; MAB, monoclonal antibody; MV, mechanical ventilation; RD, remdesivir; TF, tofacitinib

Conclusion

- ✓ The symptoms and the treatment of COVID-19 in KTx recipients and CKD patients are similar to the general population, the treatment is based on symptoms management and immunosuppressant are adjusted on a patient-to-patient basis, depending upon the symptoms, severity and recovery state.
- ✓ The chances of becoming infected from the virus are > patients on hemodialysis treatment> among the KTx recipients, and it is the least among the general population.
- ✓ The severity of the COVID-19 infection and mortality is highest among KTx recipients> patients on hemodialysis and is lowest in the general population.
- ✓ Vaccinations are advisable for KTx recipients, as well as for the dialysis patients.
- ✓ The ideal time for becoming vaccinated is at least 2 weeks prior to transplant surgery, and three months post-transplant if no incident of acute rejection is observed post-transplant.

AST Recommendation For The Management Of Covid-19 Renal Transplanted Patients

- ✓ Reduction of immunosuppression may be considered for infected recipients who have not had recent rejection episodes.
- ✓ Many providers have decreased or discontinued cell cycle inhibitors or reduced calcineurin inhibitor levels,
- ✓ Patients with maintenance corticosteroids have been maintained on it during therapy.
- ✓ The decision to reduce immunosuppression should be based on severity of COVID-19 disease in comparison with rejection risk.
- ✓ No comparative data regarding these interventions are available.

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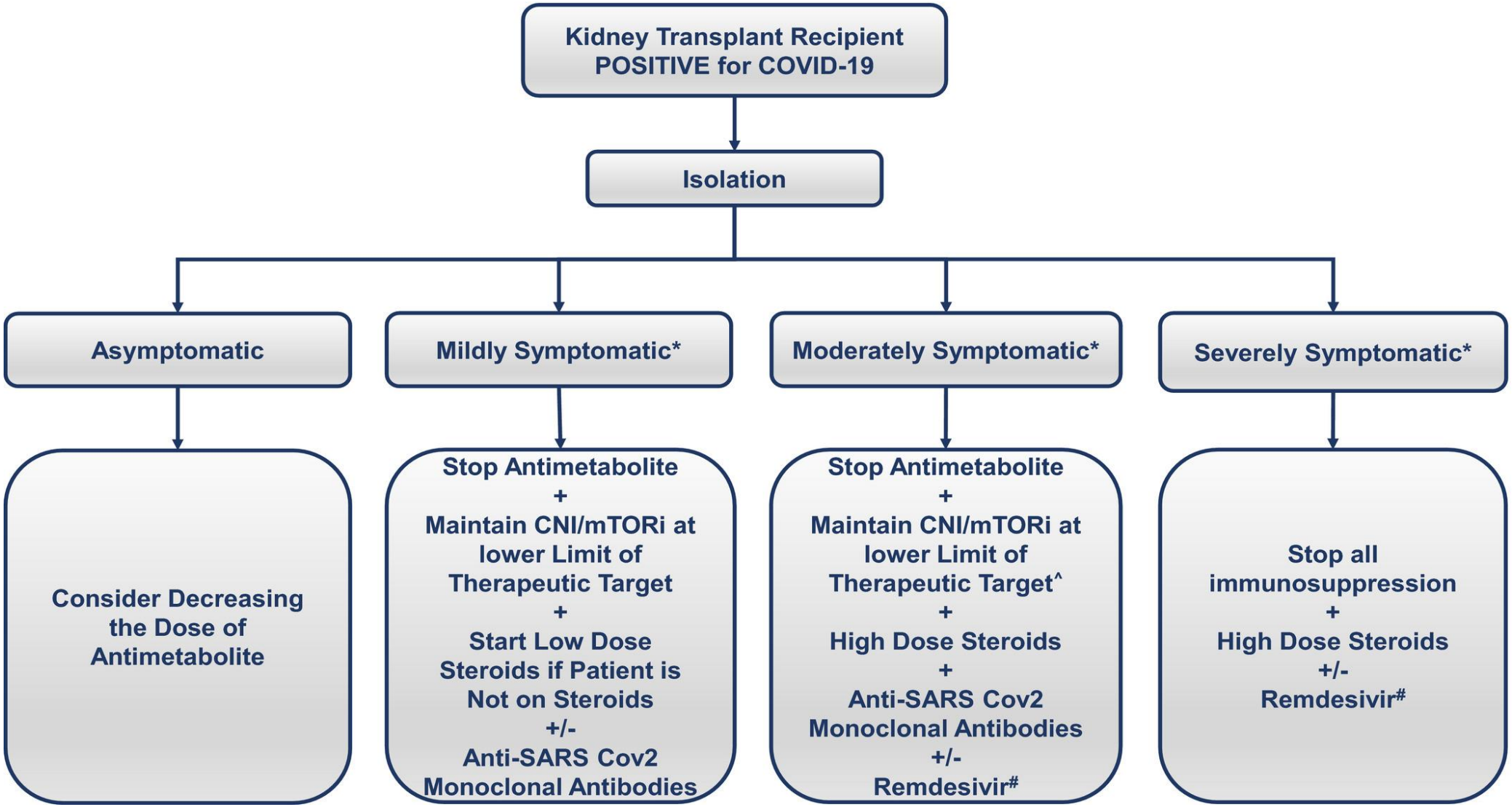
Updated: August 9, 2021

Suggested Algorithm For The Management Of The Covid-19-positive Kidney Transplant Recipient



Transplant International 2021; 34: 612–621

AST On COVID-19 And Organ Donation

- ✓ Living donors:
  - ❖ Who have been to high-risk areas
  - ❖ Or exposed to someone diagnosed or being evaluated for COVID-19 infection

Postpone donation for 14 to 28 days after returning

- ✓ Some organ procurement organizations **are testing donors for COVID-19**.
- ✓ Living donors are being asked to:
  - ❖ **Not travel to high-risk areas for at least 14 days** before donation and monitor for symptoms.

✓ The risk of acquiring COVID-19 from organ donation is low

Message

- ✓ In KT recipients with COVID-19, any modification of IS therapy should be individualized and careful monitoring of IS drugs serum levels is advisable.
- ✓ The decision to reduce immunosuppression should be based on severity of COVID-19 disease in comparison with rejection risk.
- ✓ The most frequently used approach for the management of IS therapy is, nowadays, the discontinuation of ADs (MMF, MPA, or azathioprine) and mTOR inhibitors in all patients.
- ✓ Antiviral drugs commonly used for the treatment of COVID-19 may have several drug–drug interactions, causing increased serum levels of CNIs and mTOR inhibitors, That may result in adverse reactions, which may require the suspension of IS therapy.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المعهد القومي للكلى
والمسالك البولية
Thank You

Immunosuppressant Management in Renal Transplant Patients with COVID-19

Kidney transplant patients with COVID-19	Immunosuppression management
Mild infection	(i) In case of high risk of transplant rejection, continue immunosuppressant with the minimum effective dose (ii) If possible, reduce immunosuppression by discontinuing anti-metabolite drugs (mycophenolate, azathioprine)/family of mTOR inhibitors and continue administration of prednisolone and CNI with minimal effective blood concentration (iii) In mycophenolate+ mTOR inhibitor receiving patients, replace mTOR inhibitor with CNIs
Moderate to severe infection	(i) Continue prednisolone regimen with stress dose or replace it with intravenous hydrocortisone in case of shock (ii) If possible, disconnect other immunosuppressant agents (iii) In case of high risk of transplant rejection, discontinue antimetabolite immunosuppressants (mycophenolate, azathioprine)/mTOR inhibitors and replace mTOR inhibitor to CNI with minimal effective blood concentration (iv) In lupinavir/ritonavir or atazanavir/ritonavir treaed patients, usually even with discontinuation of mTOR and CNI inhibitors, adequate blood concentration of these immunosuppressants due to the prohibition of their metabolism continues during the course of antiviral therapy

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