IN THE NAME OF GOD

Management of patients with kidney transplant During covid -19 Infection

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IUMS

GLOBAL COVID-19 GUIDANCE

- many patients had co-morbidities in the reported series, data on transplant patients is limited
- Hence a description of the disease in transplant recipients is still not available
- **strict infection prevention** practices are essential.

The NOTIFY Library has developed a compendium of guidelines relevant to transplantation (https://www.notifylibrary.org/background-documents#SARS-CoV-2).

Guidance on Coronavirus Disease 2019 (COVID-19) for Transplant Clinicians
Updated 16 March 2020
2019 Novel Coronavirus-Important Information for Clinicians. JAMA 2020.

DECEASED DONORS

- Persons who returned from **countries with >10 infected patients** or who have been exposed to a patient with **confirmed or suspected COVID-19 within 14 days should not be accepted as a donor.**

- Likewise donors with **unexplained respiratory failure leading to death should be excluded.**

- **Some** national guidelines recommend **routine testing of donors by PCR/NAT** of for SARS-CoV-2.

- While the true risk of donor-derived transmission is unclear, **RNAemia** was reported in **at least 15% in one case series.**

- There is no clear reason to suspend deceased donor transplants in countries only experiencing sporadic cases of COVID-19 cases.

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020

LIVING-RELATED TRANSPLANTS

- Living donation should not be performed on either a donor or recipient who has returned from countries **with >10 infected patients** or who have been exposed to a patient with **confirmed or suspected COVID-19 within 14 days.**

- Donors should not be utilized if they have **fever and/or respiratory symptoms** unless SARS-CoV-2 is excluded.

- If transplantation is required as a life-saving procedure, it can be conducted with appropriate assessment of infection in donor and recipient and with appropriate informed consent.

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020

TRANSPLANT RECIPIENTS

- Like all persons, transplant recipients should adhere to travel advisories issued by their respective health authorities/government bodies.

- This may necessitate postponing travel to countries with >10 infected patients.

- Recipients should avoid travel to all locations where SARS-CoV-2 is currently circulating.

- Transplant recipients should avoid all cruise ship travel.

TRANSPLANT RECIPIENTS RETURNING FROM ABROAD

Teams should follow local health department guidelines for isolating, quarantining, testing, and monitoring returned travellers from endemic areas.

Examples of such guidelines include

CDC: https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html

PHE: https://www.gov.uk/guidance/wuhan-novel-coronavirus-information-for-the-public#advice-for-travellers

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CORONAVIRUS DISEASE 2019 (COVID-19): FREQUENTLY ASKED QUESTIONS FROM TRANSPLANT CANDIDATES AND RECIPIENTS

Updated on April 6, 2020

Information regarding COVID-19 is changing rapidly. This document will be updated as able with new information. Please contact your transplant center with specific concerns. A PDF version of this information can be found here. A PDF version of this information can be found here.

Q: Are transplant recipients at higher risk for the virus?

A: We do not have specific information on whether COVID-19 infection will be **more severe** in transplant recipients compared to healthy people; however, other viruses **often** cause more severe disease in people whose immune system is low, such as transplant recipients.

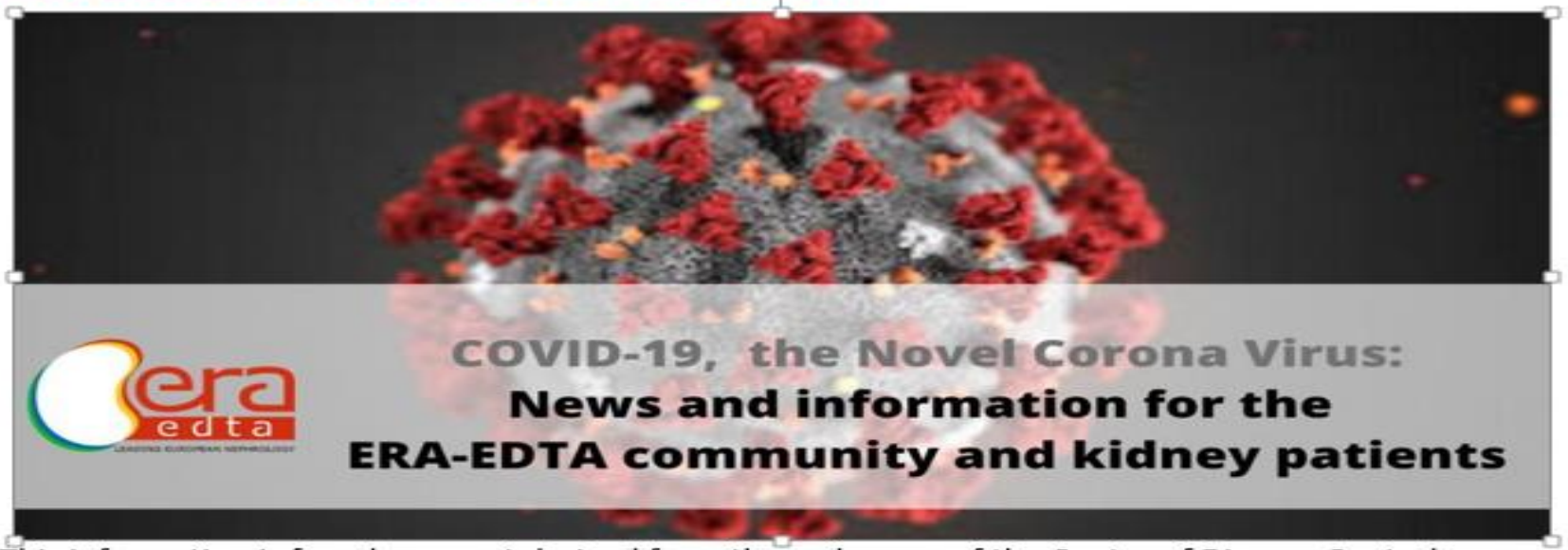
For this reason, it is **important to take precautions to prevent infection**.

Infection occurs **mostly** through close, direct contact with someone who is **carrying** the virus.

This text has been prepared by the ERA-EDTA Working Group Descartes for patients living with a kidney transplant

Patients living with a kidney transplant have the same risk to become infected as the general population.

INFORMATION FOR KIDNEY PATIENTS



This information is for a large part derived from the webpages of the Center of Disease Control (CDC). This information may change over time. Please check the CDC website therefore regularly: https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/high-risk-complications.html

General information for patients with chronic kidney disease (CKD)

General Introduction

Journal Pre-proof

Management Of Patients On Dialysis And With Kidney Transplant During SARSCOV-2 (COVID-19) Pandemic In Brescia, Italy

Federico Alberici, Elisa Delbarba, Chiara Manenti, Laura Econimo, Francesca Valerio,
Alessandra Pola, Camilla Maffei, Stefano Possenti, Simone Piva, Nicola Latronico, Emanuele Focà, Francesco Castelli, Paola Gaggia, Ezio Movilli, Sergio Bove, Fabio Malberti, Marco Farina, Martina Bracchi, Ester Maria Costantino, Nicola Bossini, Mario Gaggiotti, Francesco Scolari, on behalf of the Brescia Renal COVID Task Force

PII: S2468-0249(20)31170-0
DOI: https://doi.org/10.1016/j.ekir.2020.04.001 Reference: EKIR 943

To appear in: *Kidney International Reports*

Received Date: 2 April 2020

We will now provide preliminary outcome data on the patients directly followed in our Nephrology unit in Brescia at the 22 of March 2020, more detailed reports will follow.

As of march 22nd, among our 20 transplant patients admitted, 5 patients died, 4 were admitted to the ICU and 3 were discharged after an average of 13 days.

Journal Pre-proof

COVID-19 infection in kidney transplant recipients

Debasish Banerjee, Joyce Popoola, Sapna Shah, Irina Chis Ster, Virginia Quan, Mysore Phanish

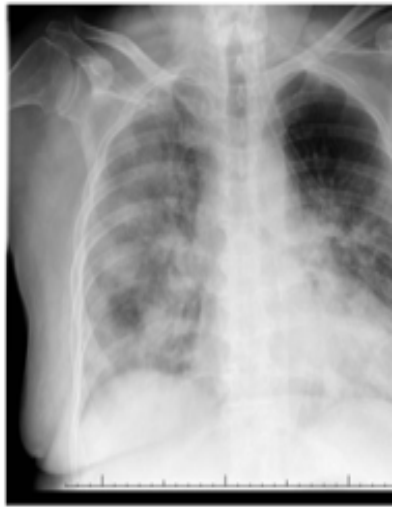
PII: S0085-2538(20)30361-6

DOI: https://doi.org/10.1016/j.kint.2020.03.018 Reference:

SARS-CoV-2 a virus similar to SARS and MERS is causing a pandemic. We report 7 cases of COVID 19 in kidney transplant recipients from South London , UK

- All presented with fever & respiratory symptoms
- 2 patients were within 3 months of transplant
- Most treated with supportive care and reduced immunosuppression
- 4 needed ITU admission, 1 died
- High D dimer, ferritin, troponin levels and lymphopenia are seen in severe cases, are likely to be of prognostic value
- Extra pulmonary involvement contributes to mortality

Case	Transplant Date	Diabetes	Immuno suppression	Outcome
48y	1989		Pred,AZA	Home
67y	03/19	Diabetes	Pred,Tac,MMF	ITU, died
54y	12/19	Diabetes	Pred,Tac,MMF	ITU
65y	08/18		Pred,Tac,MMF	ITU, ward
69y	02/20	Diabetes	Pred,Tac,MMF	ITU, ward
54y	05/13		Tac,MMF	Home
45y	09/17		Pred,Tac,Aza	Ward



Chest Xray for case 5

CONCLUSION:

COVID 19 infection in kidney transplant patients can cause severe illness, requiring ITU admission with high rate of AKI

Prompt reduction in immunosuppression is required in severe cases

Older and diabetic patients may be at higher risk

People at any age with significant immunosuppression, as defined as:

- Haematologic neoplasms: leukemias, lymphomas, myelodysplastic syndromes
- Post-transplant: solid organ, haematopoietic stem cell transplant (within 24 months or on treatment for GVHD)
- Immunocompromised due to primary or acquired immunodeficiency (including HIV infection)
- Current chemotherapy or radiotherapy
- **High-dose corticosteroids ≥20 mg of prednisone per day, or equivalent for ≥14 days**
- **All biologics and most (DMARDs) as defined as follows:**
  - ✓ Azathioprine >3.0 mg/kg/day
  - ✓ 6-Mercaptopurine >1.5 mg/kg/day
  - ✓ Methotrexate >0.4 mg/kg/week
  - ✓ Prednisone >20 mg/day. If <14 days treatment, can resume work when treatment ceased
  - ✓ Tacrolimus (any dose)
  - ✓ Cyclosporine (any dose)
  - ✓ Cyclophosphamide (any dose)
  - ✓ Mycophenolate (any dose)
  - ✓ Combination (multiple) DMARDs irrespective of dose

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Management of kidney transplant immunosuppression

Kidney transplant recipient < 60 years:

Without pulmonary infiltrates:

Maintain immunosuppressive treatment unchanged.

If you start treatment with hydroxychloroquine, **decrease tacrolimus and iMTOR** dose **by 20% of input** and then always **monitor levels every 48 hours** and maintain **tacrolimus levels: 4-6 ng/ml**

Management of kidney transplant immunosuppression…

Kidney transplant recipient < 60 years:

With pulmonary infiltrates:

- **Without hipoxemia or fever:**

Stop only MMF and **maintain tacrolimus** (levels 4-6 ng/ml) and **prednisone 20 mg daily.**

- **With hipoxemia (with need of oxigen) or fever:**

1.- **Stop tacrolimus and MMF (or iMTOR) and keep only with prednisone 20 mg daily for the first 4 days.**

2.- From the 5th day of admission, if the clinical situation improves (no fever and does not need oxygen): Restart tacrolimus[1] to maintain levels of 4-6 ng/ml associated with 20 mg prednisone.

3.- From the 5th day of admission, if the clinical situation does not improve (persists with fever or need for oxygen), maintain only with prednisone 20 mg daily. Tacrolimus[1] will be started again as in point 2 when it improves.

Management of kidney transplant immunosuppression

Kidney transplant recipient > 60 years:

Without pulmonary infiltrates:

Stop MMF and maintain tacrolimus (levels 4-6 ng/ml) and prednisone (**usual dose, do not increase to 20 mg**)

Kidney transplant recipient > 60 years:

With pulmonary infiltrates:

❑ **Without hipoxemia or fever:**

1.- Stop MMF, decrease tacrolimus for levels 3-5 ng/ml and maintain prednisone (**usual dose, do not increase to 20 mg)**

❑ **With hipoxemia (need for oxygen) or fever**:

1.- **Stop tacrolimus and MMF (or i MTOR) and keep only with prednisone 20 mg daily for the first 4 dyas**

2.- From the 5th day, if the clinical situation improves (no fever and does not need oxygen): Restart tacrolimus[1] to maintain levels of 3-5 ng/ml associated with predniosne 20 mg daily

3.- From the 5th day, if the clinical situation does not improve, maintain only with prednisone 20 mg daily. Tacrolimus will be started again as in point 2 when it improves.

Italy protocol for patients with kidney transplant

Practitioner Hospital

University of Brescia

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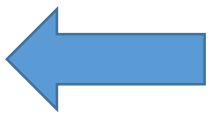
2. Asymptomatic/paucisymptomatic transplant patients (with mild symptoms: fever >37.5°C but <38°C, cough, cold WITHOUT dyspnoea) and negative chest X-ray

Hospitalization or home management, to be clinically decided on a case-by-case basis. Daily monitoring when at home, of fever and O2 saturation (if possible) with daily telephone visit by the transplant centre.

Immunosuppressive therapy:

- Stop MMF or azathioprine
- Stop calcineurin inhibitor 
- Glucocorticoids: initiation of methylprednisolone 16 mg

NOTE: If progression is favourable, the timing of and methods for immunosuppressive therapy resumption are not yet clear and should be evaluated by carefully weighing the benefit-risk ratio in the individual patient.
Our proposed approach is to resume the calcineurin inhibitor at half of the previous dosage, starting at least 15 days after disappearance of symptoms and swab negativization, with the aim of gradually reaching a blood level of 3-5 ng/ml of tacrolimus and 200-300 ng/ml of cyclosporine at the second hour.
Further increase in the calcineurin inhibitor dosage should be considered after at least another 15 days with no symptoms and an additional negative swab. In the calcineurin inhibitor re-titration period, it is recommended to maintain the dose of methylprednisolone at 8-16 mg/day, based on clinical judgement.
Case-by-case evaluation of subsequent re-initiation of MMF, azathioprine and m-TOR inhibitors.

Antiviral therapy (duration: 5-20 days to be determined based on clinical progression)*

4. Transplanted patients with severe symptoms (fever >38°C, cough, dyspnoea) and/or positive chest X-ray

Hospitalization

Immunosuppressive therapy:

- Stop MMF or azathioprine
- Stop calcineurin inhibitor
- Glucocorticoids: initiation of methylprednisolone 16 mg

Antiviral therapy (duration: 5-20 days to be determined based on clinical progression)*

[1]Università degli Studi di Brescia, Dipartimento di Specialità Medico-Chirurgiche, Scienze Radiologiche e Sanità Pubblica, Brescia, Italy

prophylaxis

Kidney transplant patient who has been contact with a positive coronavirus patient and has no symptons:

Start with hydroxychloroquine 200 mg/12 hours during 5 days.

- **Decrease tacrolimus or iMTOR dose by 20% during the 5 days and then return** to tacrolimus and iMTOR usual dose Rest of immunosuppression unchanged

Antivirals & interactions

- **Hydroxychloroquine:** 200 mg/12 hours 5-7 days: It interacts with CNI and iMTOR. Close monitoring of levels is recommended. When starting, decrease the dose of CNI and iMTOR by 20%
- **ritonavir/lopinavir** :Avoid the use of ritonavir/lopinavir with iMTOR ins . and with CNI it can be used but levels increase. Avoid its use for important side effects too.
- **Remdesevir**: can be used without interactions, but is subject to clinical trial.
- **Tocilizumab**: can be used without interactions
- **Iv Ig:** its use is not recommended

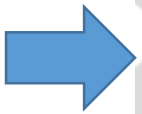
COVID-19 in Kidney Transplant Recipients

Ilaria Gandolfini, MD[1], Marco Delsante, MD[1], Enrico Fiaccadori, MD, PhD[1],
Gianluigi Zaza, MD, PhD[2], Lucio Manenti, MD[1], Anna Degli Antoni, MD[3], Licia Peruzzi, MD[4],
Leonardo V. Riella, MD, PhD[5], Paolo Cravedi, MD, PhD[6], Umberto Maggiore, MD[1]

in **extensive pneumonia, which may require intubation our current therapeutic approach includes: stopping the immunosuppressive therapy (using steroids as the only antirejection drugs) to help promote the specific anti-viral immune response.**

As the cytokine storm triggered by the coronavirus seems to be particularly responsible for morbidity of COVID-19, withdrawal of antirejection therapy can be associated with exacerbation of inflammatory response to viral infection.

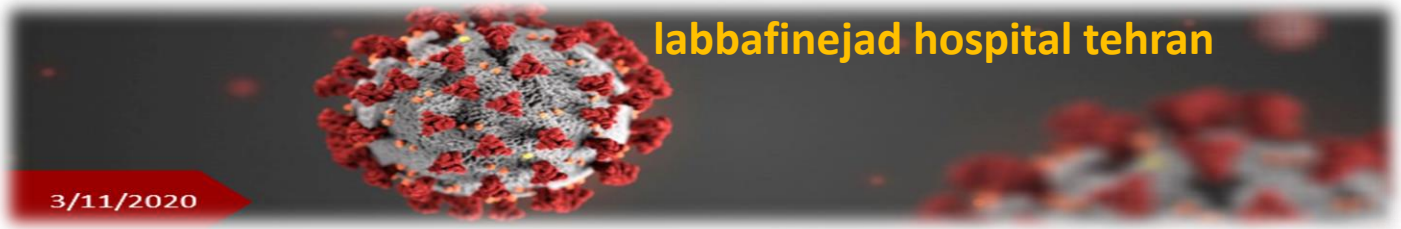
Therefore, IL-6 targeting therapies are being proposed to control ARDS; currently being tested in a randomized trial in China; ChiCTR2000029765).



In the presented kidney transplant recipients, the course of COVID-19 did not significantly differ from that of non-transplant individuals. Immunosuppression interruption combined to the anti-inflammatory effects of colchicine may have synergized with antiviral therapy and hydroxychloroquine to lower viral replication and minimize the cytokine storm triggered by SARS-CoV-2.

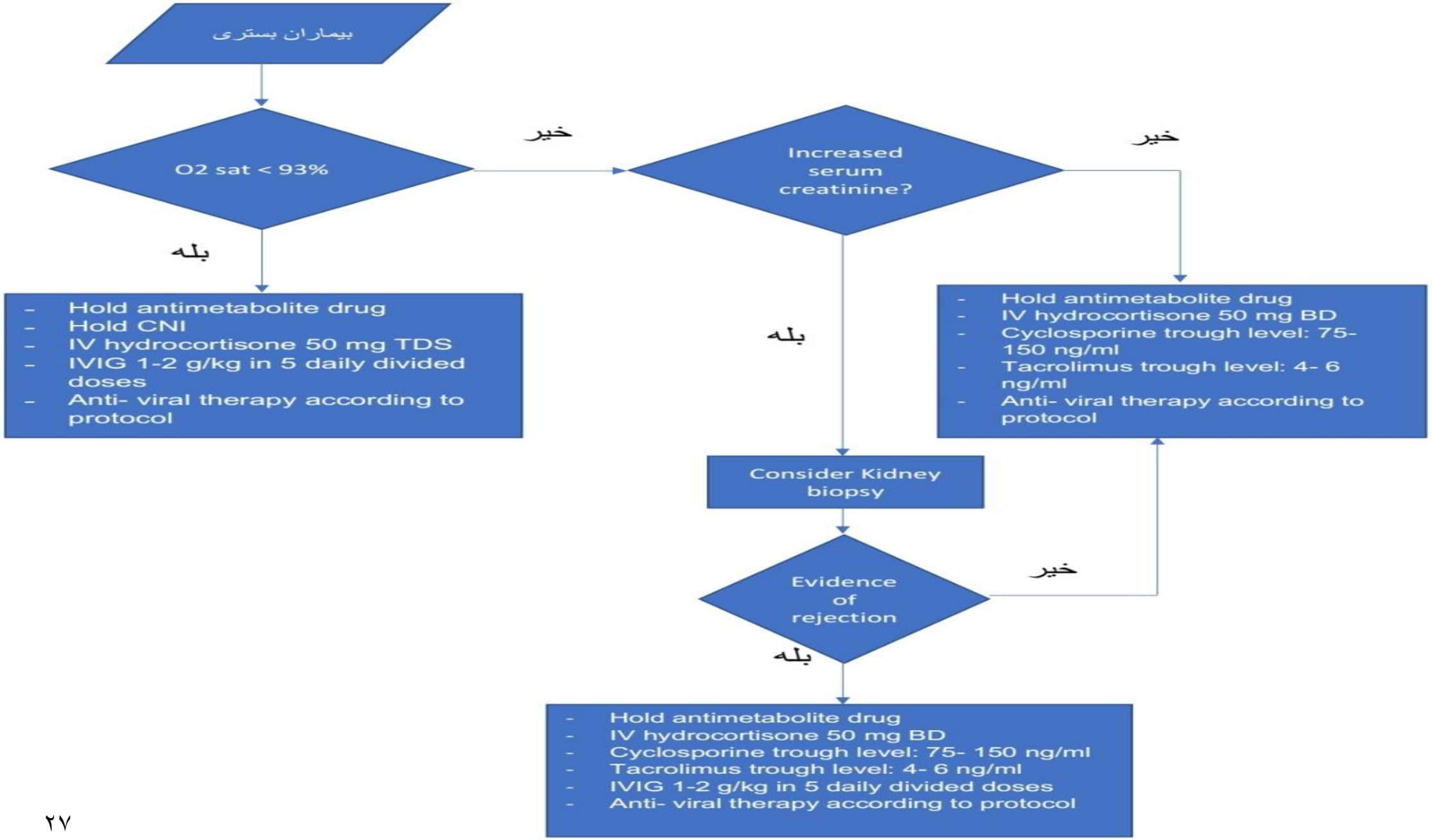
O2 saturation > 93%

- Hold antimetabolite drug
- **IV hydrocortisone 50 mg BD**
- **Cyclosporine trough level: 75- 150 ng/ml**
- **Tacrolimus trough level: 4- 6 ng/ml**
- Anti- viral therapy according to protocol
- Consider drug interaction with anti-viral treatment*
- Check drug level every other day
- Check BUN, creatinine: daily
- Check FBS, Na, K, Ca, Mg, CBC & Diff, CRP: every other day
- CXR: on the 5th day



O2 saturation < 93%

- Hold antimetabolite drug
- **Hold CNI**
- **IV hydrocortisone 50 mg TDS**
- **IVIG 1-2 g/kg in 5 daily divided doses**
- Anti- viral therapy according to protocol
- Consider drug interaction with anti-viral treatment*
- Check drug level every other day
- Check BUN, creatinine: daily
- Check FBS, Na, K, Ca, Mg, CBC & Diff, CRP: every other day - CXR: on the 5th day
- Check Procalcitonin, PPD or IGRA, IL-6


بیماران بستری
O2 sat < 93%
بله
خیر
- Hold antimetabolite drug
- Hold CNI
- IV hydrocortisone 50 mg TDS
- IVIG 1-2 g/kg in 5 daily divided doses
- Anti- viral therapy according to protocol
Increased serum creatinine?
بله
خیر
- Hold antimetabolite drug
- IV hydrocortisone 50 mg BD
- Cyclosporine trough level: 75-150 ng/ml
- Tacrolimus trough level: 4- 6 ng/ml
- Anti- viral therapy according to protocol
Consider Kidney biopsy
Evidence of rejection
خیر
بله
- Hold antimetabolite drug
- IV hydrocortisone 50 mg BD
- Cyclosporine trough level: 75- 150 ng/ml
- Tacrolimus trough level: 4- 6 ng/ml
- IVIG 1-2 g/kg in 5 daily divided doses
- Anti- viral therapy according to protocol

Journal of Cellular & Molecular Anesthesia (JCMA)

Review Article

Review of Therapeutic Agents for Treatment of COVID-1

Shadi Ziaie[1, 2], Mehran Koucheck[3], MirMohammad Miri[3], Sara Salarian[3], Seyedpouzhia Shojaei[3], Mehrdad Haghighi[4], Mohammad Sistanizad[1, 3*]

Intravenous Immunoglobulin (IVIG)

At this time some guidelines stated that IVIG could be used in solid organ and BMT recipients if IgG level is less than 400 (42), COVID-19 infection characterized by heart damage (50) and because theoretically, it might suppress viremia, it's better to start at the early stage of infection

IVIG…

If it started at the right time with high dose (25 g/ day for 5 days), it shows no side effect and could effectively **block the progression of disease cascade**, and improve the outcome of covid19 infected patients (48).

Therefore, it seems that **high dose IVIG could be a choice of immunomodulatory treatment for patients with autoimmune or inflammatory disease, and for prophylaxis and treatment of severely infected immunocompromised patients**

https://www.massgeneral.org/news/coronavirus/treatmentguidances.

 High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. Open Forum Infect Dis. 2020

داروهای CNI + لوپیناویر/ریتوناویر یا آتازاناویر/ریتوناویر
تاکرولیموس (سطح هدف تاکرولیموس :ng/ml 4-6)
اگر در شروع درمان سطح تاکرولیموس در حد هدف باشد در هفته اول تاکرولیموس hold شود
اگر بیمار در بدو بستری سطح خونی کمتراز 3 ng/ml دارد، تنها یک نوبت دیگر دوز روتین خود یا یک دوز1میلی گرمی (هر کدام کمتر است) را مصرف کند و سپس تاکرولیموس در هفته اول درمان آنتی وایرال hold شود
اگر امکان گرفتن سطح وجود ندارد، در هفتهٔ اول درمان تاکرولیموس hold شود و در صورتی که درمان آنتی وایرال فوق بیش از یک هفته ادامه یافت، تنها یک تک دوز 1 میلی گرمی تاکرولیموس در ابتدای هفته دوم درمان تجویز شود.
بلافاصله بعد از قطع درمان آنتی وایرال فوق، تاکرولیوس با دوز معمول قبلی بیمار مجدد ا شروع گردد.

* بر گرفته از مالحظات فارماکوتراپی بیماران پیوند اعضاء مبتال به COVID91-نسخه دوم ۱۹ اسفند ۰۲)دکتر سیمین دشتی خویدکی، دکتر حسین خلیلی، دکتر کیهان محمدی، متخصص فارماکوتراپی(و دستورالعمل کشوری COVID-91

سایکلوسپورین (سطح هدف سایکلوسپورین :ng/ml 75-150)

اگر بیمار در بدو شروع درمان آنتی وایرال سطح خونی سیکلوسپورین در محدوده هدف یا بالاتر از هدف داشته است دوز روزانه حدود 20 ٪ یا بیشتر کاهش یابد.
اگر امکان گرفتن سطح خونی سیکلوسپورین وجود ندارد دوز سیکلوسپورین حدود 50- 20درصد با در نظر گرفتن مدت زمان گذشته از پیوند، نوع ارگان پیوندی، بیمار پیوند مجدد است یا نه، سابقه رد پیوند..) کم شود.

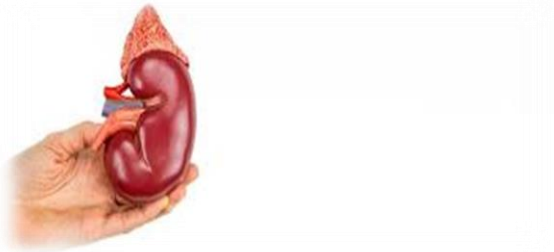
* بر گرفته از مالحظات فارماکوتراپی بیماران پیوند اعضاء مبتال به COVID91-نسخه دوم ۱۹ اسفند ۰۲)دکتر سیمین دشتی خویدکی، دکتر حسین خلیلی، دکتر کیهان محمدی، متخصص فارماکوتراپی(و دستورالعمل کشوری COVID-91

داروهای mTOR + لوپیناویر/ریتوناویر یا آتازاناویر/ریتوناویر
اورولیموس (سرتیکان)
تجویز همزمان + لوپیناویر/ریتوناویر یا آتازاناویر/ریتوناویر با اورولیموس در اکثر منابع ممنوع اعلام شده است
سیرولیموس (راپامیون) سطح هدف سیرولیموس: 4-6 ng/ml
تداخل دارویی در حد نسبتا قوی بوده و کاهش دوز 90-50 % در دوز داروی سیرولیموس نیاز است
اگر سطح خونی قبل از شروع درمان در محدوده هدف بوده است سیرولیموس با دوز قبلی بیمار ولی با افزایش فاصله تجویز به هفته ای یک بار ادامه یابد .
اگر سطح خونی سیرولیموس بیش از 6 ng/ml بوده است سیرولیموس طی دوران درمان آنتی وایرال حتی اگر دوره درمان دو هفته ای باشد hold گردد.
اگر امکان گرفتن سطح خونی سیرولیموس وجود ندارد، ایمن ترین روش این است که طی دوران تجویز ترکیب آنتی وایرال، سیرولیموس hold گردد
پایش سطح خونی به صورت هر 7 روز با شروع یا قطع داروی تداخل کننده یا هر تغییر در دوز سیرولیموس پیشنهاد می گردد.
بلافاصله بعد از قطع درمان آنتی ویرال فوق، سیرولیموس با دوز معمول قبلی بیمار مجدد ا شروع گردد.

* بر گرفته از مالحظات فارماکوتراپی بیماران پیوند اعضاء مبتال به COVID91-نسخه دوم ۱۹ اسفند ۰۲)دکتر سیمین دشتی خویدکی، دکتر حسین خلیلی، دکتر کیهان محمدی، متخصص فارماکوتراپی(و دستورالعمل کشوری COVID-91

MASSACHUSETTS GENERAL HOSPITAL

Massachusetts General Hospital
COVID-19 Treatment Guidance

Heart/Liver/Kidney Transplant Recipients 	**Guided by transplant and transplant ID teams – please call/consult** Consider decreasing tacrolimus/cyclosporine **by 50%,** stop mycophenolate (CellCept/Myfortic) and Azathioprine in kidney/liver transplant patients and reduce dose by 50% in heart transplant patients. Kidney patients approximate target **tacro level 3-5 ng/ml, cyclosporine level target 25-50 ng/ml.** In the setting of ground glass opacities can consider **switching mTor to CNI** (tacrolimus) given possibility of pneumonitis w/ mTor; discuss with heart transplant before making switch Critical illness – in liver and kidney – **stop all immunosuppression** except for **prednisone** if they are on it at baseline	Screen for drug-drug interactions with anti-viral agents, if they are being used


be healthy
be happy