In the name of God

CNI use in COVID-19

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Objects

1. **Is it necessary to withdraw CNI in COVID-19?**
2. **Can we prescribe CNI in the management of COVID-19?**

سوال

- آیا از اول اسفند ۱۳۹۸ پیوند کلیه جدید انجام داده اید؟

A. بله

B. خیر

سوال

- چه تعداد پیوند کلیه از اول اسفند ۱۳۹۸ انجام داده اید؟

A. ۱-۲

B. ۳-۴

C. ۵-۷

D. ۸-۱۰

E. بیشتر از ۱۰

The NEW ENGLAND JOURNAL of MEDICINE

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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.

Virologic & Immunologic Features of SARS-CoV-2

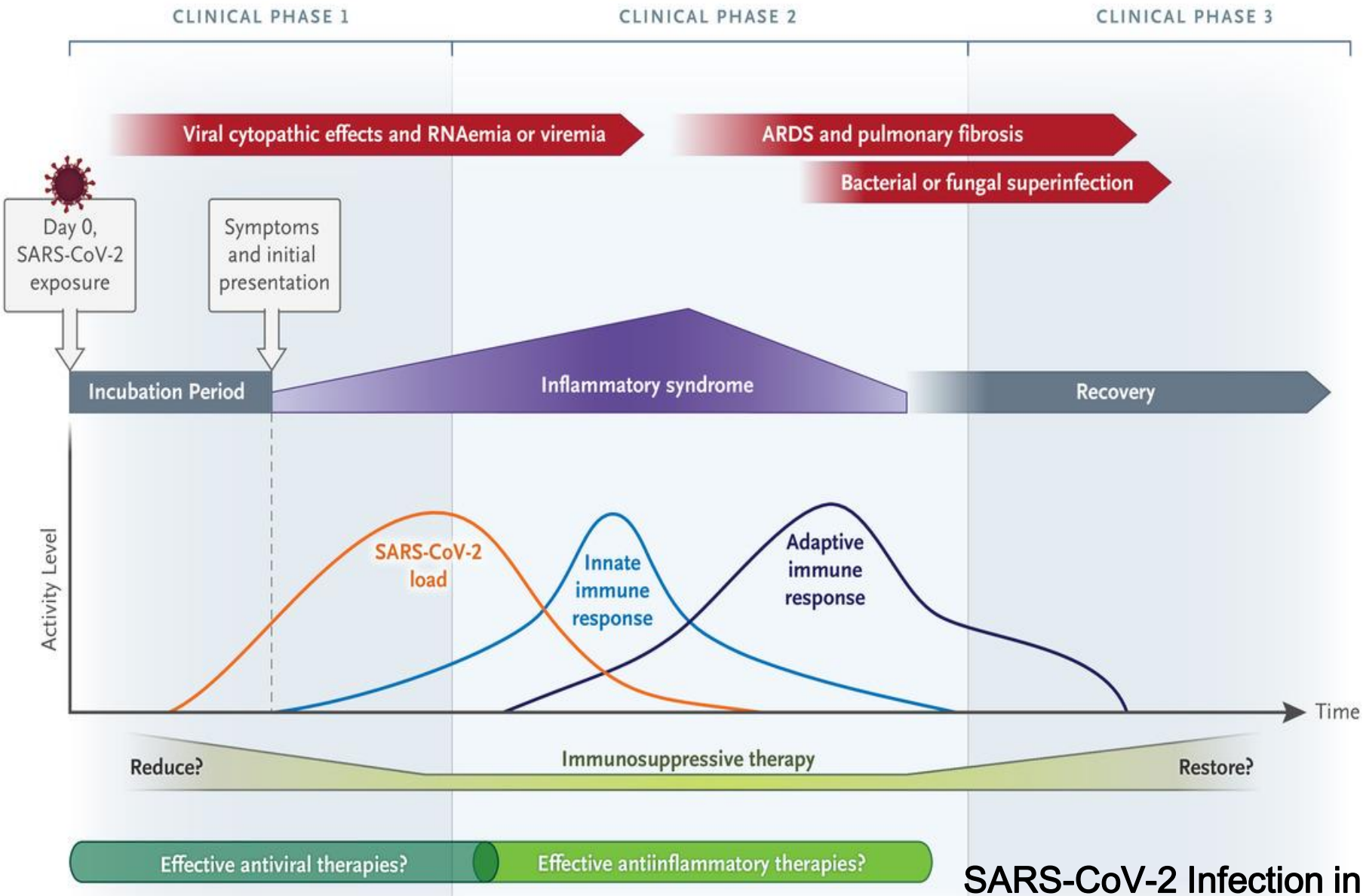
- It has a reproductive number of **2 to 4**, indicating a high level of infectivity.
- Incubation period of **3 to 5** days, after which high SARS-CoV-2 loads (several million copies) become detectable in respiratory secretions; this often occurs before symptoms are noted.
- There is little preexisting or cross-reactive virus specific adaptive immunity in the human population during the Covid-19 pandemic.

Virologic & Immunologic Features of SARS-CoV-2

- Among convalescent patients with Covid-19, neutralizing antibody titers correlate with the numbers of virus specific T cells.
- SARS-CoV-2–reactive CD4+ T cells are found in 40 to 60% of unexposed persons, suggesting some cross-reactive T-cell recognition between circulating “common cold” coronaviruses & SARS-CoV-2.

SARS-CoV-2 Infection in Organ Transplant Recipients

- In the **first phase** of illness in a SOT recipient, symptoms are typically mild, & the patient's condition remains relatively stable.
  - In some transplant recipients, abrupt clinical deterioration occurs, & of the patients who are hospitalized, **> 50%** receive intensive care.
- The **second phase** of illness appears to be driven by the development of innate & adaptive immune responses to viral infection, accompanied by a concurrent exuberant inflammatory response to infection that amplifies the viral cytopathic lung injury.



SARS-CoV-2 Infection in Organ Transplant Recipients

SARS-CoV-2 Infection in Organ Transplant Recipients

- It is not known whether the period of initial stability (the first phase) is related to exogenous immunosuppression & whether empirical reduction in immunosuppression contributes to the pathogenesis of the inflammatory processes of the second phase, as well as to graft rejection.

سوال

- در مطالعات جدید تمامی موارد زیر علائم poor prognostic برای کووید ۱۹ می باشد بجزء؟

A. elevated D-dimer

B. elevated CRP

C. low Albumin

D. elevated ESR

SARS-CoV-2 Infection in Organ Transplant Recipients

- In immunocompromised hosts, laboratory data — notably biomarkers associated with inflammation & Covid-19 — have less intrinsic value in predicting a patient's clinical course than do trends.
- Procalcitonin levels generally remain low for (< 0.5-0.8 ng/ml) the first 7 to 10 days of SARSCoV-2 infection & may subsequently rise, even in the absence of superinfection.

Mortality

- Mortality is high among symptomatic SOT recipients (10 to 28%) & intubated SOT recipients (52 to 75%).

Mortality

- This may reflect immunosuppression & the preponderance of coexisting risk factors:
  - Older age
  - Obesity
  - DM
  - CVD
  - Renal dysfunction for poor outcomes among transplant recipients.

سوال

- در مطالعات انجام شده شایعترین comorbidity در بیماران پیوند کلیه مبتلابه کووید ۱۹ کدامیک از موارد زیر بوده است؟

A. هیپرتانسیون

B. چاقی

C. دیابت ملیتوس

D. بیماری ایسکمیک قلب

IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT)

ISN 60 years

COVID-19

French nationwide registry

	Died during F/U	Died due to COVID-19	Alive on June 1, 2020
Kidney transplant candidates *ESRD patients in the national waiting list (active or inactive) alive on Feb 1, 2020* **n = 16,210**	n = 144	n = 60	n = 16,042
Kidney transplant recipients *Patients with a functioning graft alive on Feb 1, 2020* **n = 42,812**	n = 275	n = 122	n = 42,537

The excess of risk of death due to COVID-19 was similar for recipients and candidates in high viral risk area but four-fold higher for candidates in the low viral risk area

High viral risk area

>10% of emergency service admission for a suspicion of COVID-19 and/or > 80% of COVID-19 patients in ICUs

11.9 per 10^5 inhabitants

Low viral risk area

5.8 per 10^5 inhabitants

Conclusion: In case of a second epidemic wave, kidney transplantation should be suspended in high viral risk areas but maintained outside those areas, both to reduce the excess of deaths of candidates and avoid wasting precious resources.

Thaunat O, Legeia C, Anglicheau D, et al. ***IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT).*** Kidney Int.

Visual Abstract by Edgar Lerma @edgarvlermamd

COVID-19 has high mortality rate in kidney transplant recipients

French solid organ transplant registry data

kidney INTERNATIONAL | ISN 60 years

n = 279

Recipients with COVID-19

243 Hospitalized

36 At home

106 Severe COVID-19 (ICU/ Mechanical Ventilation/ Death)

43 Died

Risk factors for severe disease

	HR [95% CI]
BMI >25 Kg/m²	1.65 [1.05, 2.60]
Fever	2.01 [1.09, 3.71]
Dyspnea	2.23 [1.47, 3.39]

Risk factors for 30 day mortality

	HR [395% CI]
Age > 60 yrs	3.81 [1.56, 9.31]
Cardiovasc disease	2.04 [1.07, 3.90]
Dyspnea	2.35 [1.23, 4.49]

Conclusion: COVID-19 in KT recipients portends a high mortality rate. Risk factors for severe disease are close to that of general population.

Caillard, Sophie, et al. **An initial report from the French SOT COVID Registry suggests high mortality due to Covid-19 in recipients of kidney transplants.** Kidney International (2020).

Visual Abstract by Divya Bajpai @divyaa24

سوال

- بیمار پیوندی شما دچار COVID-19 شده در چه صورتی CNI وی را قطع می کنید؟

A. بروز اولین علائم بیماری
B. نوع متوسط
C. نوع شدید
D. نوع Critical
E. قطع نمی کنم

biology

MDPI

Review

The Antiviral Properties of Cyclosporine. Focus on Coronavirus, Hepatitis C Virus, Influenza Virus, and Human Immunodeficiency Virus Infections

Paulina Glowacka [1], Lidia Rudnicka [1,*], Olga Warszawik-Hendzel [1], Mariusz Sikora [1], Mohamad Goldust [2,3,4], Patrycja Gajda [1], Anna Stochmal [1], Leszek Blicharz [1], Adriana Rakowska [1] and Malgorzata Olszewska [1]

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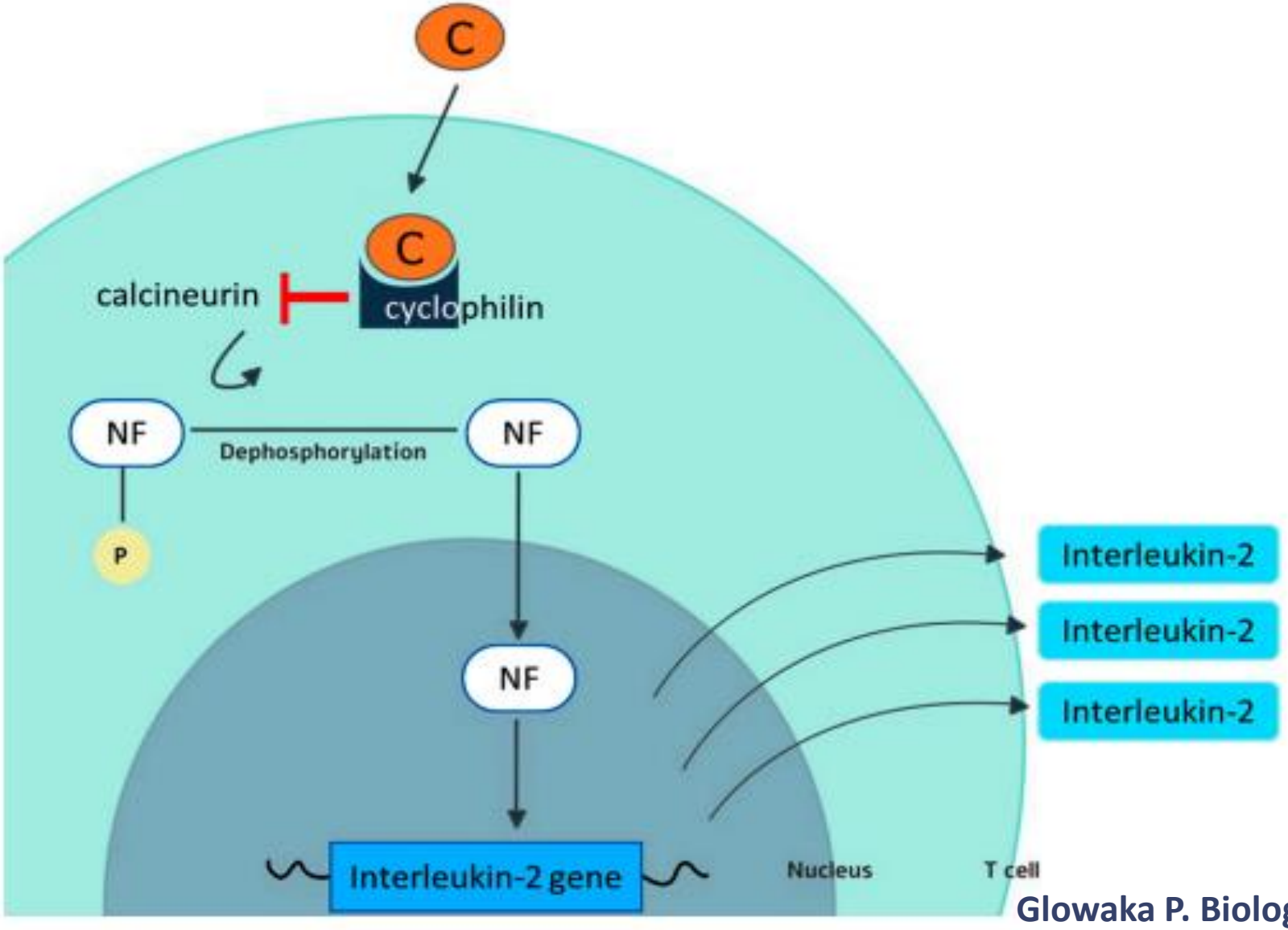
Impact of cyclosporine on the course of viral diseases in humans

- Cyclosporine is a CNI that acts selectively on **T cells**.
- It was isolated from **Tolypocladium inflatum fungi** in 1970, & now it is widely used as an IS drug in such areas of medicine as dermatology, transplantology, nephrology, rheumatology & ophthalmology.
- The main approved **indications** are psoriasis, atopic dermatitis, the prevention of graft rejection following SOT & BM transplantation, the treatment of GVHD, endogenous uveitis, Behçet uveitis, nephrotic syndrome & RA.

Tolypocladium inflatum fungi

Mechanism of action of Cyclosporine

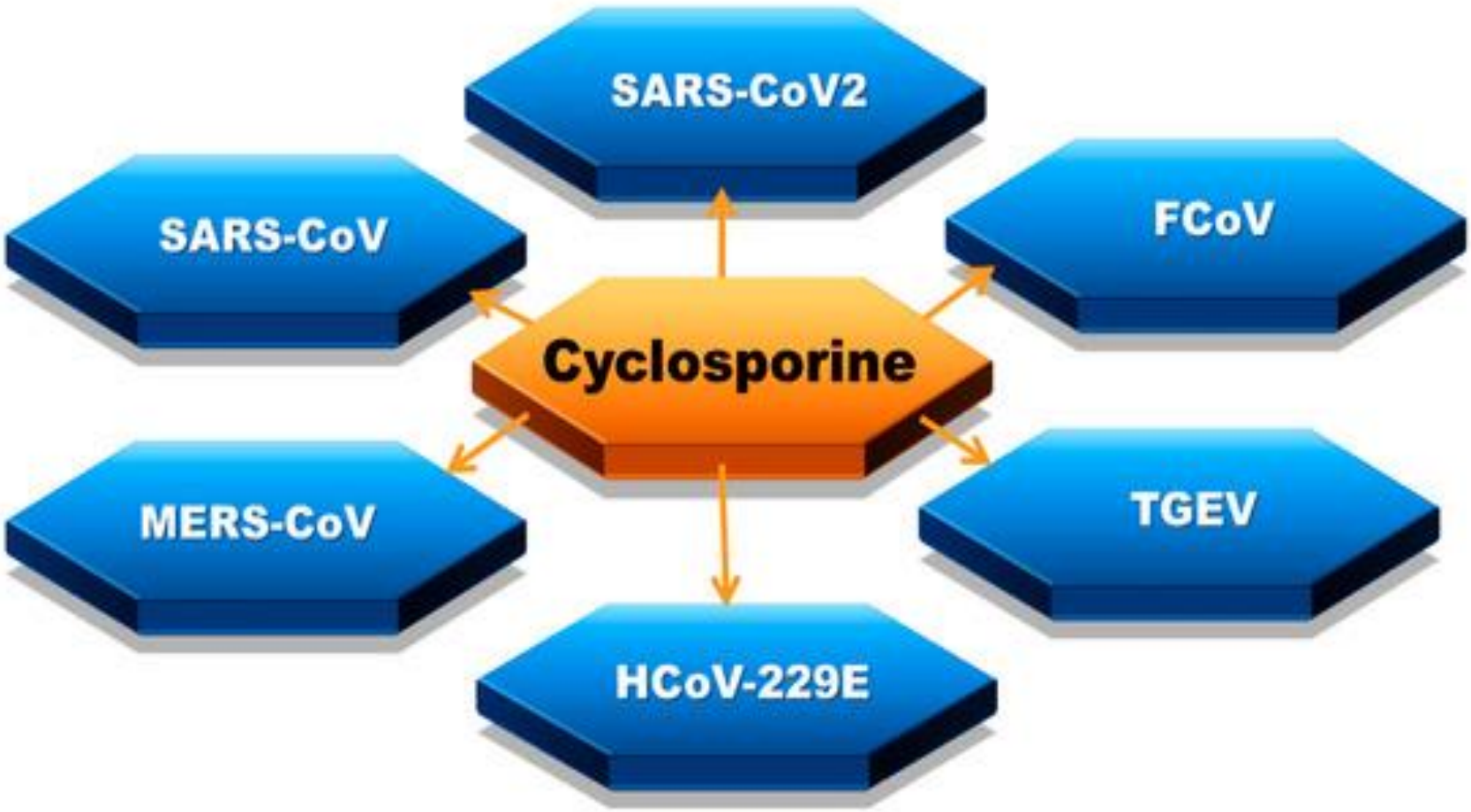


Glowaka P. Biology 2020

Cycophilins

- Cycophilins are a ubiquitously distributed protein group, belonging to the **immunophilin** family.
- Cyclophilin A is a key pathogenic player in numerous **inflammatory diseases**.
- It also is a mediator for many CVDs, & a crucial mediator in Alzheimer's disease & amyotrophic lateral sclerosis.
- The expression of cyclophilin increases during inflammatory diseases, such as psoriasis or RA.
- Cyclophilin A facilitates the **replication of several viruses** & is considered a potential target for antiviral therapy.

Coronaviruses affected by Cyclosporine



Glowaka P. Biology 2020, 9

Impact of cyclosporine on the course of viral diseases in humans

- With very limited data available, there are results that allow us to hypothesize the possible impact of cyclosporine on the course of viral diseases in humans:
  - Possible **Positive** Effect of Cyclosporine on Disease Course
    1. Hepatitis C
    2. Influenza virus infection
    3. Rotavirus infection
    4. HIV infection
    5. **Coronavirus infection**

Impact of cyclosporine on the course of viral diseases in humans

- With very limited data available, there are results that allow us to hypothesize the possible impact of cyclosporine on the course of viral diseases in humans:

- **Conflicting** Results:
  1. Hepatitis B
  2. Hepatitis D
  3. Herpes simplex infection
  4. Herpes Zoster Virus infection

Impact of cyclosporine on the course of viral diseases in humans

- With very limited data available, there are results that allow us to hypothesize the possible impact of cyclosporine on the course of viral diseases in humans:
  - Possible **Negative** Effect of Cyclosporine on Disease Course:
    1. Hepatitis E
    2. CMV infection
    3. HPV infection
    4. Human Herpesvirus-8 (Kaposi Sarcoma virus)

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AST | AMERICAN SOCIETY OF TRANSPLANTATION | ASTS

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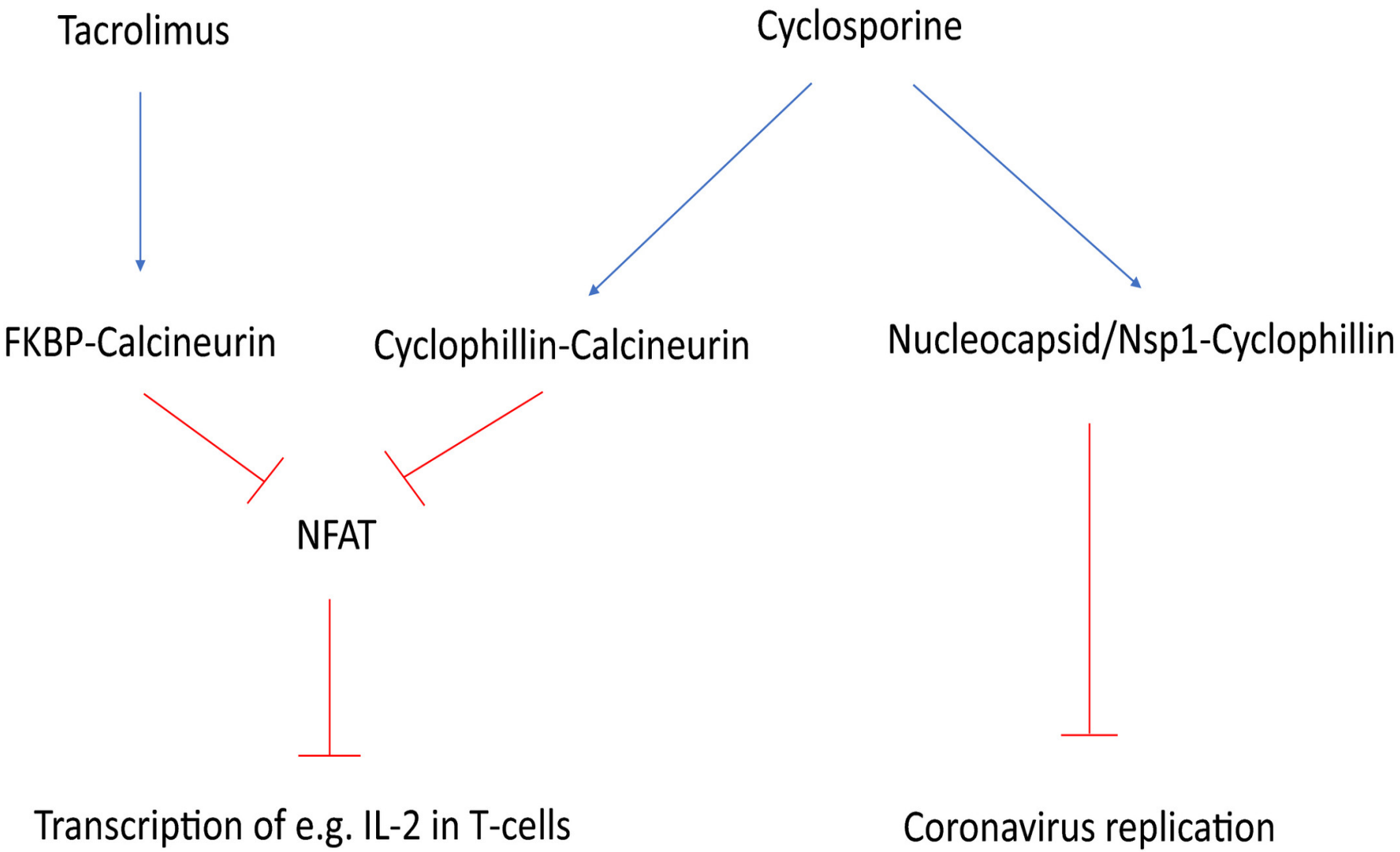
MINIREVIEW | Free Access

Cyclosporine and COVID-19: Risk or favorable?

Nadia Nicholine Poulsen, Albrecht von Brunn, Mads Hornum, Martin Blomberg Jensen

First published: 10 August 2020 | https://doi.org/10.1111/ajt.16250

Overview of the 2 most commonly used CNIs & the possible effects on COVID-19



Cyclosporine & COVID-19: Risk or favorable?

- Several independent studies have shown that coronavirus replication & growth depend on active **immunophilin** pathways.
- The immunophilin pathway is inhibited by both tacrolimus & cyclosporine.
- Cyclosporine at noncytotoxic concentrations induces a strong inhibition of the replication of several coronaviruses including SARS-CoV, MERS-CoV, & HCoV-229E **invitro**.
- Tacrolimus in low noncytotoxic concentrations inhibits the growth of numerous human coronaviruses including SARS-CoV invitro.

Alisporivir

- Several cyclosporine & tacrolimus analogs, which are pharmaceutical agents similar to either cyclosporine or tacrolimus but designed **to lack the immunosuppressive** effect, including the drug **Alisporivir,** have demonstrated potent suppressive effects on replication of multiple coronaviruses invitro such as SARS-CoV , HCoV-NL63,.. & now 2 independent studies have found that Alisporivir inhibits SARS-CoV-2 invitro.
- Alisporivir was tested **invivo** but was unable to diminish morbidity or mortality in an invivo mouse model.

Cyclosporine & COVID-19: Risk or favorable?

- The cyclosporine concentration required to inhibit virus replication **exceeds by far** the serum concentrations that typically are well below 200 ng/mL.
- This implies that the dosage used to treat most patients with cyclosporine is too low to effectively eradicate the virus.
- The main virus load is in the **airways & lungs** & not in serum & the concentration of cyclosporine in the lungs is lower than in serum.
- Moreover, the required dosage for actively treating patients with severe COVID-19 would be **3-6 fold** higher, which in turn would cause severe adverse & possible toxic effects especially nephrotoxicity.

Poulsen. AJT, 10 August 2020

Cyclosporine & COVID-19: Risk or favorable?

- The only way to reach high local tissue concentrations would be through **cyclosporine inhalation**.
- Inhaled cyclosporine has been tested in animals, healthy volunteers, & lung transplant recipients & the lung concentration of inhaled cyclosporine is **3 times** higher than when systemically administered.
- It is generally well tolerated, although a few cases of transient reduced FEV1 following inhalation have been reported.

Cyclosporine & COVID-19: Risk or favorable?

- All of these studies show that cyclosporine is **safe** to give to a broad range of **critical ill** patients
- The available data reviewed here are not sufficient to recommend replacing tacrolimus with cyclosporine during severe COVID-19.
- We do suggest that revised guidelines should recommend continuing cyclosporine to patients during COVID-19 except in cases of:
  - RF
  - Severe leucopenia
  - High serum cyclosporine levels

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BRIEF COMMUNICATION | Free Access

Should cyclosporine be useful in renal transplant recipients affected by SARS-CoV-2?

Beatriz Rodriguez-Cubillo, Maria Angeles Moreno de la Higuera, Rafael Lucena, Elena V. Franci, Maria Hurtado, Natividad C. Romero, Antolina R. Moreno ... See all authors

First published: 12 June 2020 | https://doi.org/10.1111/ajt.16141 | Citations: 12

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Pages 3173-3181

Should cyclosporine be useful in renal transplant recipients affected by SARS-CoV-2?

- We studied 29 KTRs who were admitted with COVID-19 between March 15 & April, 24, 2020.
- MMF &/or mTORi were discontinued in all patients.
- Two therapeutic strategies were compared:
  - Group 1, minimization of CNIs (N = 6).
  - Group 2, cyclosporine-based therapy (N = 23), with 15 patients switched from tacrolimus. CSA target concentration was around **50-100 ng/mL**.
- Hydroxychloroquine was considered in both strategies but antivirals in none.

Rodriguez-Cubilo, AJT Nov 2020

Should cyclosporine be useful in renal transplant recipients affected by SARS-CoV-2?

- Renal function did not deteriorate & signs of rejection were not observed in any patient on the second treatment regime.
- **In conclusion**, immunosuppressant treatment based on cyclosporine could be safe & effective for KTRs diagnosed with COVID-19.

	Total (N:29)	Group 1 (N:6)	Group 2 (N:23)	P value
Mortality (%)	**20.6**	**50**	**12.5**	**0.047**
Mechanical ventilation	**17.7**	**16.7**	**17.4**	**1**
Discharge	**79.3**	**50**	**87**	

Rodriguez-Cubilo, AJT Nov 2020

Tocilizumab, n (%)		9 (31)	2 (33.3)	7 (30.4)	1.000
IG, n (%)		8 (27.6)	3 (50)	5 (21.5)	.300
Anticoagulation, n (%)		24 (82.2)	3 (50)	21 (91.3)	.046
Outcomes					
Radiologic worsening, n (%)		19 (65.5)	5 (83)	14 (60.9)	.633
Analytical worsening, n (%)		16 (55.2)	6 (100)	10 (43.5)	.017
Ferritin max, ng/mL, m (IQR)		1226 (496-2027)	2090 (1190-3482)	923 (443-1887)	.140
LDH max, IU/l m (IQR)		713(457-981)	1167 (768-1466)	645 (448-829)	.021
AKI recovered, n (%)		10 (34.48)	0 (0)	10 (43.4)	.145
AKI with HD, n (%)		3 (10.3)	0(0)	3 (13)	.145
Oxygen requirement increase	Yes, n (%)	16 (55.2)	5 (83.3)	11 (47.8)	.119
	Day, m (IQR)	4 (2-7)	8 (3.5-5)	3.5 (5.5-10)	.006
Max oxygen requirement	Basal, n (%)	11 (37.9)	1 (16.7)	10 (43.5)	.035
	NG, n (%)	9 (31)	1 (16.7)	8 (34.8)	
IMV, n (%)		5 (17.2)	1 (16.7)	4 (17.4)	1.000
Death, n (%)		6 (20.7)	3 (50)	3 (13)	.047
Discharge, n (%)		23 (79.3)	3 (50)	20 (87)	

Abbreviations: AKI, acute kidney injury; BPS, bilateral patchy shadowing; max, maximum; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CPAP, continuous positive airway pressure; HD, hemodialysis, IG, immunoglobulins; IMV, invasive mechanical ventilation; IQR, interquartile range; m, median; NG, nasal glasses (2-3 lpm); R, reservoir (15 lpm); VM, venturimask (8-10 lpm).

Actual status (May 19, 2020). Units: D dimer (ng/mL): normal range < 500 ng/mL, ferritin (ng/mL) normal range 30-350 ng/mL, LDH, lactate dehydrogenase (UL/l), normal range 240-480 U/ l. Day, day of oxygen requirement increase from admission.

5 | CONCLUSIONS

Given that SARS-CoV-2 infection has two principal phases—

to identify the stage of the disease and prescribe specific treatment.

Among KTRs the immune system is altered by the immunosup-

SARS-CoV-2 Infection in Organ Transplant Recipients

- Most current immunosuppressive drugs target T cells, the main component of the immune system that is responsible for viral clearance.
- The potential benefit of reducing immunosuppression in a patient is associated with augmenting the antiviral response.
- It has been shown that a suboptimal T-cell response contributes to the pathological changes observed in SARS.

SARS-CoV-2 Infection in Organ Transplant Recipients

- The pathophysiological processes of SARS-CoV-2 infection involve the initiation of an uncontrolled inflammatory response, which contributes to the development of ARDS, thrombotic complications, & eventually pulmonary fibrosis.
- The use of IS agents may provide benefit by reducing inflammation & associated injury.

Summery

- In recipients of a **non-lifesaving organ** who are at risk for the rapid development of severe respiratory impairment despite ongoing maintenance IS treatment, the dose of CNIs may be reduced until clinical improvement occurs, at which time the use of other antiinflammatory agents could be considered for controlling lung injury.
- Temporary discontinuation of CNIs should be considered if the patient is receiving additional antiinflammatory & IS drugs, such as IV glucocorticoids, IL-6 receptor inhibitors (e.g., tocilizumab or sarilumab) with or without concomitant glucocorticoids, or… .

Summery

- In contrast, continuation of CNIs, even at a reduced dose, is usually recommended in recipients of **lifesaving organs** (especially organs with the highest immunogenicity, such as the heart & lungs), irrespective of the degree of severity of the viral disease & of any additional IS treatment, because of the potential life-threatening consequences of acute rejection.

Summery

- The **most controversial issue** regarding IS treatment in patients with SARS-CoV-2 infection is the appropriate management of glucocorticoids.
- In the absence of viable alternatives, the early use of higher-dose glucocorticoids can be considered in transplant recipients receiving respiratory support.
- Treatment with MMF, azathioprine, or mTORIs may be **stopped**, or the dose reduced, initially because of their unfavorable side-effect profiles.

سوال

- بیمار پیوندی شما دچار COVID-19 شده در چه صورتی CNI وی را قطع می کنید؟

A. بروز اولین علائم بیماری
B. نوع متوسط
C. نوع شدید
D. نوع Critical
E. قطع نمی کنم