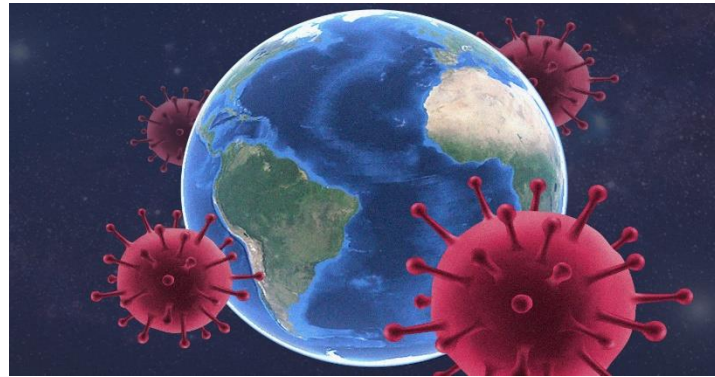
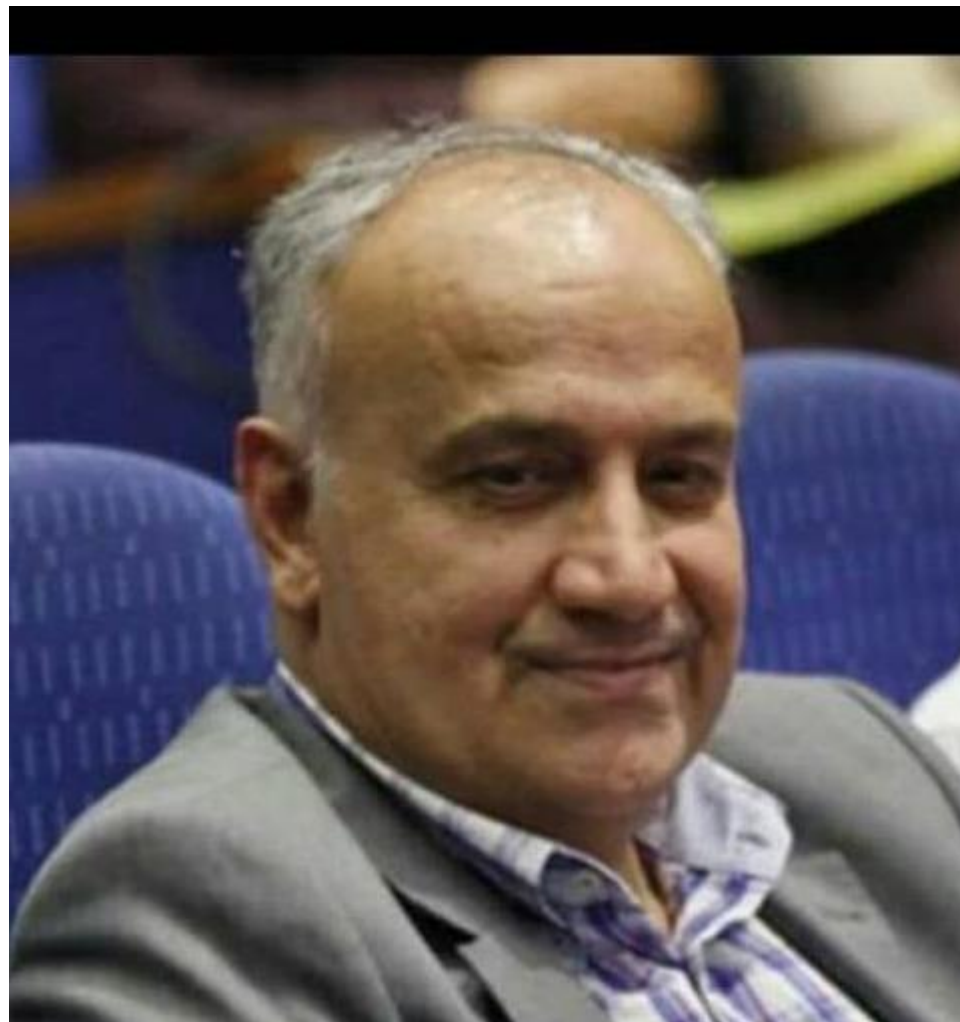


Covid-19 and kidney transplantation



***M.Hakemi, M.D.
Nephrology ward, shariati hospital
TUMS, Tehran.Iran***



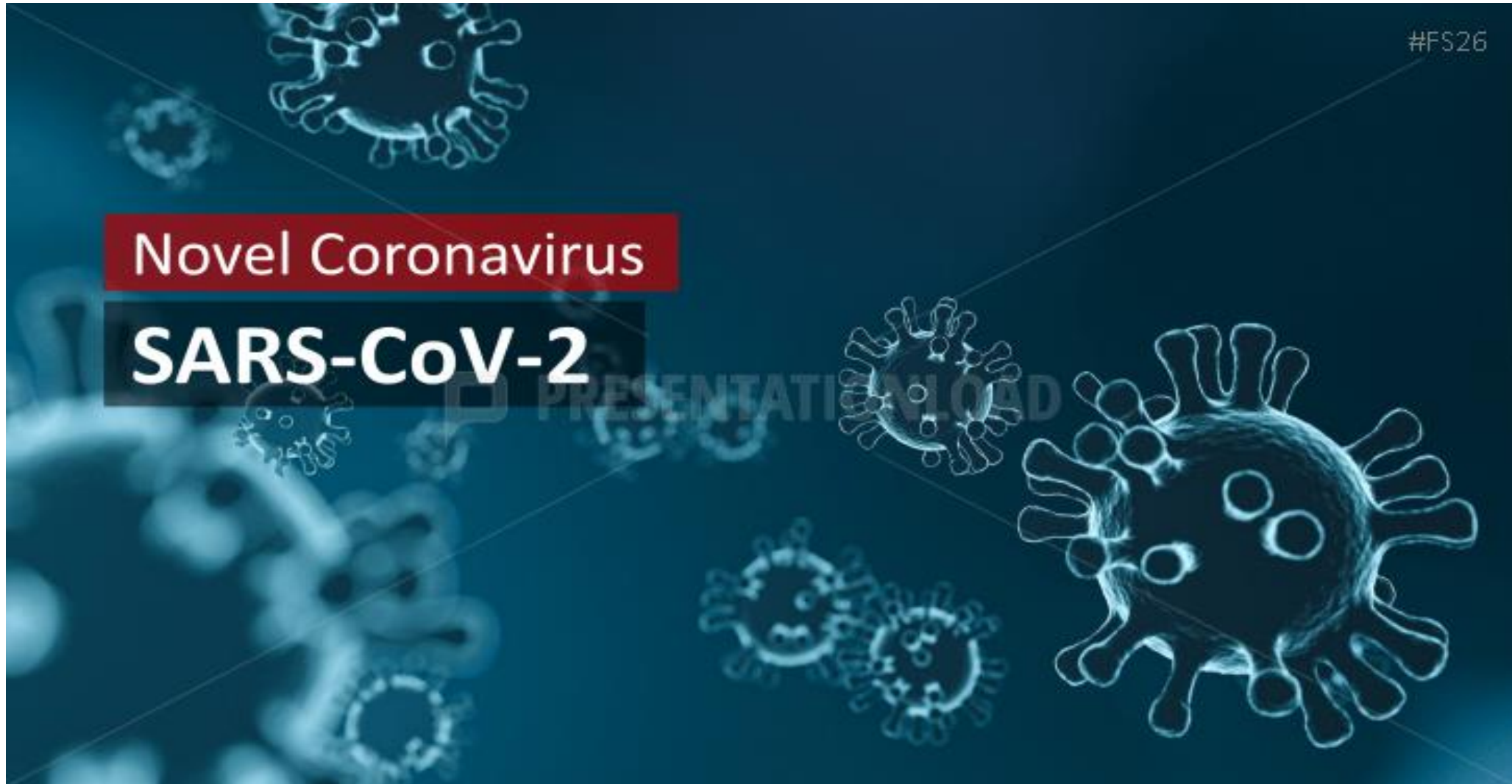
روحش شاد و در آرامش ابدی

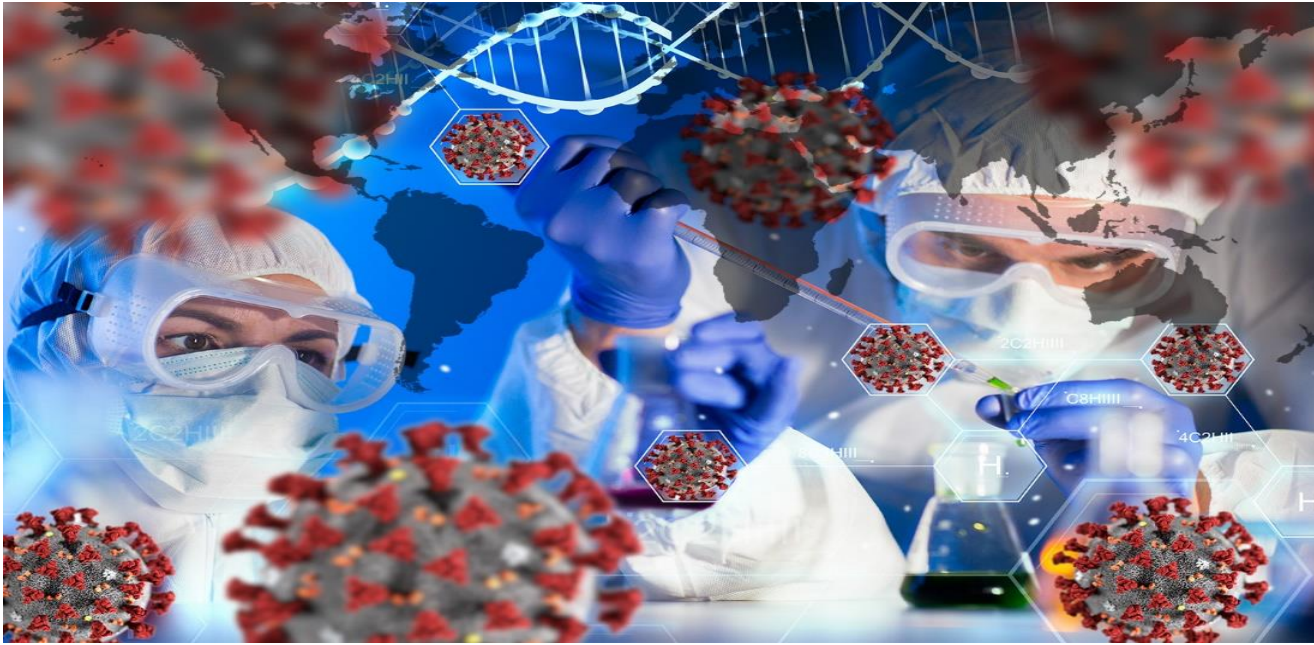
Due to the evolving nature of COVID-19 and our current knowledge gaps, a portion of this presentation is likely to prove wrong in the future!!!

The novel Coronavirus 2019 (or coronavirus disease 2019 [COVID-19]) infection, which originated in the city of Wuhan, in Hubei province, China, in December 2019 shares close similarities in its genomic structure with the severe acute respiratory syndrome coronavirus (SARS-CoV) that caused the SARS global pandemic in 2003 and the Middle East respiratory syndrome (MERS) epidemic in 2012 (MERS-CoV), and even closer similarities to bat SARS-like betacoronavirus (bat-SLCoVZC45 betacoronavirus and bat-SLCoVZXC21).

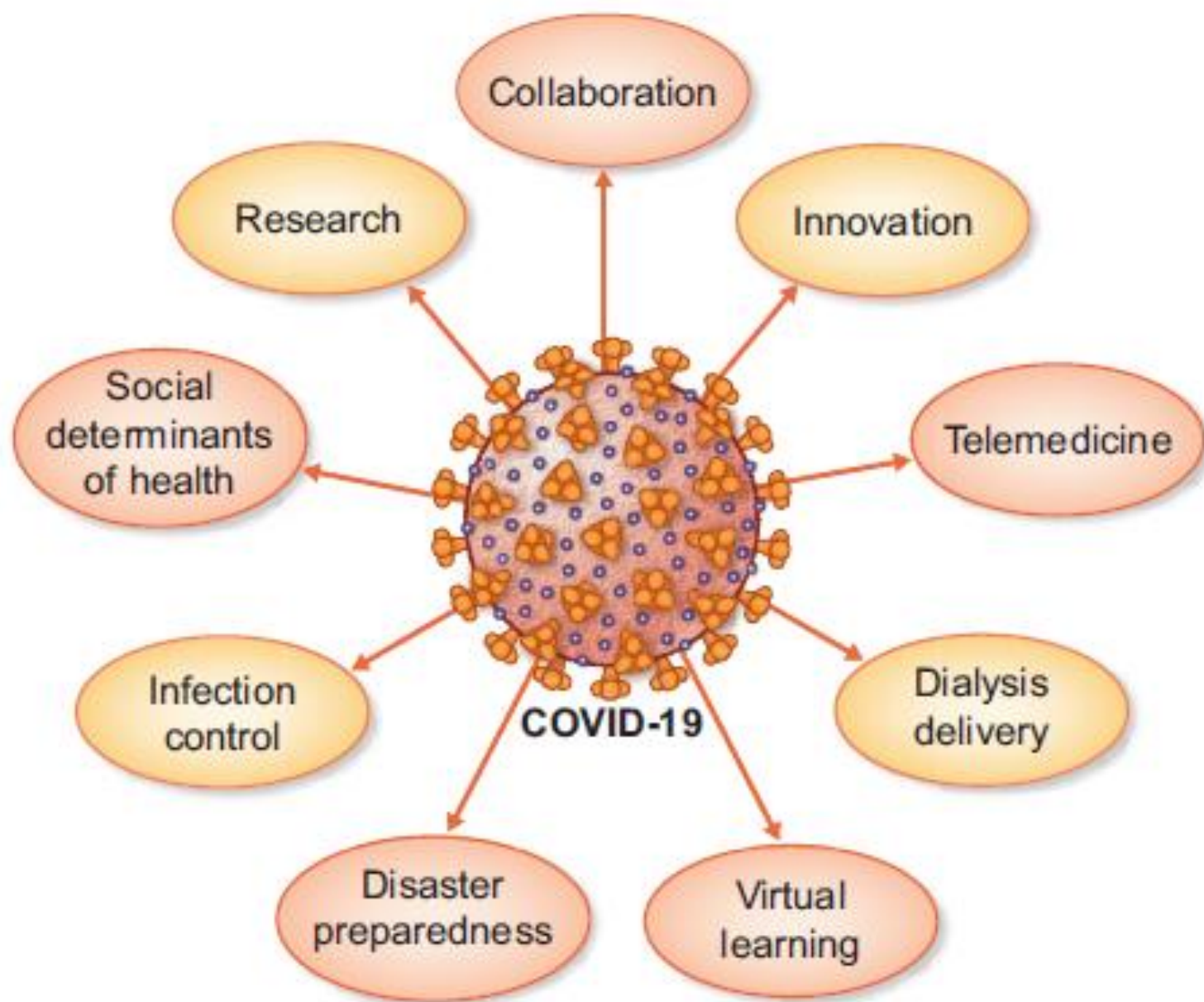


Pandemic is ongoing





THE STORY CONTINUES

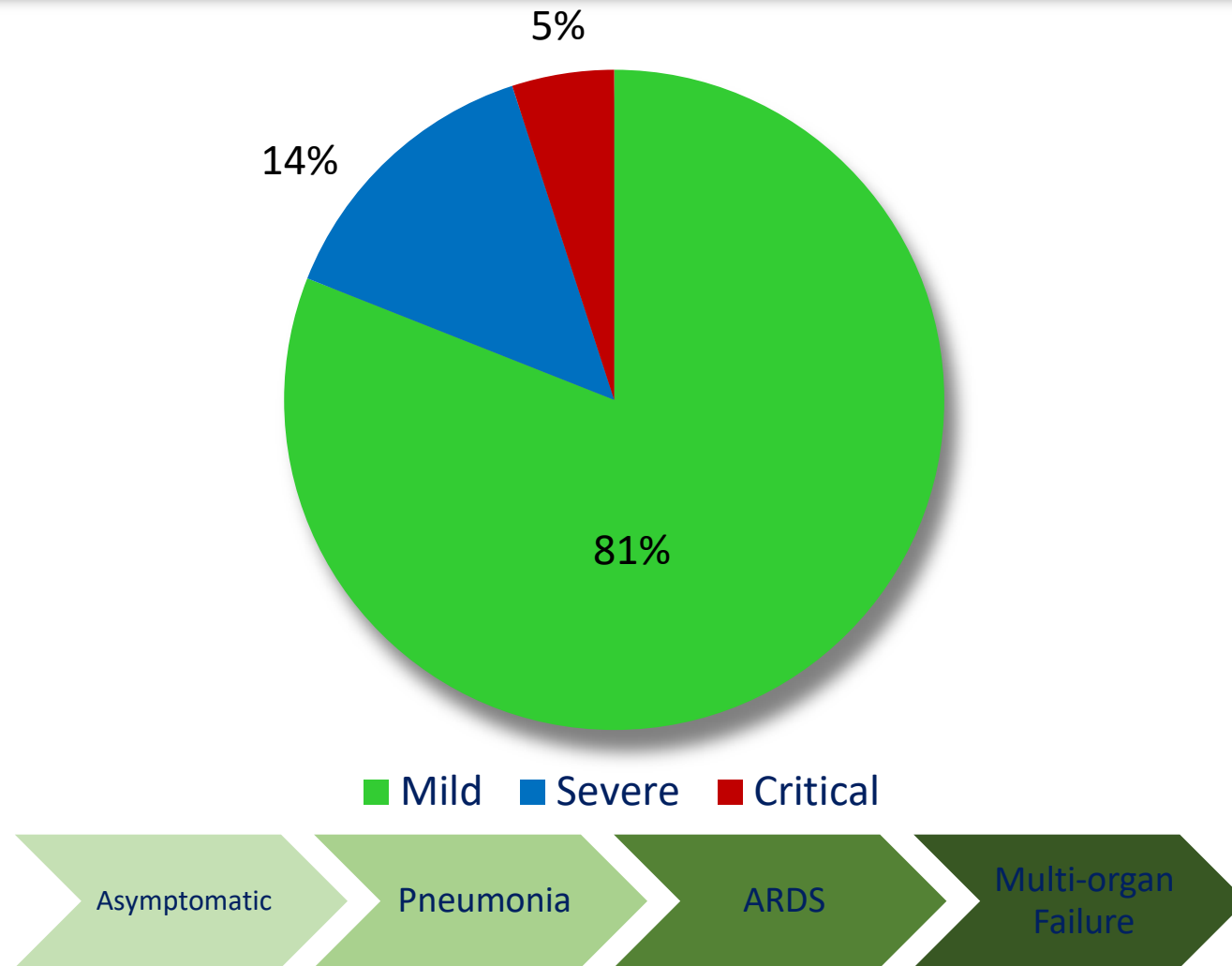


The disease caused by SARS-CoV-2 is named Corona Virus Disease 2019 (COVID-19)

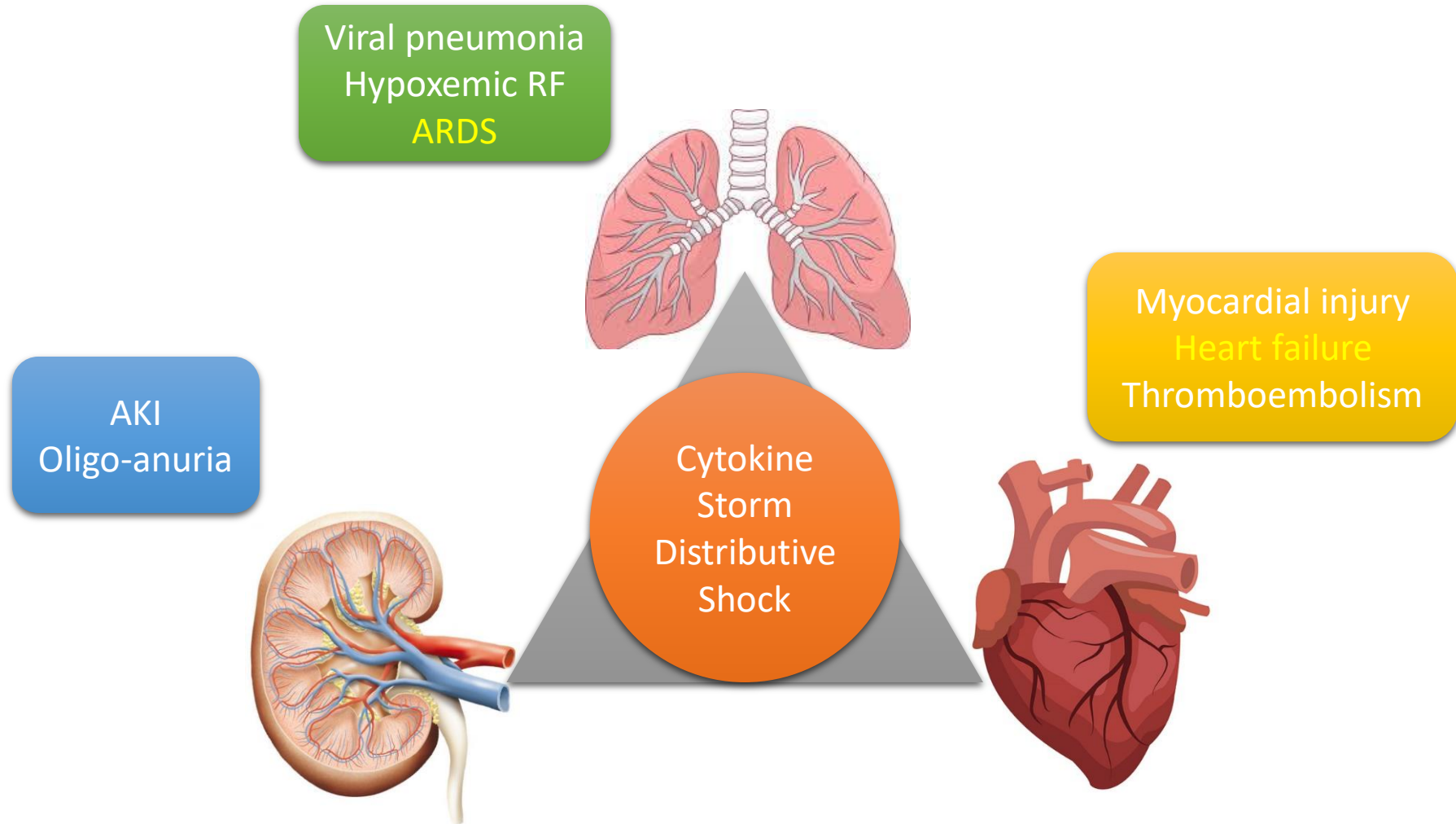
- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, which was first reported in Wuhan, China, in December, 2019, >>> has had an enormous impact on China and the whole world.
- Although most patients infected with SARS-CoV-2 had a mild illness, about 5%-10% of patients had severe lung injury or even multiorgan dysfunction, resulting in a 1.4% case fatality ratio.

Whilst COVID-19 is predominantly a respiratory disease, in severe cases it can cause kidney and multi-organ failure.

Spectrum of COVID-19 Severity



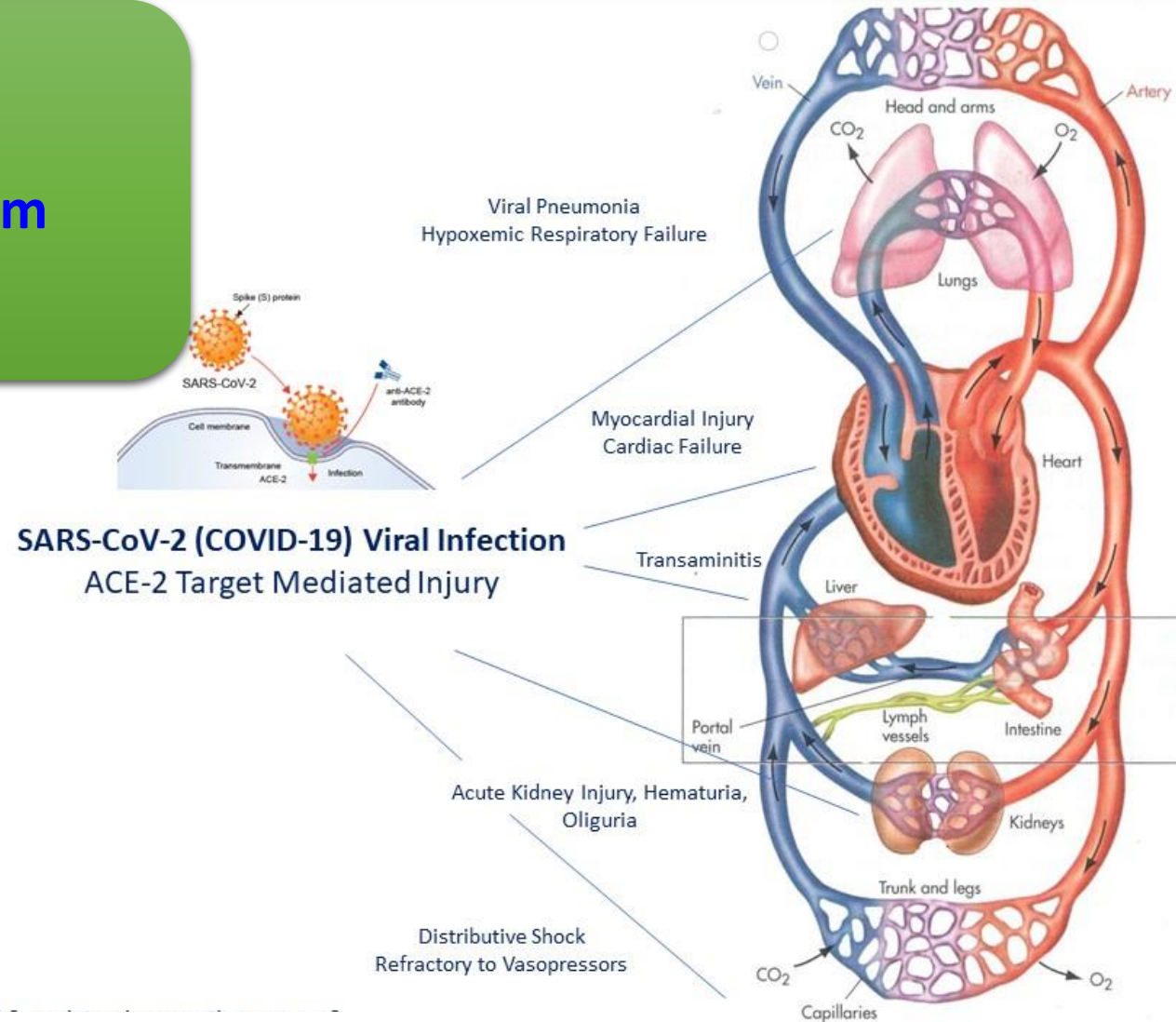
COVID-19: A Systemic Disease



COVID-19: A Systemic Disease

Highest ACE-2 Expression

- Kidney
- Endothelium
- Lung
- Heart



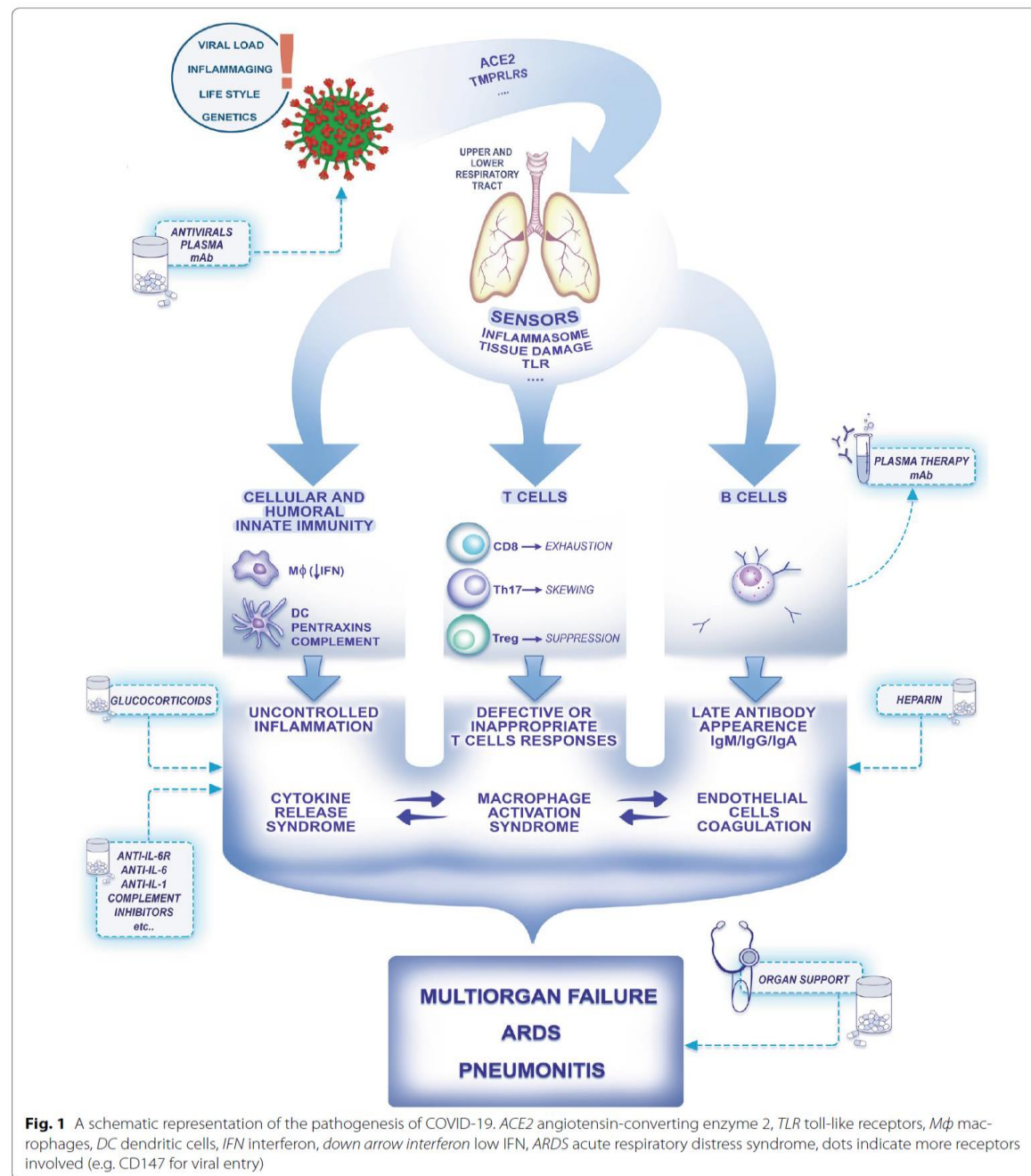








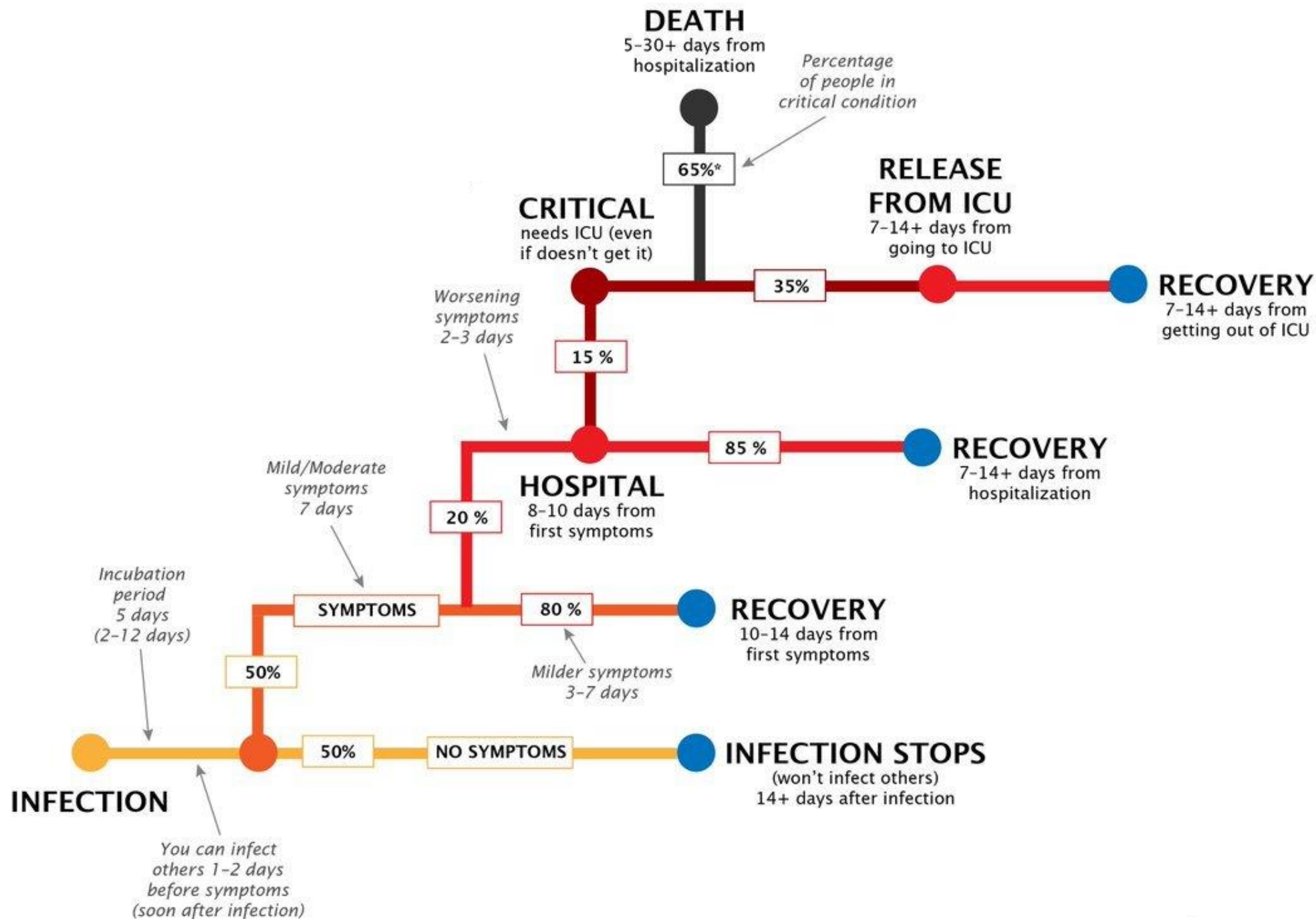


Fig. 1 A schematic representation of the pathogenesis of COVID-19. ACE2 angiotensin-converting enzyme 2, TLR toll-like receptors, Mφ macrophages, DC dendritic cells, IFN interferon, down arrow interferon low IFN, ARDS acute respiratory distress syndrome, dots indicate more receptors involved (e.g. CD147 for viral entry)

TABLE 1.

Classification of COVID-19 severity used in various studies

Classification	Features	Comments
 Chinese CDC classification ⁹⁶	Mild	Most commonly cited in the literature
	Nonpneumonia or mild pneumonia	
	Severe	Maintains uniformity over multiple studies
	Dyspnea	
 Pereira et al ⁵	Respiratory rate > 30/min	
	Blood oxygen saturation ≤ 93%	
	PaO ₂ /FiO ₂ ratio < 300	
	Lung infiltrates > 50% of lung fields within 24–48 h	
 WHO-China Joint Mission Classification ⁹⁷	Critical	Relies on center-specific practices
	Respiratory failure	
	Septic shock	
	Multiorgan dysfunction or failure	
 WHO-China Joint Mission Classification ⁹⁷	Mild disease	Similar to Chinese CDC classification
	Outpatient care only	
	Moderate disease	
	Admission to the general inpatient floor	
 WHO-China Joint Mission Classification ⁹⁷	Severe infection	Mild–moderate severity distinction based upon imaging
	Mechanical ventilation, admission to ICU or death	
	Mild	
	Clinical symptoms without manifestation of viral pneumonia on chest CT scans	
 WHO-China Joint Mission Classification ⁹⁷	Moderate	Mild–moderate severity distinction based upon imaging
	Symptoms such as fever and respiratory tract symptoms, etc., with manifestation of viral pneumonia on chest CT scans	
	Severe	
	Patients who met any of the following criteria:	
 WHO-China Joint Mission Classification ⁹⁷	Respiratory rate > 30/min	Mild–moderate severity distinction based upon imaging
	Blood oxygen saturation ≤ 93%	
	PaO ₂ /FiO ₂ ratio < 300	
	Lung infiltrates > 50% of lung fields within 24–48 h	
 WHO-China Joint Mission Classification ⁹⁷	Critical	Mild–moderate severity distinction based upon imaging
	Patients that met any of the following criteria: (1) occurrence of respiratory failure requiring mechanical ventilation;	
	(2) shock; and/or; (3) other organ failure that requires monitoring and treatment in the intensive care unit	



SARS-CoV-2

- Kidney involvement is frequent in COVID-19
- >40% of cases have abnormal proteinuria at hospital admission
- Cheng Y, Luo R, Wang K, et al. *Kidney disease is associated with in-hospital death of patients with COVID-19.* *Kidney Int* 2020; **97**: 829–38.

Acute kidney injury (AKI) is common among critically ill patients with COVID-19, affecting approximately 20–40% of patients admitted to intensive care according to experience in Europe and the USA and it is considered a marker of disease severity and a negative prognostic factor for survival.

COVID-19 & KIDNEY TRANSPLANTATION

***Do transplant patients do
worse than the general population???***

Despite the heterogeneity of case descriptions, it does appear that the incidence of severe complications & mortality of COVID-19 may be higher in KTRs

Kidney-transplant recipients

appear to be at particularly high risk for critical Covid-19 illness due to chronic immunosuppression and coexisting conditions

COVID-19 and kidney transplant

Case reports: 7

Case series: 4

N 8 to 46

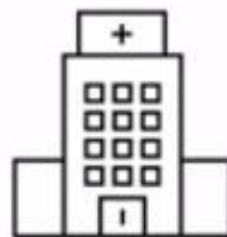
Countries:

USA, Italy, China,
Spain



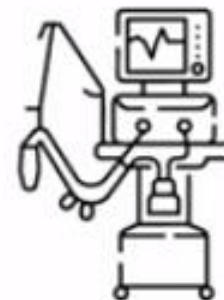
112

Reported



92%

Hospitalized



24%

Ventilated



19%

Died

Do transplant patients do worse
than the general population? **Yes**



CORRESPONDENCE

Covid-19 and Kidney Transplantation

Kidney transplant recipients are more likely to develop Covid-19 & they are really high risk for [severe and critical disease](#).

Kidney-transplant recipients appear to be at particularly high risk for critical Covid-19 illness due to [chronic immunosuppression](#) and [coexisting conditions](#) .

COVID-19 Infection in Kidney Transplant Recipients: Disease Incidence and Clinical Outcomes

Michelle Elias,¹ Daniele Pievani,¹ Christine Randoux,² Kevin Louis ,³ Blandine Denis,⁴ Alexandra Delion,¹ Océane Le Goff,¹ Corinne Antoine,¹ Clarisse Greze,² Evangeline Pillebout,¹ Imad Abboud ,¹ Denis Glotz,^{1,3} Eric Daugas,² and Carmen Lefaucheur  ^{1,3}

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³Paris Translational Research Center for Organ Transplantation, INSERM (Institut National de la Santé et de la Recherche Médicale), UMR-S970, Paris, France

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ABSTRACT

Background COVID-19 has been associated with high morbidity and mortality in kidney transplant recipients. However, risk factors for COVID-19 disease in patients with kidney transplants remain poorly defined.

Methods We enrolled patients who underwent kidney transplantation and were actively followed up in two hospitals in Paris on March 1st, 2020. Patients were screened for baseline and transplant characteristics, functional parameters, comorbidities, and immunosuppressive therapies. COVID-19 disease was assessed. Patients were followed up during the pandemic until April 30th, 2020 by the COVID-19 SLS KT survey program, including teleconsulting, at-home monitoring for patients with COVID-19, and a dedicated phone hotline platform.

Results Among 1216 patients with kidney transplants enrolled, 66 (5%) patients were identified with COVID-19 disease, which is higher than the incidence observed in the general population in France (0.3%). Their mean age was 56.4 ± 12.5 years, and 37 (56%) patients were men. The following factors were independently associated with COVID-19 disease: non-White ethnicity (adjusted odds ratio [OR], 2.17; 95% confidence interval [95% CI], 1.23 to 3.78; $P=0.007$), obesity (OR, 2.19; 95% CI, 1.19 to 4.05; $P=0.01$), asthma and chronic pulmonary disease (OR, 3.09; 95% CI, 1.49 to 6.41; $P=0.002$), and diabetes (OR, 3.33; 95% CI, 1.92 to 5.77; $P<0.001$). The mortality rate related to COVID-19 disease was 1% in the overall study population and 24% in COVID-19–positive patients.

Conclusions Patients with kidney transplants display a high risk of mortality. Non-White ethnicity and comorbidities such as obesity, diabetes, asthma, and chronic pulmonary disease were associated with higher risk of developing COVID-19 disease. It is imperative that policy makers urgently ensure the integration of such risk factors on response operations against COVID-19.

COVID-19 in Kidney Transplantation: Epidemiology, Management Considerations, and the Impact on Kidney Transplant Practice

Ashish Kataria, MD,¹ Idris Yakubu, PharmD,² Ryan Winstead, PharmD,² Madan Gowda, MD,³ and Gaurav Gupta, MD²

Abstract. The novel severe acute respiratory syndrome coronavirus 2 was identified in the late 2019 as the cause of coronavirus disease 2019 (COVID-19), an acute respiratory viral illness. Patients with chronic underlying conditions may have an increased risk of morbidity and mortality from COVID-19. Kidney transplant recipients may be at a uniquely increased risk of serious complications from COVID-19 as compared to the general population because of a chronically immunosuppressed state and a high prevalence of comorbidities like diabetes, heart disease, and lung disease. Early data suggest that the mortality of patients on dialysis may be comparable to those with kidney transplants, although more research is needed. This concise review aims to describe the epidemiology of COVID-19 in kidney transplant recipients, manifestations, appropriate management, and clinical outcomes based on the available literature. Current evidence on many of the specific antiviral measures against COVID-19 has not shown a clear-cut benefit in smaller studies and the results of several ongoing larger clinical trials are awaited. In addition, we also highlight the impact of COVID-19 on kidney transplant center practice and volumes; potential living or deceased donors, recipients; and induction immunosuppression and surgical strategies.

(*Transplantation Direct* 2020;6: e582; doi: 10.1097/TXD.0000000000001031. Published online 15 July, 2020.)

Activate Windows
Go to Settings to activate Windows.

In the general population, COVID-19 could manifest with varying degrees of severity ranging from asymptomatic/mild self-limited infections (~80%) to all the way to severe (14%) and critical ventilator-dependent (5%) illness.

Despite the heterogeneity of case descriptions, the incidence of **severe complications of COVID19** may be higher in KTRs than the general population in various studies.

ARDS requiring mechanical ventilation (27%–39%)
and **severe AKI** needed to dialysis (20%–40%).

Renal involvement

It is unclear whether the AKI is secondary to hemodynamic alterations or a direct infection by SARSCoV-2.

It is, however, plausible that the cytokine release syndrome (CRS) associated with COVID-19 combined with a reduction in Immuno Suppressive medications may predispose KTR to Acute Rejection.

AKI

Direct viral effects

Collapsing glomerulopathy
Endothelitis

Indirect viral effects

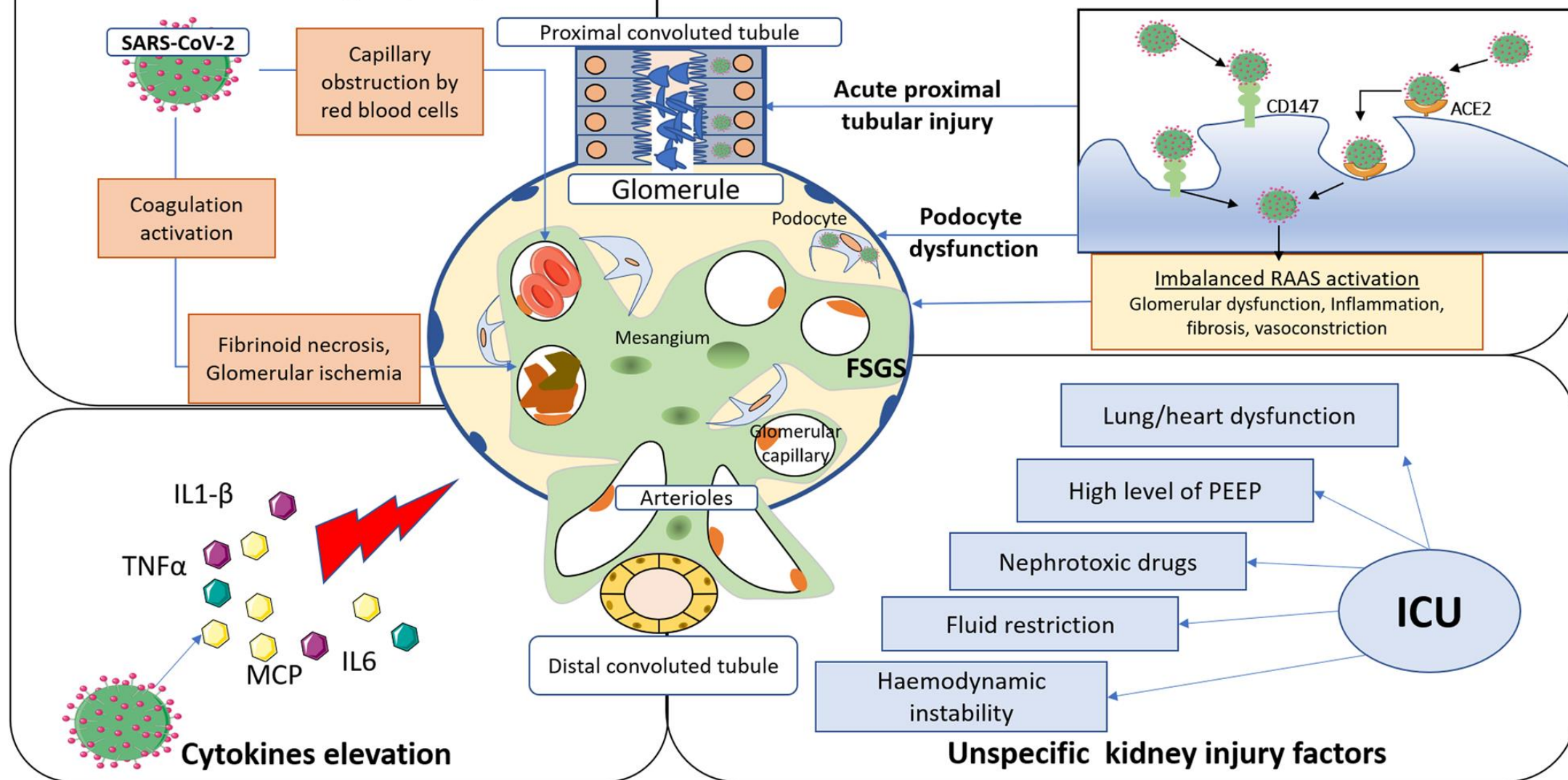
Hypovolemia
Lung injury
Superinfection
Multiorgan failure
Rhabdomyolysis

Clinical management effects

Nephrotoxins
Hypervolemia
Lung- kidney talk

Vascular consequences of SARS-CoV-2 induced coagulopathy

Kidney invasion via SARS-CoV-2 entry in proximal tubular cells and podocytes



Risk of AKI

- ✓ **Glomerular changes- Nephritis**
- ✓ **Endothelialitis**
- ✓ **Acute rejection(CRS, reduction in IS)**

Associated with higher mortality

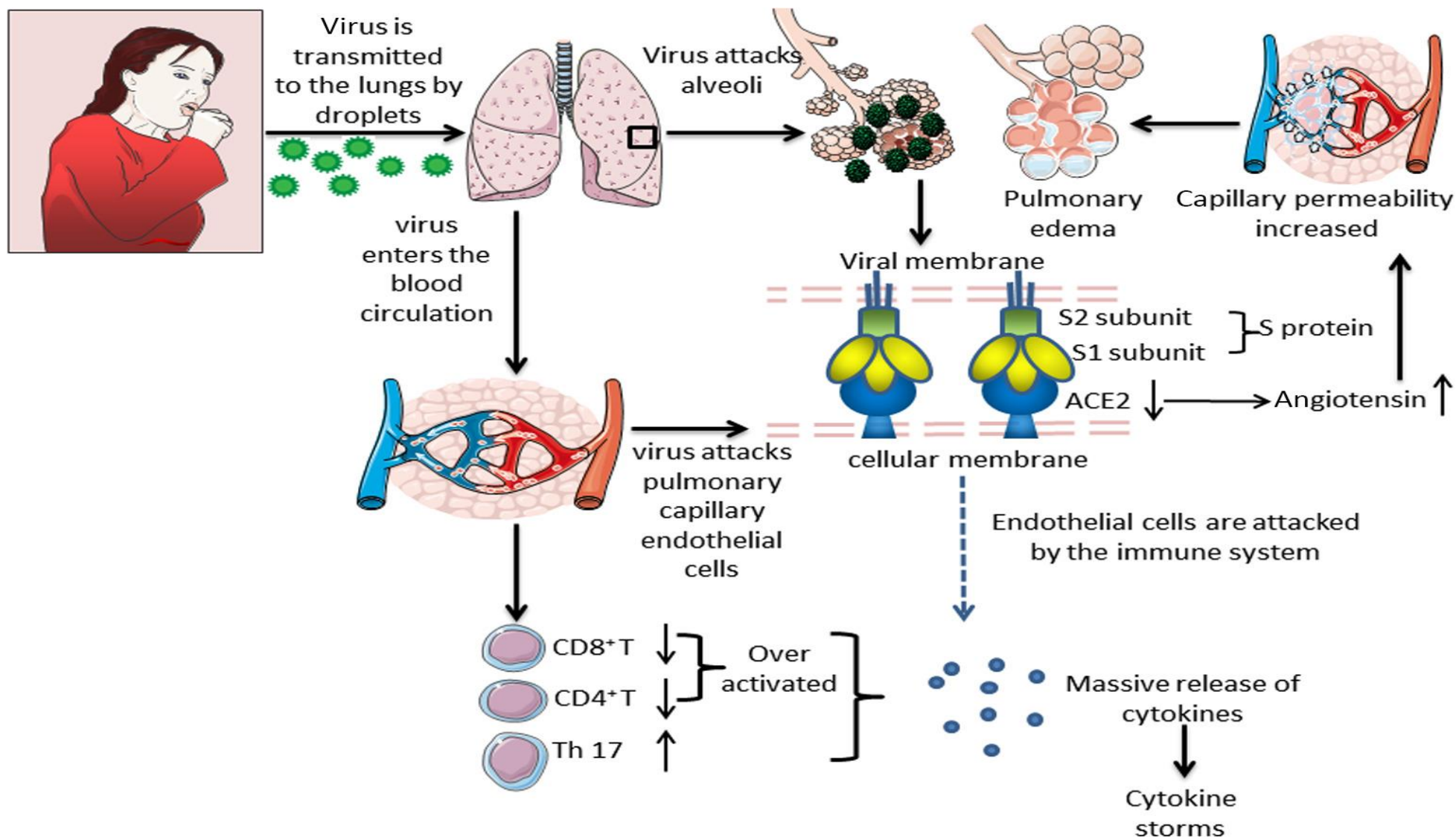
Possible mechanisms of cytokine storms in COVID-19:

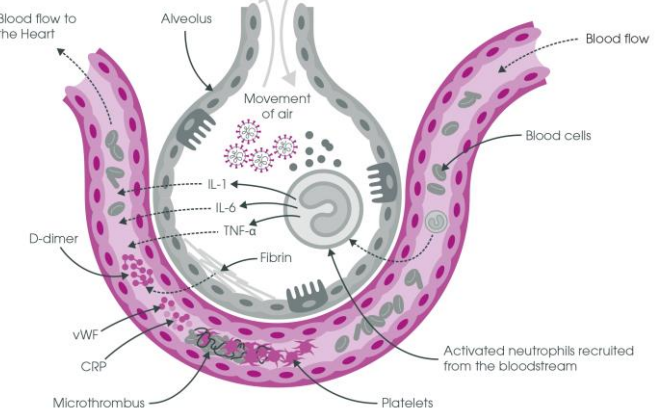
The imbalance of lymphocyte subsets characterized by the decrease of CD4⁺, CD8⁺ T cells, the increase of the number of proinflammatory Th17 cells and the increase of CD8⁺ cytotoxic particles, aggravated the disorder of host immune system.

Inflammatory monocytes amplify cytokines production.
(CSS)

CSS implies that the levels of released cytokines are injurious to host cells. Distinguishing an appropriate from a **dysregulated inflammatory response** in the pathophysiology of critical illness, however, has been a major challenge.

Cytokine storm syndrome in coronavirus disease 2019: A narrative review





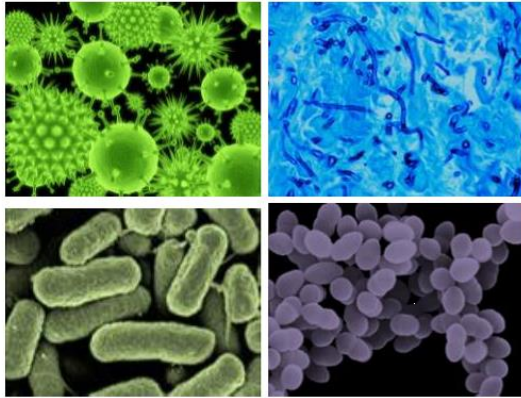
Infection

**Dysregulated
Immune Response**

Organ Damage

Excessive immune response of the host can trigger cytokine storms by multiple excessive inflammatory responses throughout the body and damage the multiple target organs involved.

we are under attack by Cytokines
>>> signals from our cells to our bodies



Infection: Viral, Fungal,
Bacterial, Parasitic

Tissue Injury

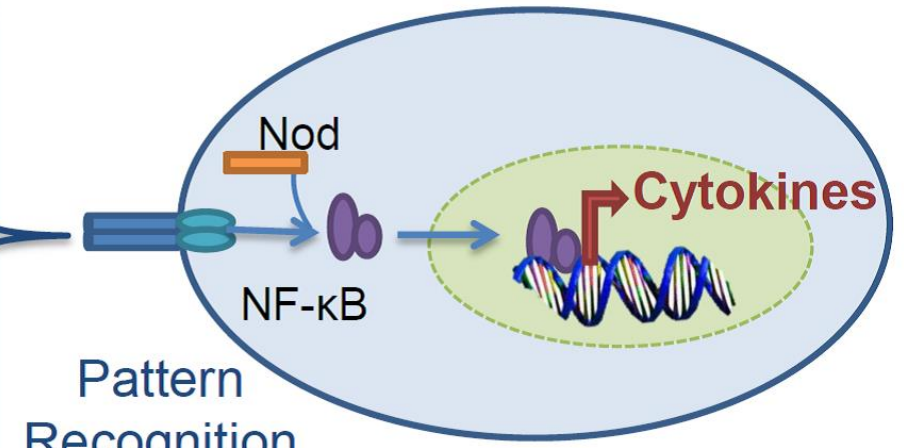


Trauma, Burn,
Pancreatitis, Surgery

Pathogen-associated
Molecular Pattern (PAMPs)

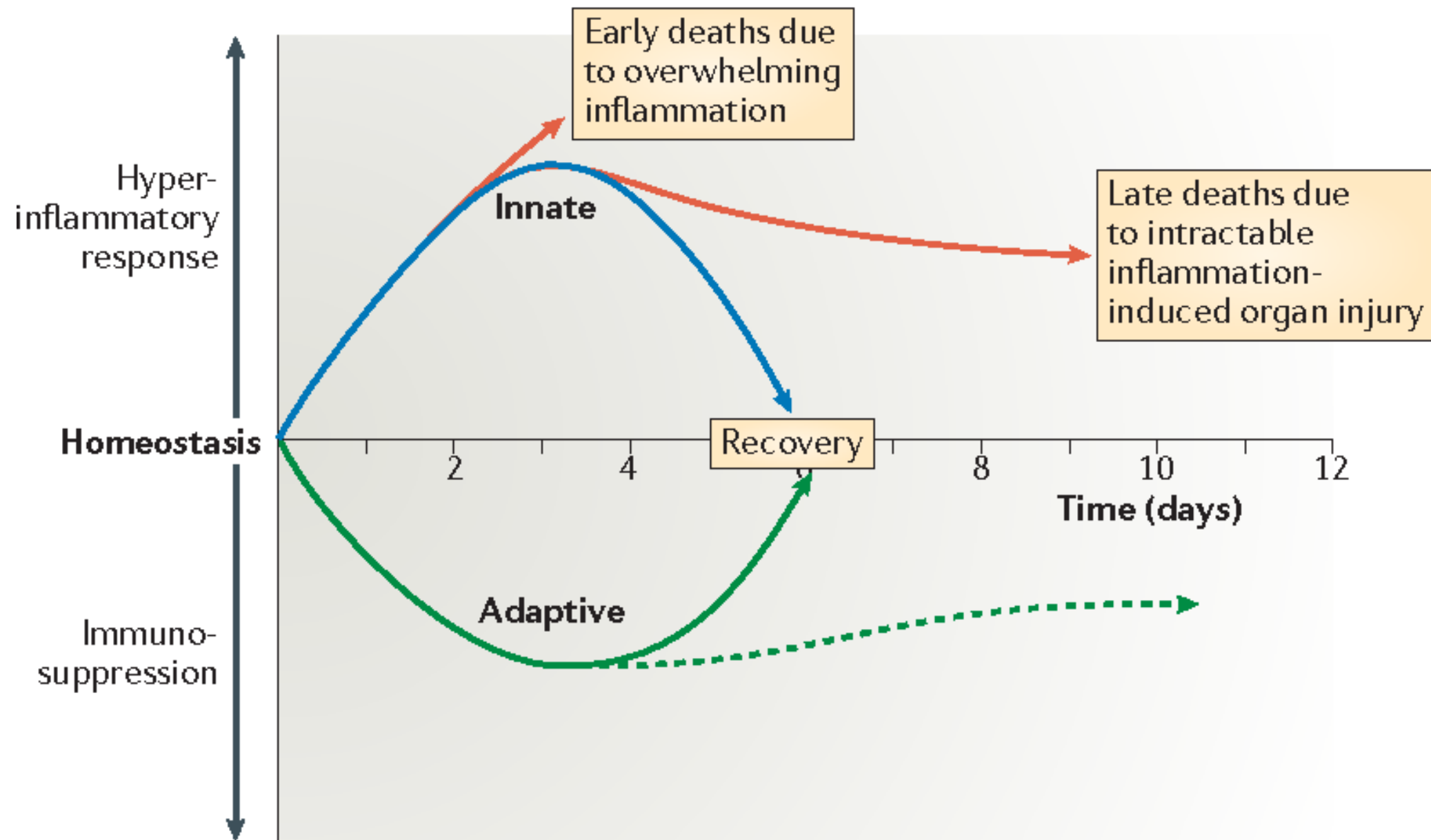


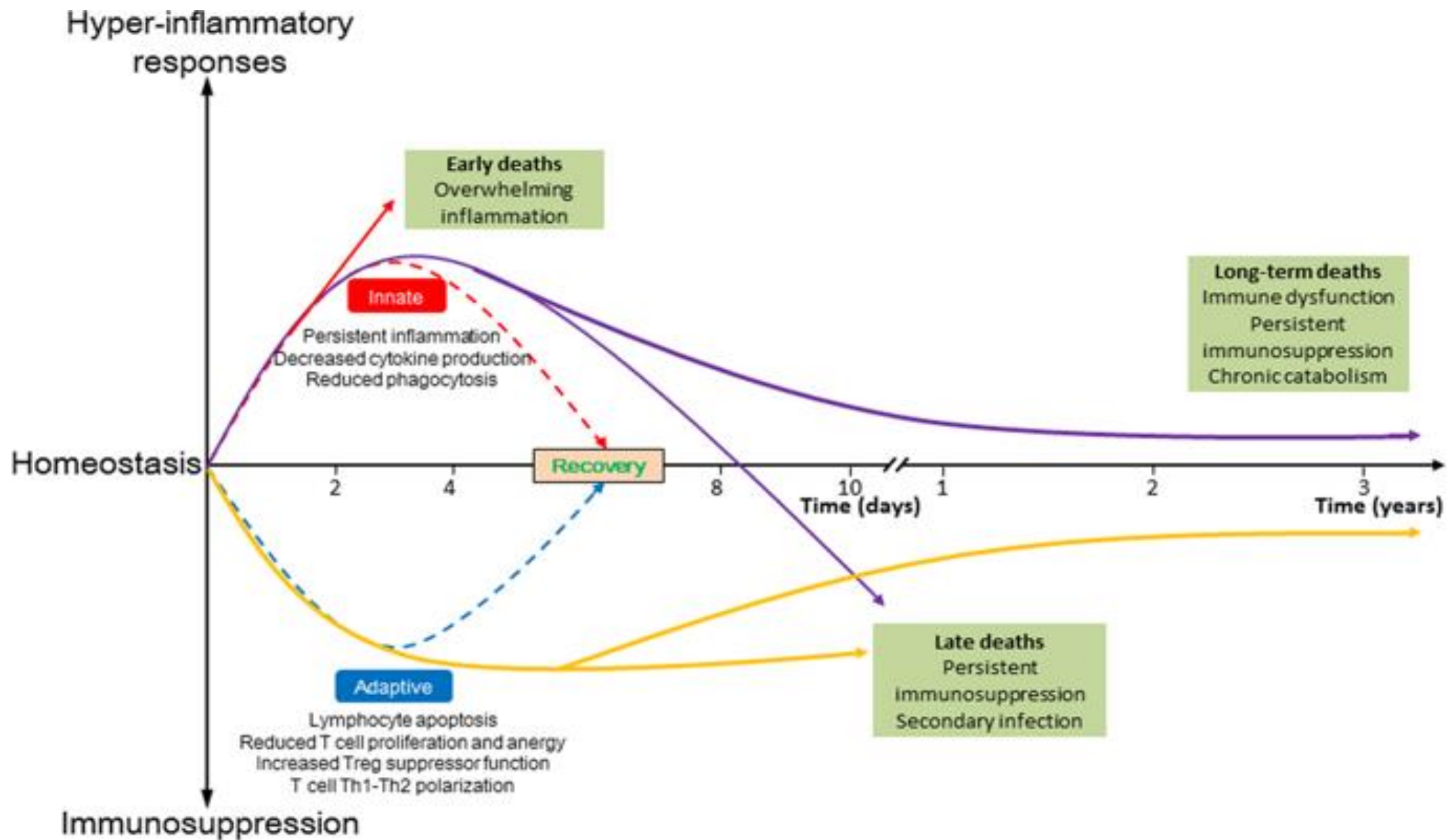
Damage-associated
Molecular Pattern (DAMPs)



Pattern
Recognition
Receptors
(PRRs)

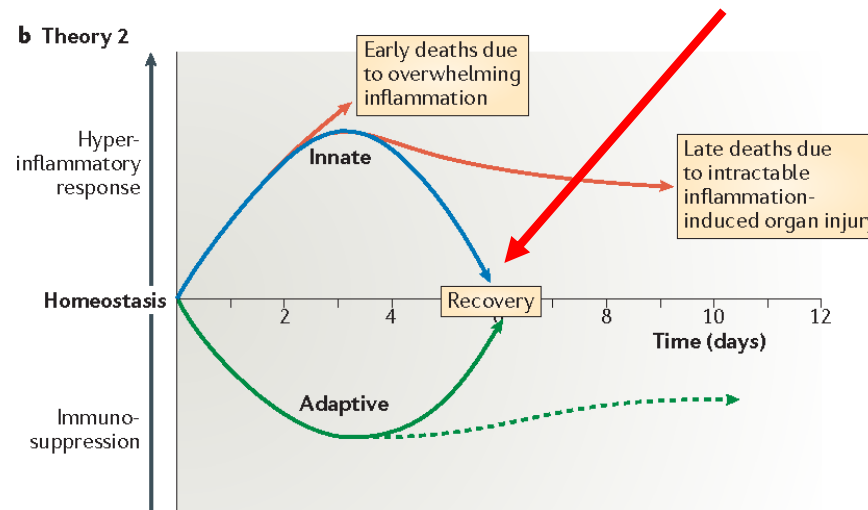
Inflammatory Cascade
“Cytokine Storm”
Tissue/Organ Damage





Anti-inflammation should keep this war under control

- When we have flu >>> we have to stay at home >>> we have high temp, shakes, aches, pain ,we feel bad and awful, >>> this means that **there is a war going on in our body**
- **Both the pro- & anti- inflammatory systems, increase their activities**
- If we are healthy >>> we will recover after 5-6 days



The problem in our pts is,...

- This **well controlled scenario goes out of hand >>>** for whatever reasons >>> **pro-inflammation overwhelms anti-inflammation and this pt can die** (due to **acute hyper-inflammatory conditions** we can call it also septic shock or whatever)

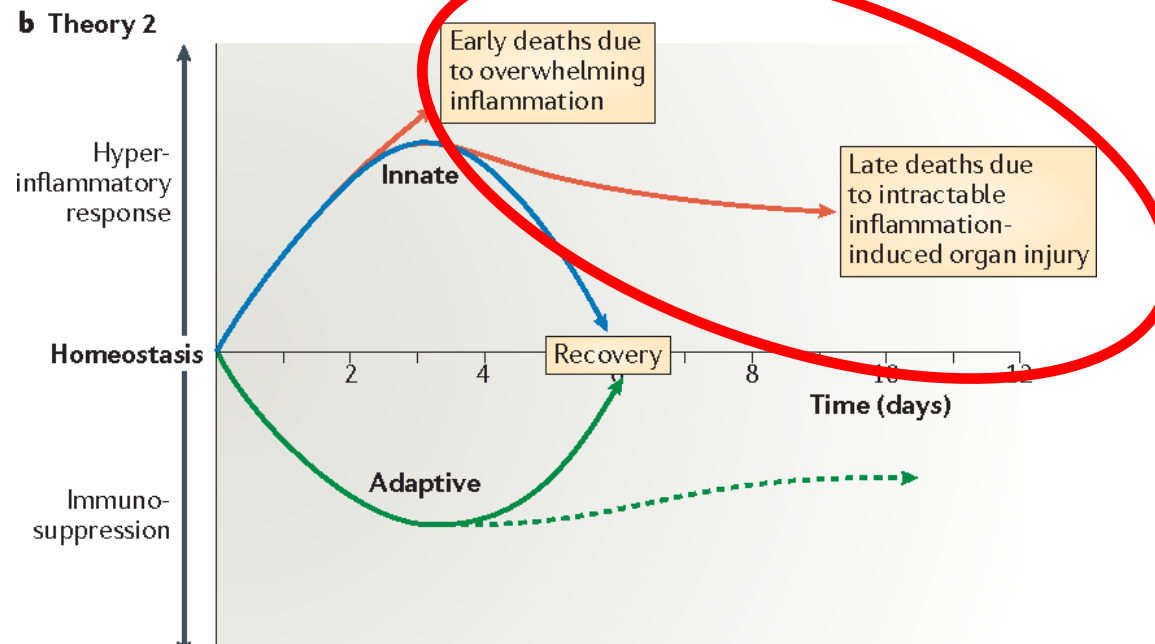
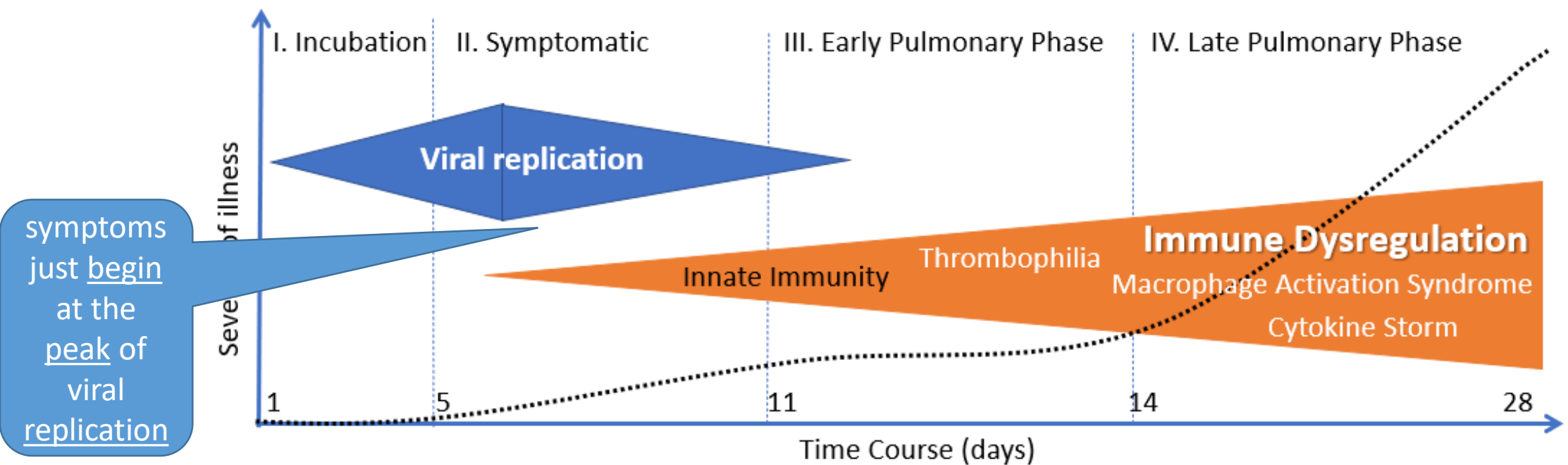


Figure 1. The course of COVID-19 and General Approach to treatment



Ground-glass infiltrates	+			
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SARS-CoV-2 and viral sepsis: observations and hypotheses



Hui Li, Liang Liu, Dingyu Zhang, Jiuyang Xu, Huaping Dai, Nan Tang, Xiao Su, Bin Cao

Since the outbreak of coronavirus disease 2019 (COVID-19), clinicians have tried every effort to understand the disease, and a brief portrait of its clinical features have been identified. In clinical practice, we noticed that many severe or critically ill COVID-19 patients developed typical clinical manifestations of shock, including cold extremities and weak peripheral pulses, even in the absence of overt hypotension. Understanding the mechanism of viral sepsis in COVID-19 is warranted for exploring better clinical care for these patients. With evidence collected from autopsy studies on COVID-19 and basic science research on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and SARS-CoV, we have put forward several hypotheses about SARS-CoV-2 pathogenesis after multiple rounds of discussion among basic science researchers, pathologists, and clinicians working on COVID-19. We hypothesise that a process called viral sepsis is crucial to the disease mechanism of COVID-19. Although these ideas might be proven imperfect or even wrong later, we believe they can provide inputs and guide directions for basic research at this moment.

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[S0140-6736\(20\)30920-X](https://doi.org/10.1016/S0140-6736(20)30920-X)

For the Chinese translation see
[Online](#) for appendix

Department of Pulmonary and
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Medicine, National Clinical
Research Center for Respiratory
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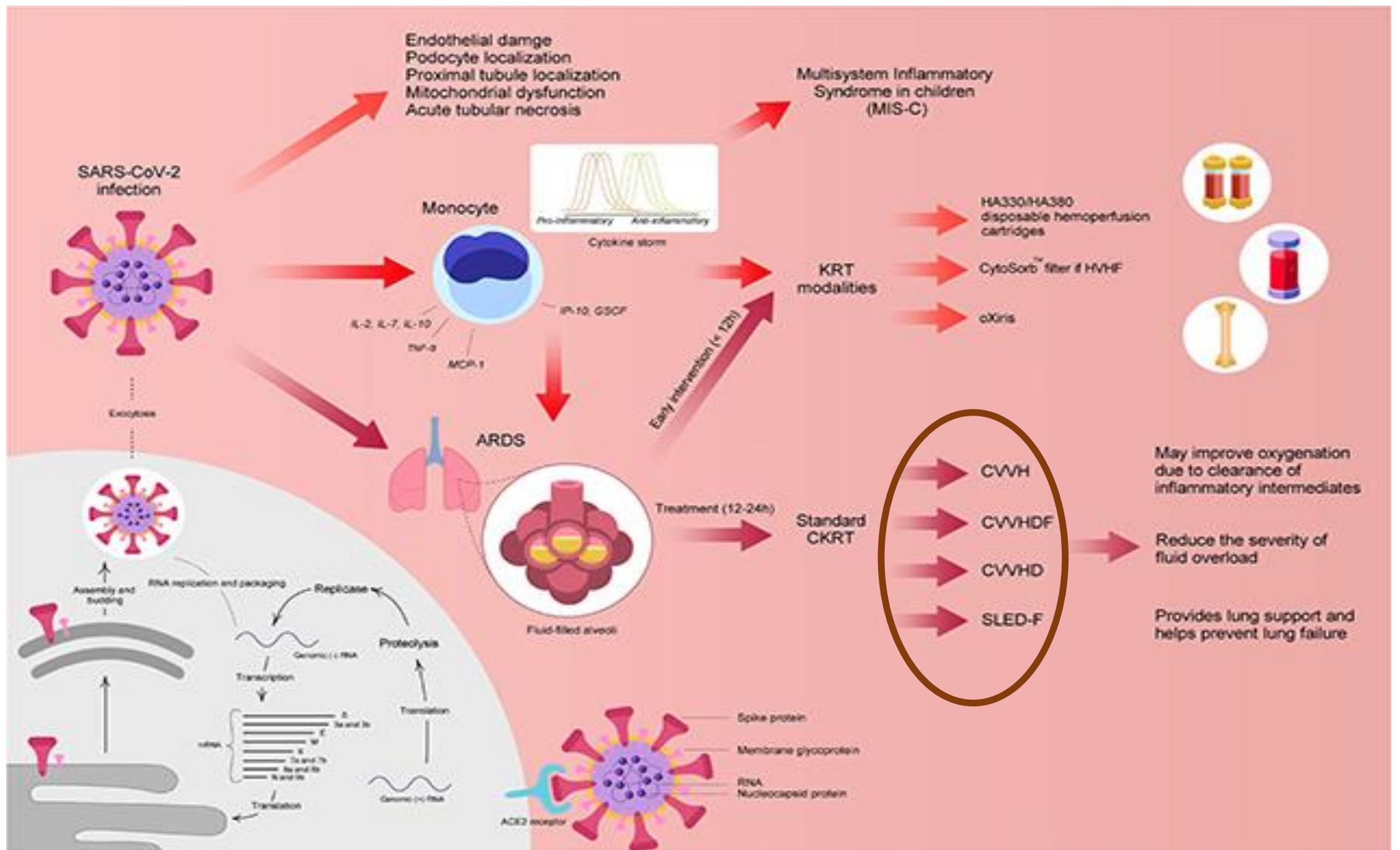
(H Li MD, Prof H Dai MD,

viral sepsis

Severe COVID-19 = Septic shock

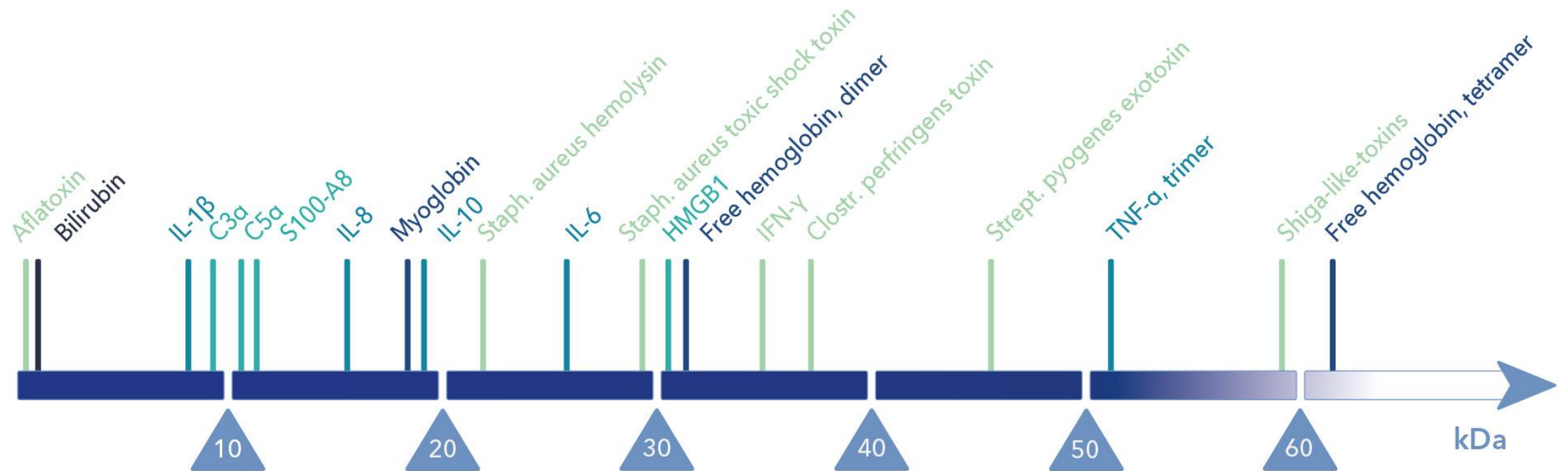
Extracorporeal treatments (Role of nephrologist)

- ✓ Finally, a **sepsis-like syndrome** might occur frequently due to **the virus itself** or to a **superimposed bacterial infection** and in this case, since pharmacological approaches have shown poor results, new **extracorporeal organ support therapies** including **haemoadsorption and haemoperfusion**, with new sorbent **cartridges designed to remove cytokines and other circulating mediators**, should be considered.



think uremia, think sepsis

“retention molecules”



But

The renal TX program should not be terminated
& it should be adjusted accordingly.

benefits might outweigh the risks



OPEN

COVID-19 in Kidney Transplantation: Epidemiology, Management Considerations, and the Impact on Kidney Transplant Practice















Ashish Kataria, MD,¹ Idris Yakubu, PharmD,² Ryan Winstead, PharmD,² Madan Gowda, MD,³ and Gaurav Gupta, MD²

✉

(*Transplantation Direct* 2020;6: e582; doi: 10.1097/TXD.0000000000001031. Published online 15 July, 2020.)



COVID-19 and kidney transplantation: an Italian Survey and Consensus

Fabio Vistoli¹  · Lucrezia Furian²  · Umberto Maggiore³  · Rossana Caldara⁴  · Vincenzo Cantaluppi⁵  ·
Mariano Ferraresso⁶  · Gianluigi Zaza⁷  · Massimo Cardillo⁸  · Giandomenico Biancofiore⁹  ·
Francesco Menichetti¹⁰  · Alessandro Russo¹⁰ · Emanuela Turillazzi¹¹  · Marco Di Paolo¹¹  ·
Giuseppe Grandaliano¹²  · Ugo Boggi¹  · on behalf of the Italian National Kidney Transplantation Network · the
Joint Committee of the Italian Society of Organ Transplantation and the Italian Society of Nephrology

Transplant processes	Adjustment methods
Donor and recipient screening	<ol style="list-style-type: none"> 1. Within 14 days, the donor or the recipient had no history of staying in the epidemic area and no history of contact with COVID-19 patients. None of the people in close contact with them had a history of sojourn in the epidemic area 2. There are no fever, progressive dyspnea, dry cough, diarrhea, and other related symptoms within 14 days before the onset of the primary disease 3. Chest CT and laboratory examination showed no pneumonia 4. Nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, feces, and other specimens tested negative for new coronavirus nucleic acid 5. All were limited to one escort, who had no epidemiological history and normal body temperature 6. The hospital ethics committee examines the authenticity of the worker's willingness to donate and the legality of the source of the donor
Donor maintenance	<ol style="list-style-type: none"> 1. Single-room medical unit, fixed personnel to participate in the maintenance 2. Screening the coordinator and donor and transplant staff 3. The apparatus and equipment needed for organ acquisition shall be packed with protection; after the operation is completed, store the protective layer of the outer packaging of the instruments should in a centralized manner and dispose of it medical waste as medical waste contaminated by viruses; after the acquisition personnel return, sterilize the exterior of the organ preservation device, refrigerator, and other instruments
Operation and postoperative management	<ol style="list-style-type: none"> 1. Strengthen the health investigation and management of medical staff 2. Independent operating room and postoperative laminar flow ward 3. In case of suspected infection of COVID-19 during the perioperative period, the transplant recipient shall be isolated in a single room immediately and report to the relevant department of the hospital for consultation. When the patient is confirmed to be infected with COVID-19, the patient is transferred to the special ward of the hospital immediately and the medical staff who contacted the patient are isolated for 14 days 4. Strict implementation of disinfection and isolation system 5. Implement the system of professional responsible persons to improve the quality of care

Management

- ✓ Antiviral treatment
- ✓ Immunosuppression modification based on severity of infection
 - TDM of CNI/ mTORi*

Table 1 A Summary of Medications Used for Management of COVID-19 Patients

Drugs	Pharmacologic Category	Mechanism of Action	Dosage Regimen in COVID-19	References
Lopinavir/Ritonavir	Antiretroviral agent	Lopinavir is an HIV-1 protease inhibitor; ritonavir increases the half-life of lopinavir via inhibiting cytochrome P450	400 mg/100 mg twice daily for 7–14 days	39,40
Chloroquine/ Hydroxychloroquine	Antimalarial (aminoquinoline)	Chloroquine inhibits quinine reductase, an essential enzyme for biosynthesis of sialic acid, which is necessary for virus fusion with host cell	Chloroquine: 400 mg daily for 10–14 days Hydroxychloroquine: 500 mg twice daily for 10 days or 200 mg 3 times daily for 10 days	30,31,121
Umifenovir	Antiviral agent	Hemagglutinin inhibitor, which inhibits virus membrane fusion with host cell	200 mg every 12 hours for 10 days	65,66
Ribavirin	Antiviral agent	Inhibits protein synthesis via blocking IMPDH during replication of virus	1200–2000 mg daily divided into twice daily for 5 days	52,54,55
Remdesivir	Antiviral agent	Interferes with RNA polymerase	200 mg IV stat and then 100 mg daily for 9 days	58,64
Interferon	Interferons	Increases phagocyte activity of macrophages and augments cytotoxicity of lymphocytes for viral cells	5 million units twice daily via atomic nebulization or SQ administration	70,75,76
Tocilizumab	Antirheumatic/IL-6 receptor antagonist	Antagonist of intracellular IL-6 receptor	400 mg IV infusion stat	84

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IMPDH, inosine monophosphate dehydrogenase; IV, intravenous; IL, interleukin.





Developing Education Science
and Care for Renal Transplantation
in European States

How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion

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Table 2. Management of immunosuppression in patients who are beyond 3–6 months after transplantation

1. Asymptomatic patients: no knowledge of COVID-19 status (ambulatory, stable patients)	No pre-emptive/proactive change of immunosuppressive medications
2. Asymptomatic patients, swab pos for COVID-19	If it is a high-risk patient: age ≥ 70 years, or comorbidities or risk factors (diabetes, cardiac or pulmonary disease, heavy smoking, BMI >30 kg/m ² , eGFR <30 mL/min/1.73 m ² , lymphocyte depletion therapy within previous 3–6 months): consider reducing/stopping AZA/MPA/mTORi if on triple therapy
3. Mild disease: the patient is alert, has only mild upper respiratory and/or gastrointestinal symptoms, temperature $<38^{\circ}\text{C}$ and does not refer symptoms suggestive of COVID-19 pneumonia such as dyspnoea, persistent chest pain and intensive cough; if available, oxygen saturation in room air is $>95\%$, respiratory rate $<25/\text{min}$; no evidence of pneumonia on either chest X-ray or CT; no need for hospitalization	If patient is on: Triple therapy Dual therapy (including steroids) Dual therapy (steroid-free) CNI + MPA CNI + mTORi MPA + mTORi
	Stop MPA/AZA/mTORi Maintain CNI + steroids Continue dual therapy Consider replacing MPA with low-dose steroids Consider replacing mTORi with low-dose steroids Consider replacing MPA or mTORi with low-dose steroids
	• Consider CNI dose reduction (to the lower bound of the therapeutic range according to the immunological risk) if there is no clear improvement over the first 3–5 days • Cautiously restart previous immunosuppression 3–7 days after symptoms have cleared
4. Evidence of mild COVID-19 pneumonia: oxygen saturation 94–95% in room air; respiratory rate 25–29/min; or suspect lesions on chest X-ray or CT scan	a. High-risk patient: age ≥ 70 years, or comorbidities or risk factors (diabetes, cardiac or pulmonary disease, heavy smoking, BMI >30 kg/m ² , eGFR <30 mL/min/1.73 m ² , lymphocyte depletion therapy within previous 3–6 months) Stop MPA/AZA/mTORi, Stop CNI Increase (or start) steroids 15–25 mg/day
	• Cautiously restart previous immunosuppression (CNI first) 5–10 days after symptoms have cleared
b. No high-risk patient (as defined above)	Stop MPA/AZA/mTORi Maintain on dual therapy CNI-steroids Reduce CNI trough levels to target CsA: 50 ± 15 ng/mL, Tac: 3 ± 1 ng/mL Continue steroids in maintenance dose
	• In patients starting antiretroviral treatment: stop CNI and monitor as detailed in the text • Cautiously restart previous immunosuppression 5–10 days after symptoms have cleared
5. More severe COVID-19 pneumonia: oxygen saturation $<94\%$ in room air, respiratory rate $\geq 30/\text{min}$, unstable or deteriorating course or requiring non-invasive ventilation or transfer to the intensive care unit (with or without mechanical ventilation)	Discontinue all immunosuppressive drugs Increase/start steroids at 15–25 mg/day (or higher according to local practice).

DESCARTES expert opinion regarding the management of immunosuppressive medication for kidney transplant patients during the COVID-19 pandemic

Adjustment of Immunosuppressive medication

1) **A**symptomatic patients, no knowledge of COVID-19 status (ambulatory, stable patients):



No change of immunosuppressive medications

2) Mild disease



Stop MPA/AZA/mTORi

3) Mild pneumonia

If high risk patient,



Stop CNI
Increase steroid 15-25mg/day

No high risk



Reduce CNI
Continue steroids
in maintenance

4) Severe covid-19 pneumonia



Discontinue all immunosuppressive drugs
Steroid at 15-25mg/d

Cyclosporine as a preferred calcineurin inhibitor in renal allograft recipients with **COVID-19 infection**

de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al.
Cyclosporin A inhibits the replication of diverse
coronaviruses.

J Gen Virol. 2011;92:2542–.2548



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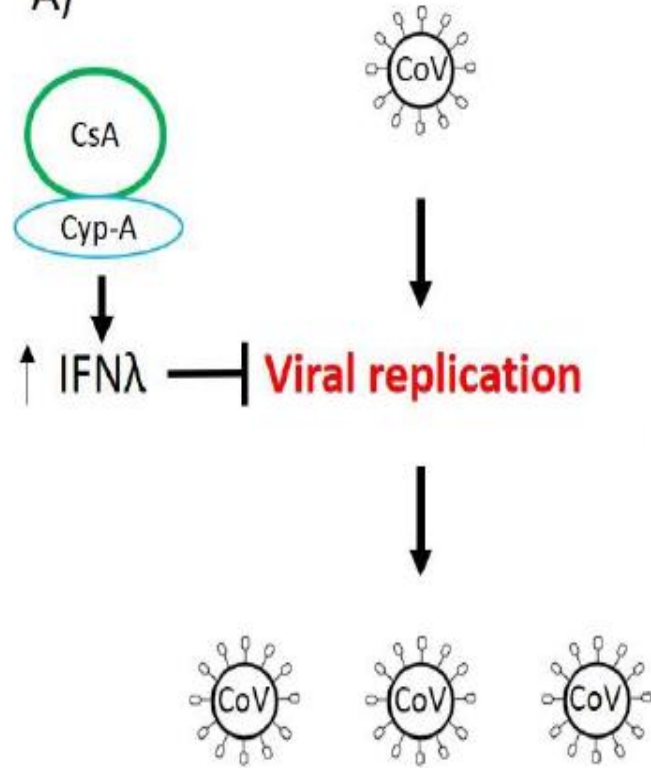
Early View

Editorial

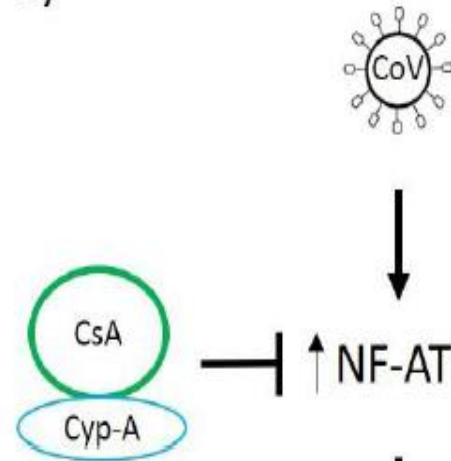
Cyclosporine: an old weapon in the fight against Coronaviruses

Adam Molyvdas, Sadis Matalon

A)



B)



C)

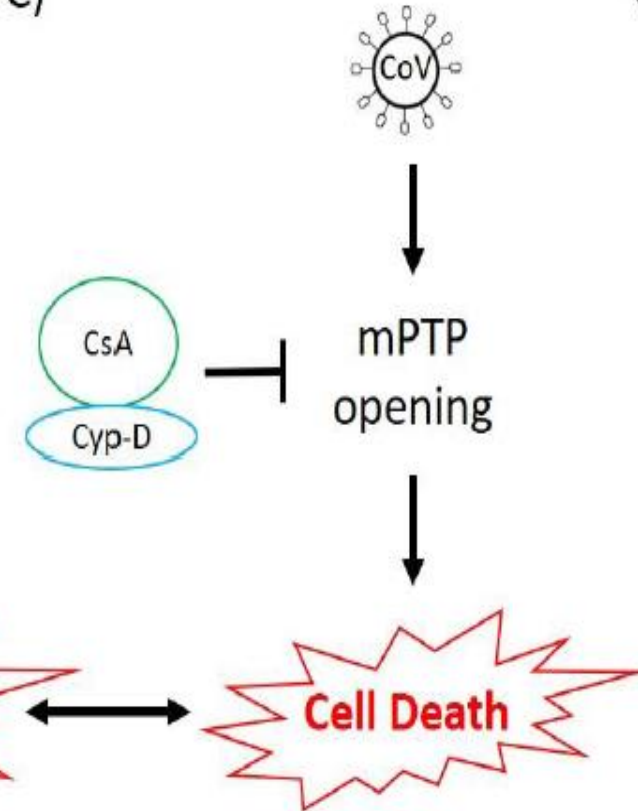
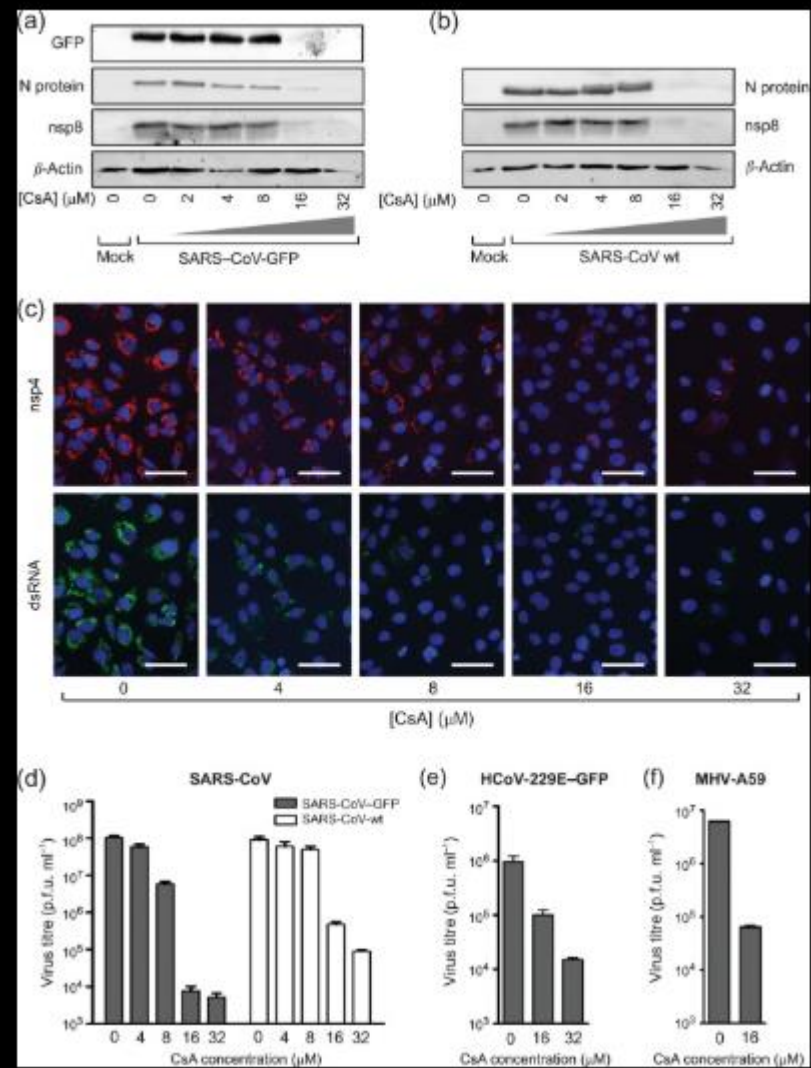


Figure 1. Schematic overview of the interactions of cyclosporine A (CsA) and coronaviruses. **A)** CsA binds to cyclophilin A (Cyp-A) and upregulates Interferon lambda ($\text{IFN}\lambda$) which blocks viral replication. **B)** Coronaviruses activate nuclear factor of activated T cell (NF-AT), which triggers the release of inflammatory cytokines and causes inflammation. The CsA-Cyp-A complex prevents the activation NF-AT reducing inflammation. **C)** Coronaviruses cause aberrant opening of the mitochondrial permeability transition pore (mPTP), which results in cell death. CsA in complex with cyclophilin-D (Cyp-D) prevents the opening of mPTP reducing cell damage and cell death.



↑ [See this image and copyright information in PMC](#)

Fig. 2. CsA treatment inhibits coronavirus protein and RNA synthesis, and the production of infectious progeny. Vero E6 cells were infected with SARS-CoV-GFP (a) or wt SARS-CoV (b) and treated with CsA from 1 to 10 h p.i. Viral protein expression was analysed by Western blotting



A call for action
(teamwork)

The *enormous demand in care for COVID-19 patients* requires an *immediate response* from the *scientific community*.



Do your best and
God will do the rest.

Nick Vujicic