COVID-19
Tedavi

24 Mart 2020

JOHNS HOPKINS UNIVERSITY & MEDICINE | Coronavirus Resource Center

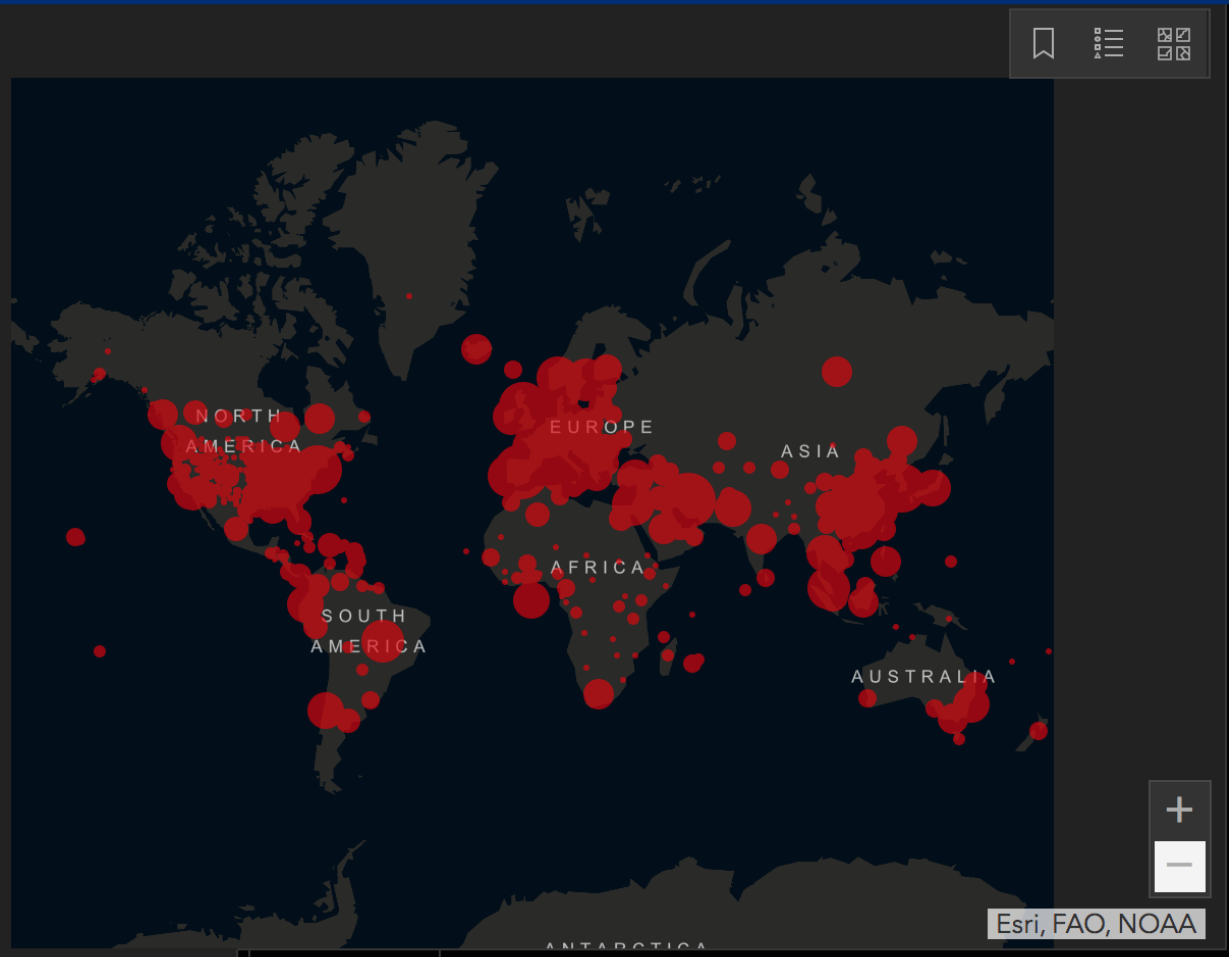
Map Information | Map FAQ

Total Confirmed
398,107

Confirmed Cases by Country/Region/Sovereignty
- 81,591 China
- 63,927 Italy
- 46,805 US
- 39,676 Spain
- 31,370 Germany
- 24,811 Iran
- 20,149 France
- 9,117 Switzerland
- 9,037 Korea, South
- 8,160 United Kingdom
- 5,578 Netherlands

Admin1

Last Updated at (M/D/YYYY)
3/24/2020, 6:07:50 PM



Cumulative Confirmed Cases | Active Cases

169 countries/regions

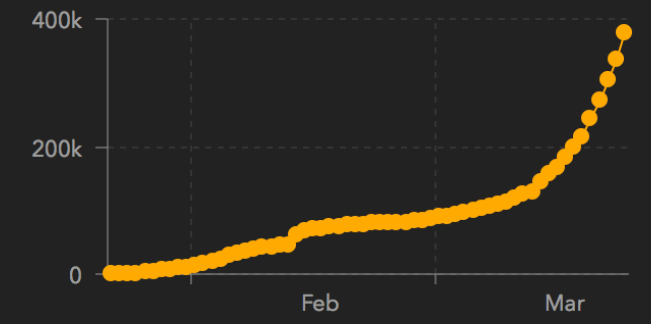
Lancet Inf Dis Article: Here. Mobile Version: Here. Visualization: JHU CSSE. Automation Support: Esri Living Atlas team and JHU APL. Contact US. FAQ.
Data sources: WHO, CDC, ECDC, NHC, DXY, 1point3acres,

Total Deaths
17,454

- 6,077 deaths Italy
- 3,160 deaths **Hubei** China
- 2,800 deaths Spain
- 1,934 deaths Iran
- 860 deaths France
- 422 deaths United Kingdom

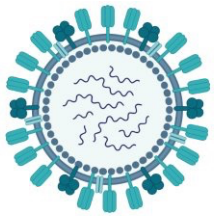
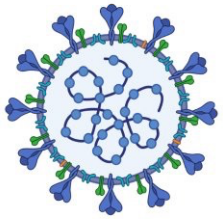
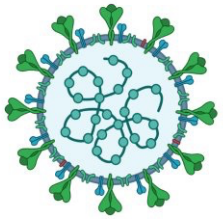
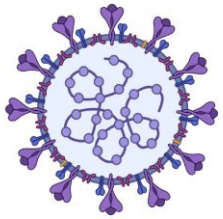
Total Recovered
103,334

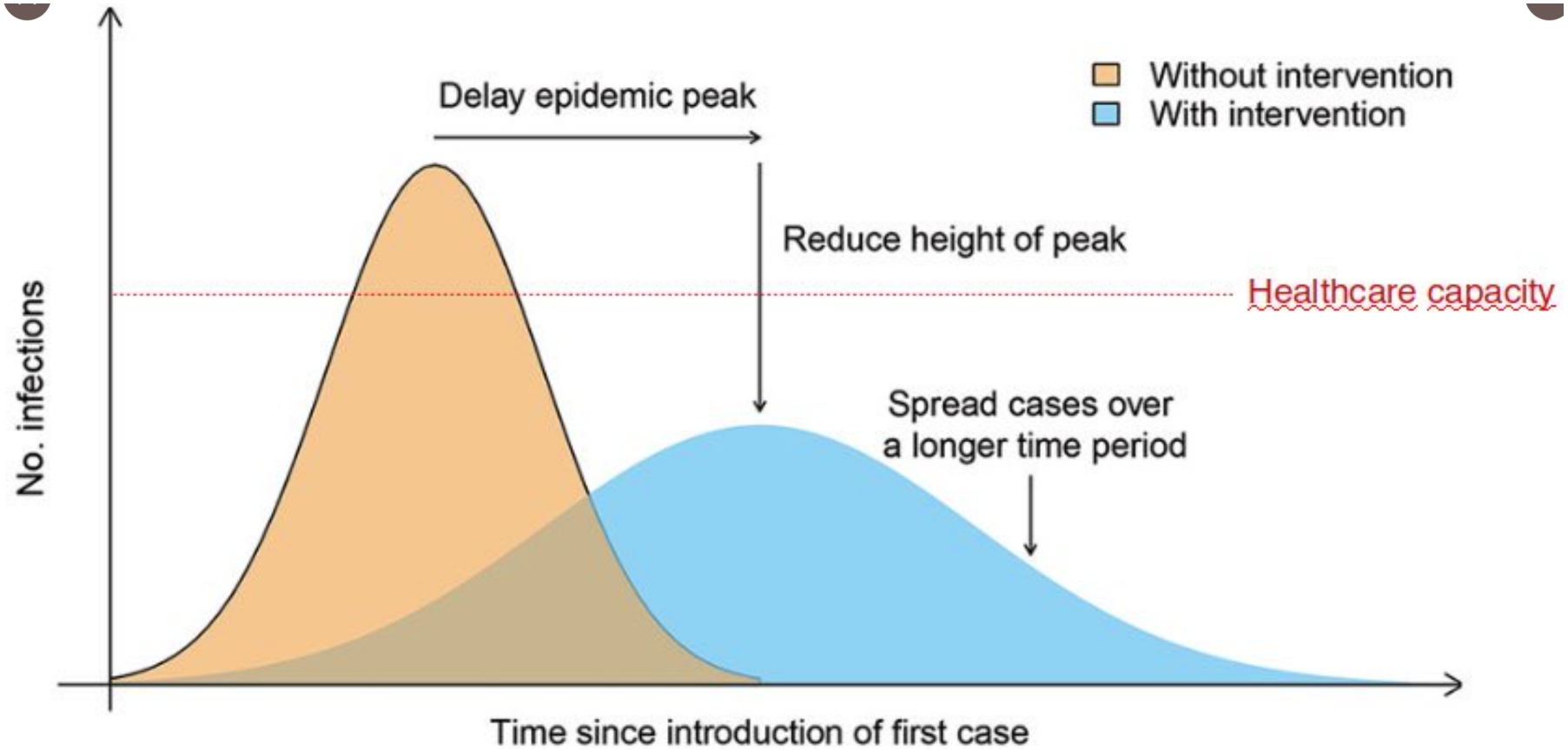
- 60,324 recovered **Hubei** China
- 8,913 recovered Iran
- 7,432 recovered Italy
- 3,794 recovered Spain
- 3,507 recovered Korea, South
- 2,200 recovered France



Confirmed | Daily Increase

Epidemiological Comparison of Respiratory Viral Infections

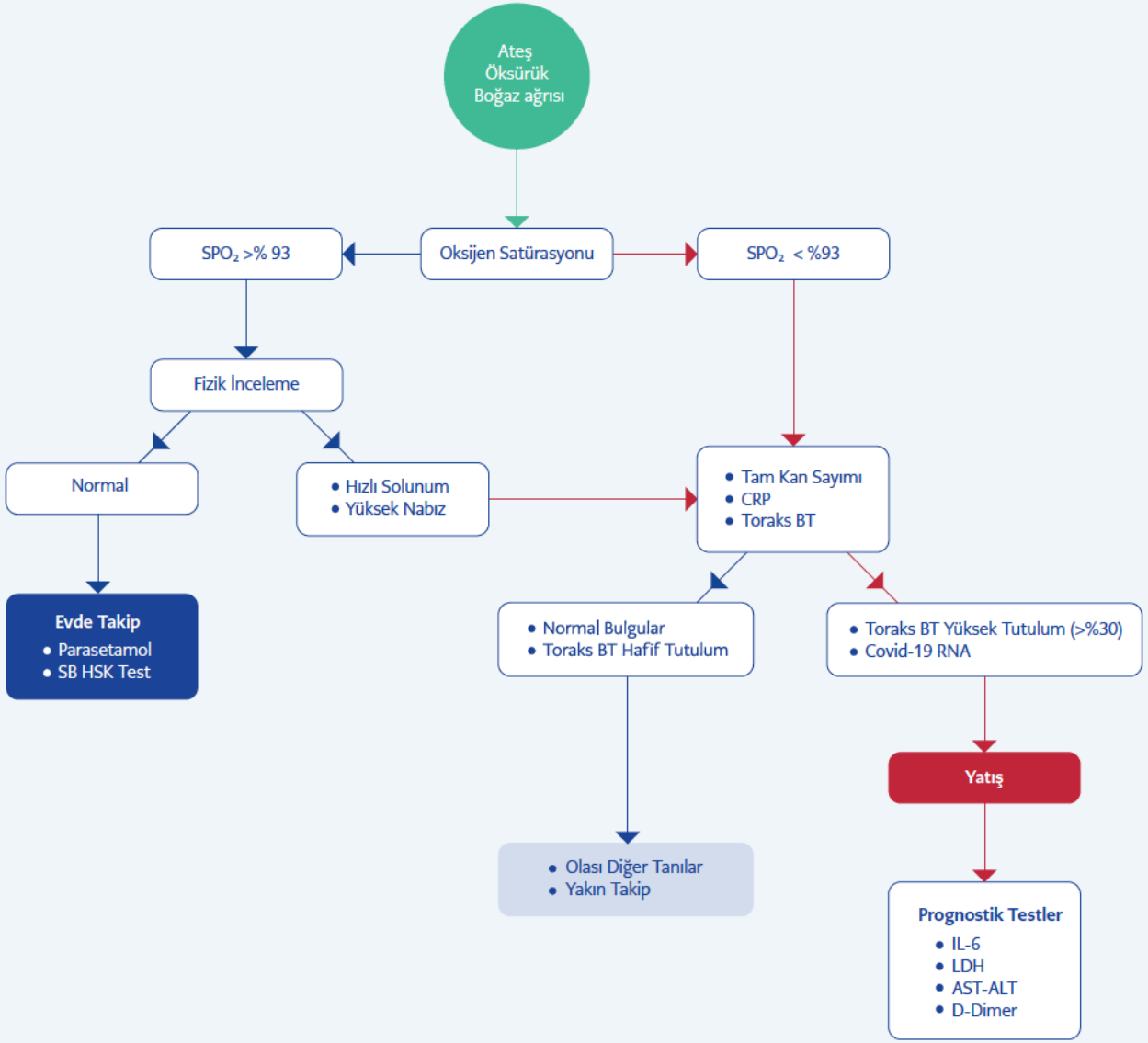
Disease	Flu	COVID-19	SARS	MERS
Disease Causing Pathogen	 Influenza virus	 SARS-CoV-2	 SARS-CoV	 MERS-CoV
R_0 Basic Reproductive Number	**1.3**	**2.0 - 2.5** *	**3**	**0.3 - 0.8**
CFR Case Fatality Rate	0.05 - 0.1%	~3.4% *	9.6 - 11%	34.4%
Incubation Time	1 - 4 days	4 - 14 days *	2 - 7 days	6 days
Hospitalization Rate	2%	~19% *	Most cases	Most cases
Community Attack Rate	10 - 20%	30 - 40% *	10 - 60%	4 - 13%
Annual Infected (global)	~ 1 billion	N/A (ongoing)	8098 (in 2003)	420
Annual Infected (US)	10 - 45 million	N/A (ongoing)	8 (in 2003)	2 (in 2014)
Annual Deaths (US)	10,000 - 61,000	N/A (ongoing)	None (since 2003)	None (since 2014)


Without intervention
With intervention
Delay epidemic peak
Reduce height of peak
Healthcare capacity
Spread cases over
a longer time period
No. infections
Time since introduction of first case

COVID-19

ŞÜPHELİ HASTA YÖNETİMİ (01)

Hazırlanma Tarihi: 21.03.2020

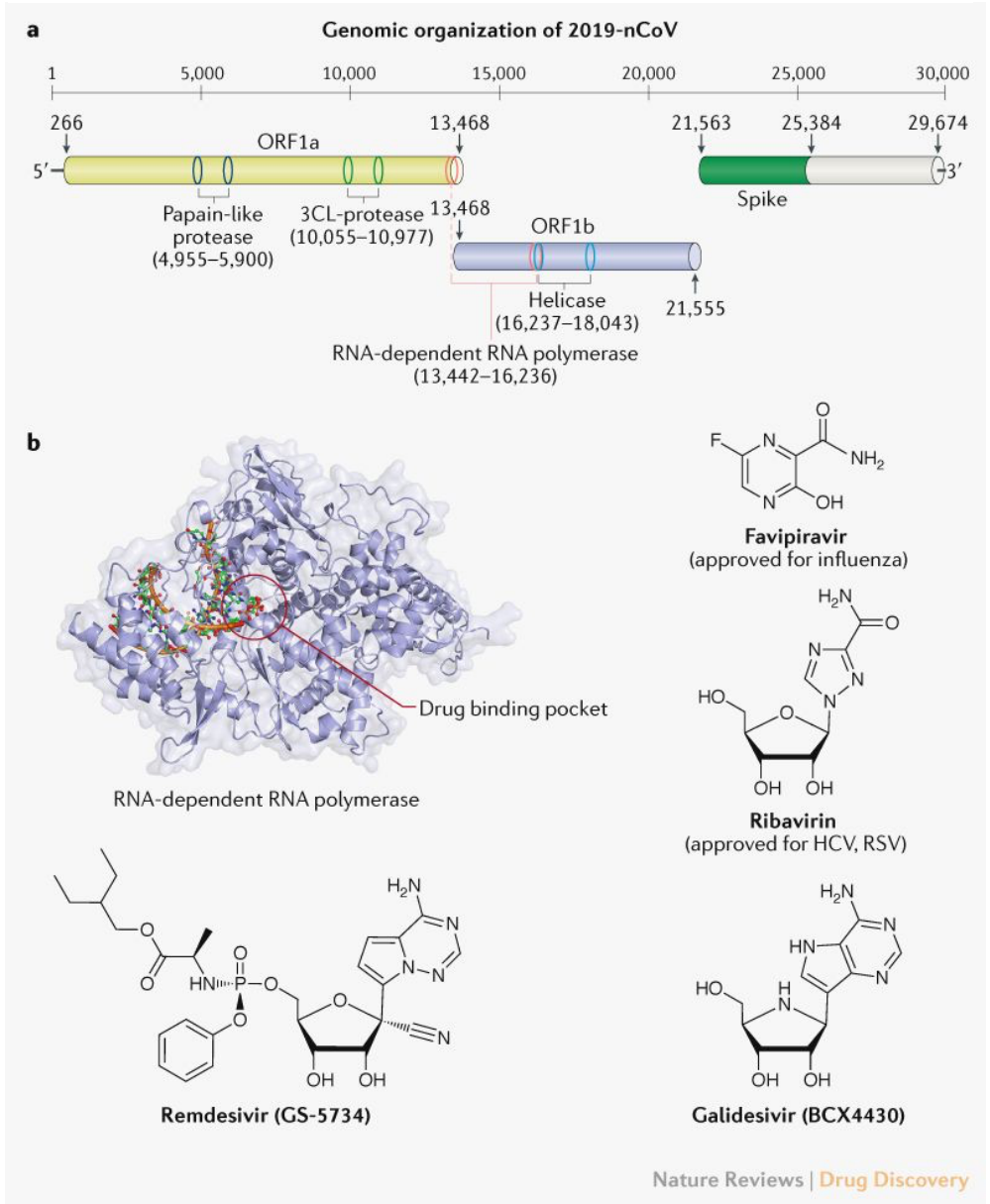


Tedavi seçenekleri

1. Hidkroksiklorokin (HQ)
   - HQ + azitromisin
2. Lopinavir/ritonavir
3. Remdesivir
4. Ribavirin
5. favipravir
6. Tocilizumab
7. Oseltamivir
8. Baloxavir
9. İnterferonlar
10. Kortikosteroidler

Therapeutic options for the 2019 novel coronavirus (2019-nCoV)

Guangdi Li[1] ✉ *and Erik De Clercq*[2] ✉



Nature 2020

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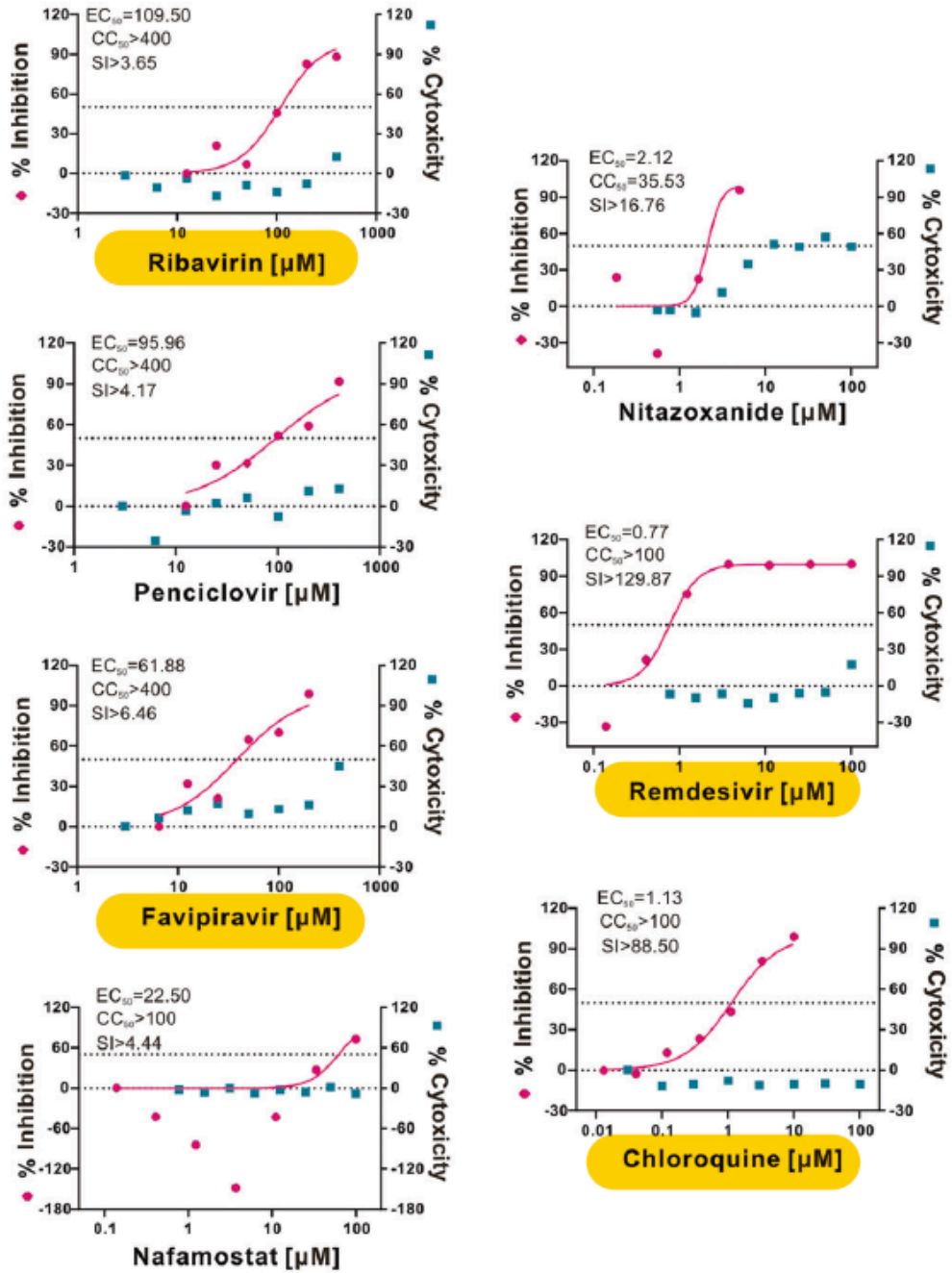


Cell Research

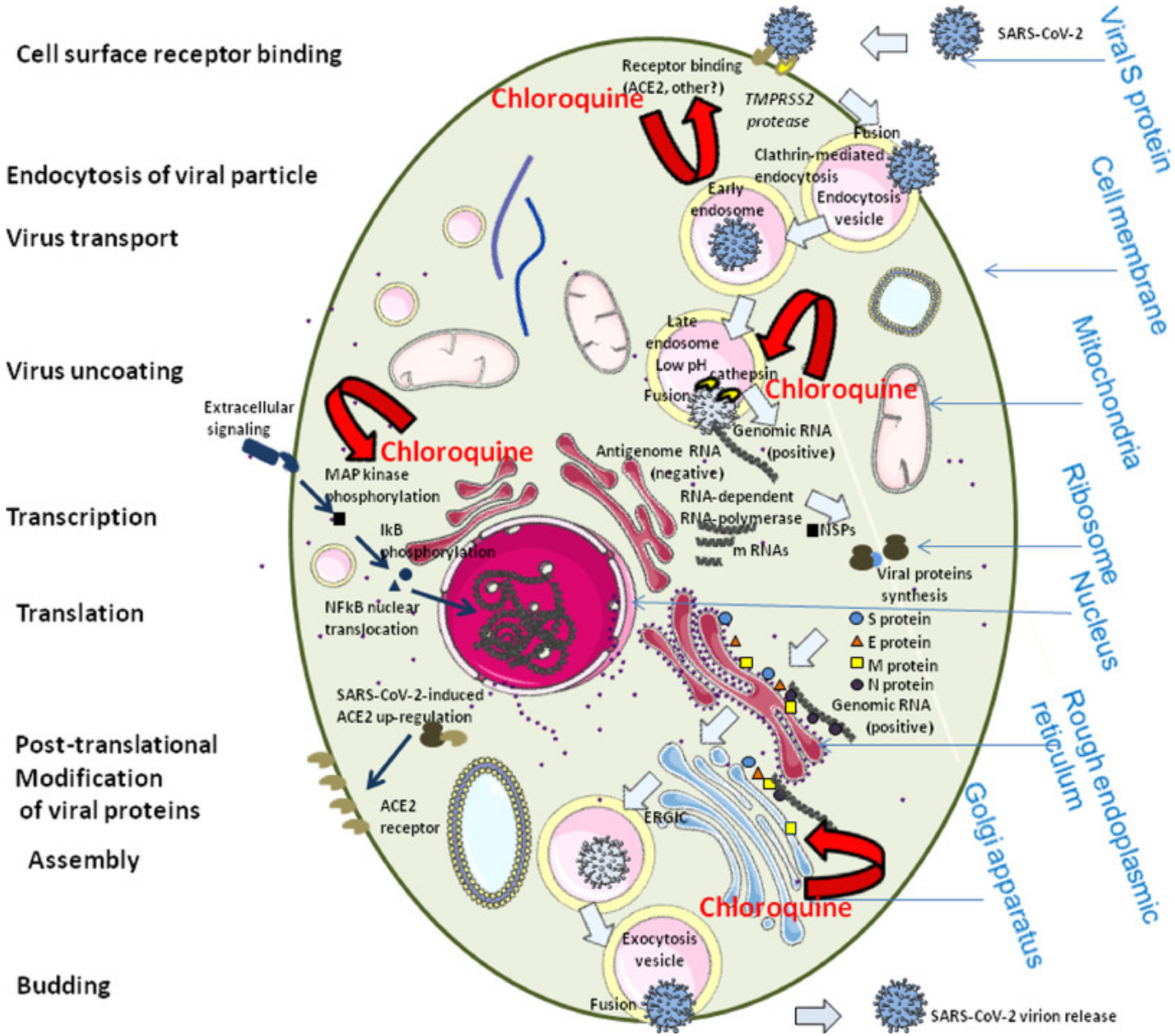
www.nature.com/cr
www.cell-research.com

LETTER TO THE EDITOR OPEN

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Cell Research (2020) 30:269–271; https://doi.org/10.1038/s41422-020-0282-0

Our findings reveal that remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro. Since these compounds have been used in human patients with a safety track record and shown to be effective against various ailments, we suggest that they should be assessed in human patients suffering from the novel coronavirus disease.



Raoult D, New Insights… IJAA 2020

HCQ + Azithromycin: Gautret, IJAA 2020

To this point, Gautret and colleagues recently published their initial experience on the impact of hydroxychloroquine 200 mg by mouth every 8 hours on viral eradication in patients with COVID-19.[20] The authors reported on 36 patients (20 hydroxychloroquine and 16 control) who were COVID-19 positive and able to have nasopharyngeal sampling for the first 6 days of therapy (in the treated arm). The investigators demonstrated that hydroxychloroquine (14/20, 70%) was superior to standard of care (2/16, 12.5%; p = 0.001) in eradicating SARS-CoV-2 from the nasopharynx. Interestingly, 6 patients were prescribed azithromycin "to prevent bacterial super-infection" and the investigators found viral eradication was numerically superior in this subgroup (6/6, 100%) compared to those who received hydroxychloroquine alone (8/14, 57%). The authors concluded that azithromycin "reinforced" the SARS-CoV-2 viral load achieved by hydroxychloroquine. While these data are intriguing, certain limitations to this data set must be acknowledged. First, while viral eradication is an important endpoint, the authors did not report clinical outcomes in these patients. Second, the cohort initially contained 26 hydroxychloroquine patients but six of them were removed from the analysis due to early cessation of hydroxychloroquine therapy including three PCR positive patients who were transferred to the ICU, 1 PCR negative patient who passed away, and 1 PCR positive patient who discontinued hydroxychloroquine due to nausea. Finally, the hydroxychloroquine monotherapy arm included patients with significantly higher viral loads, represented by lower cycle threshold (C_T) values than those who received combination therapy. If the hydroxychloroquine monotherapy patients with C_T values < 23 are separated from those with CT values ≥ 23, there is a notable discordance in viral eradication rates (1/5, 20% vs. 7/9, 78%), with this latter number approaching the 6/6 demonstrated with hydroxychloroquine and azithromycin combination therapy where all patients had CT values ≥ 23. Given this finding, the small numbers in this study, the lack of clinical outcomes presented, the potential for additive toxicity with hydroxychloroquine and azithromycin, and the desperate need to practice good antimicrobial stewardship during the COVID-19 pandemic, we would caution clinicians against using these data to support combination therapy.

Dr. Fauci and the president have publicly disagreed on how long it will take for a coronavirus vaccine to become available and whether an anti-malaria drug, chloroquine, could help those with an acute form of the virus. **Dr. Fauci has made clear that he does not think the drug necessarily holds the potential that Mr. Trump says it does.**

Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection

Emmie de Wit[a,1], Friederike Feldmann[b], Jacqueline Cronin[a], Robert Jordan[c], Atsushi Okumura[d], Tina Thomas[a], Dana Scott[b], Tomas Cihlar[c], and Heinz Feldmann[a]

[a]Laboratory of Virology, National Institute of Allergy and Infectious Diseases, NIH, Hamilton, MT 59840; [b]Rocky Mountain Veterinary Branch, National Institute of Allergy and Infectious Diseases, NIH, Hamilton, MT 59840; [c]Biology Department, Gilead Sciences, Foster City, CA 94404; and [d]Center for Infection and Immunity, Mailman School of Public Health, Columbia University, New York, NY 10032

Edited by Michael B. A. Oldstone, Scripps Research Institute, La Jolla, CA, and approved February 7, 2020 (received for review December 16, 2019)

The continued emergence of Middle East Respiratory Syndrome (MERS) cases with a high case fatality rate stresses the need for the availability of effective antiviral treatments. Remdesivir (GS-5734) effectively inhibited MERS coronavirus (MERS-CoV) replication in vitro, and showed efficacy against Severe Acute Respiratory Syndrome (SARS)-CoV in a mouse model. Here, we tested the efficacy of prophylactic and therapeutic remdesivir treatment in a nonhuman primate model of MERS-CoV infection, the rhesus macaque. Prophylactic remdesivir treatment initiated 24 h prior to inoculation completely prevented MERS-CoV–induced clinical disease, strongly inhibited MERS-CoV replication in respiratory tissues, and prevented the formation of lung lesions. Therapeutic remdesivir treatment initiated 12 h postinoculation also provided a clear clinical benefit, with a reduction in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions. The data presented here support testing of the efficacy of remdesivir treatment in the context of a MERS clinical trial. It may also be considered for a wider range of coronaviruses, including the currently emerging novel coronavirus 2019-nCoV.

MERS-CoV | antiviral | animal model | remdesivir | therapy

presence of GS-441524, a parent nucleoside that is metabolized into the same active triphosphate metabolite, were still sensitive to higher concentrations of remdesivir, and fitness was impaired in the resistant viruses as compared to wild-type MERS-CoV (9). With these promising data in mind, we tested the prophylactic and therapeutic efficacy of remdesivir treatment in a nonhuman primate model of MERS-CoV infection, the rhesus macaque (10).

Results

Remdesivir Reduces Clinical Signs in Rhesus Macaques upon Prophylactic and Therapeutic Treatment. To assess the efficacy of remdesivir to alleviate clinical signs of MERS-CoV infection, 18 rhesus macaques were randomly assigned to three groups of six animals. Three animals in the control group were treated with 1 mL/kg vehicle solution 24 h before MERS-CoV inoculation, and three animals were treated at 12 h post MERS-CoV inoculation. Another group of six rhesus macaques was treated prophylactically 24 h before MERS-CoV inoculation with 5 mg/kg remdesivir, and one group of six animals was treated therapeutically at 12 h postinoculation with MERS-CoV with 5 mg/kg remdesivir. Treatment

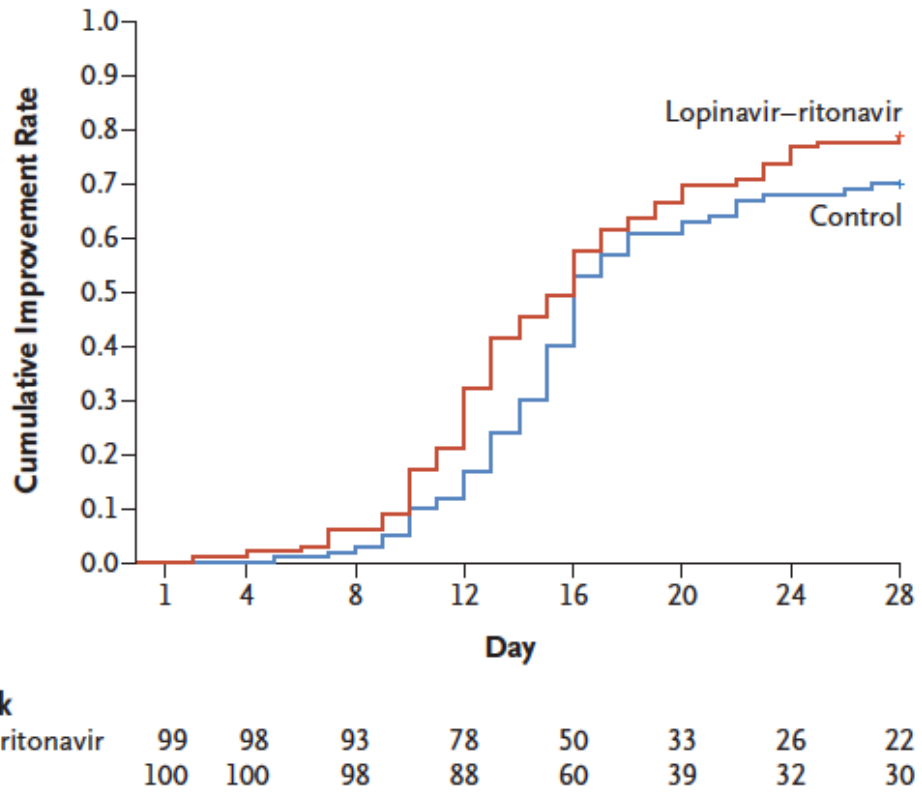
PNAS, Feb 14 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang



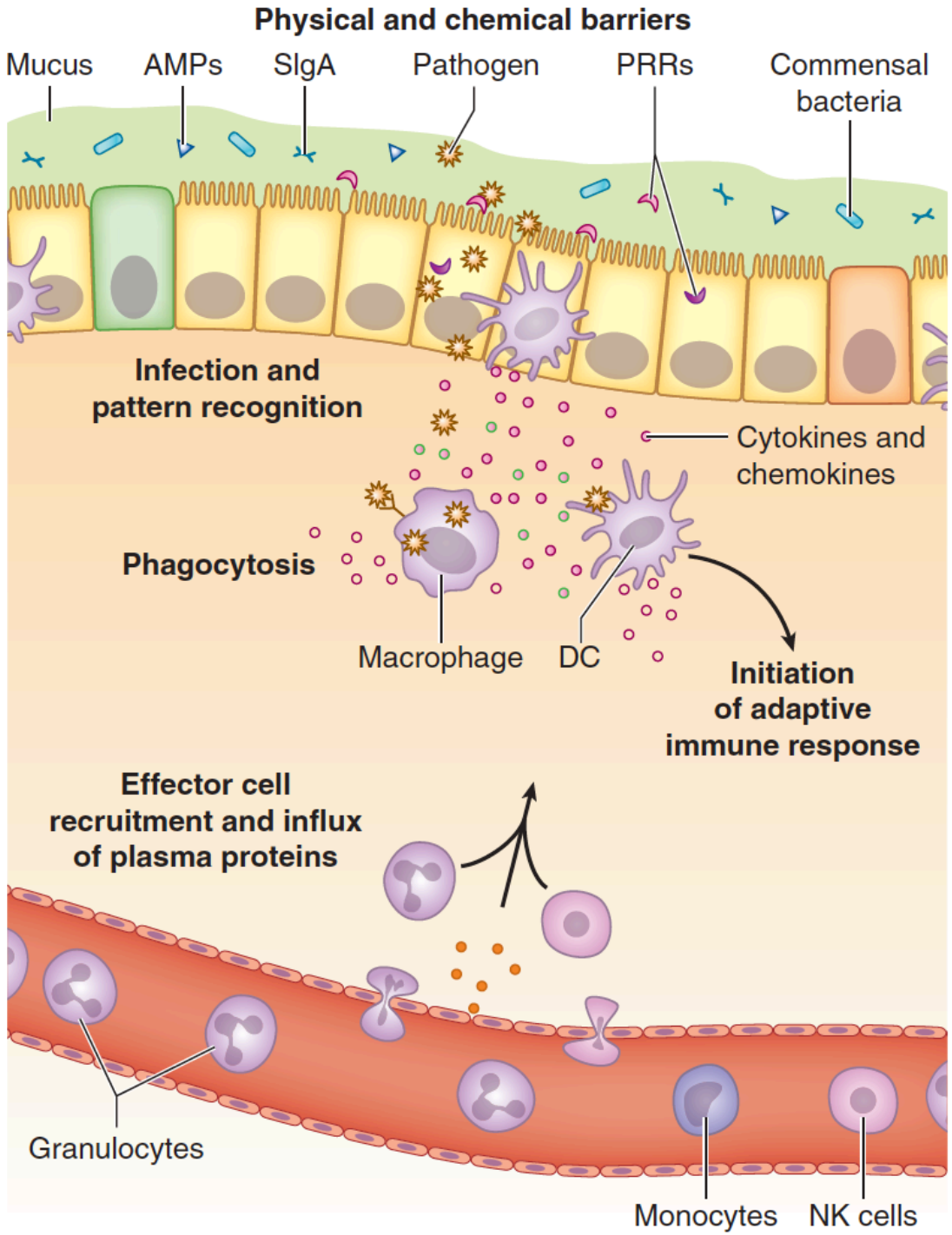
No. at Risk

Lopinavir–ritonavir	99	98	93	78	50	33	26	22
Control	100	100	98	88	60	39	32	30

Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

In conclusion, we found that lopinavir–ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious Covid-19. These early data should inform future studies to assess this and other medication in the treatment of infection with SARS-CoV-2. Whether combining lopinavir–ritonavir with other antiviral agents, as has been done in SARS[5,20] and is being studied in MERS-CoV,[15] might en-

Klorokin + Kaletra
kullanılması için veri yok
Ama eklenebilir?


Physical and chemical barriers
Mucus
AMPs
SIgA
Pathogen
PRRs
Commensal bacteria
Infection and pattern recognition
Cytokines and chemokines
Phagocytosis
Macrophage
DC
Initiation of adaptive immune response
Effector cell recruitment and influx of plasma proteins
Granulocytes
Monocytes
NK cells

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Interim Recommendations for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation

This document is intended for use by healthcare professionals only.

The recommendations are specific to the management of Patients with confirmed Severe COVID-19 with Suspected Hyperinflammation. While the recommendations are intended to strengthen clinical management of these patients they do not replace clinical judgment or specialist consultation.

Protocol: Interim Recommendations for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation		Published: 20 Mar 2020 Review: 30 Apr 2020	Version number: 1.0
Protocol Code: COVID19-TOCILIZUMAB	Approved by: Dr Vida Hamilton, HSE National Clinical Advisor and Group Lead, Acute Hospitals	Contributors: Prof C Bergin, N Conlon, A O'Leary, R Adams, F King, P Gilvarry.	Page 1 of 14

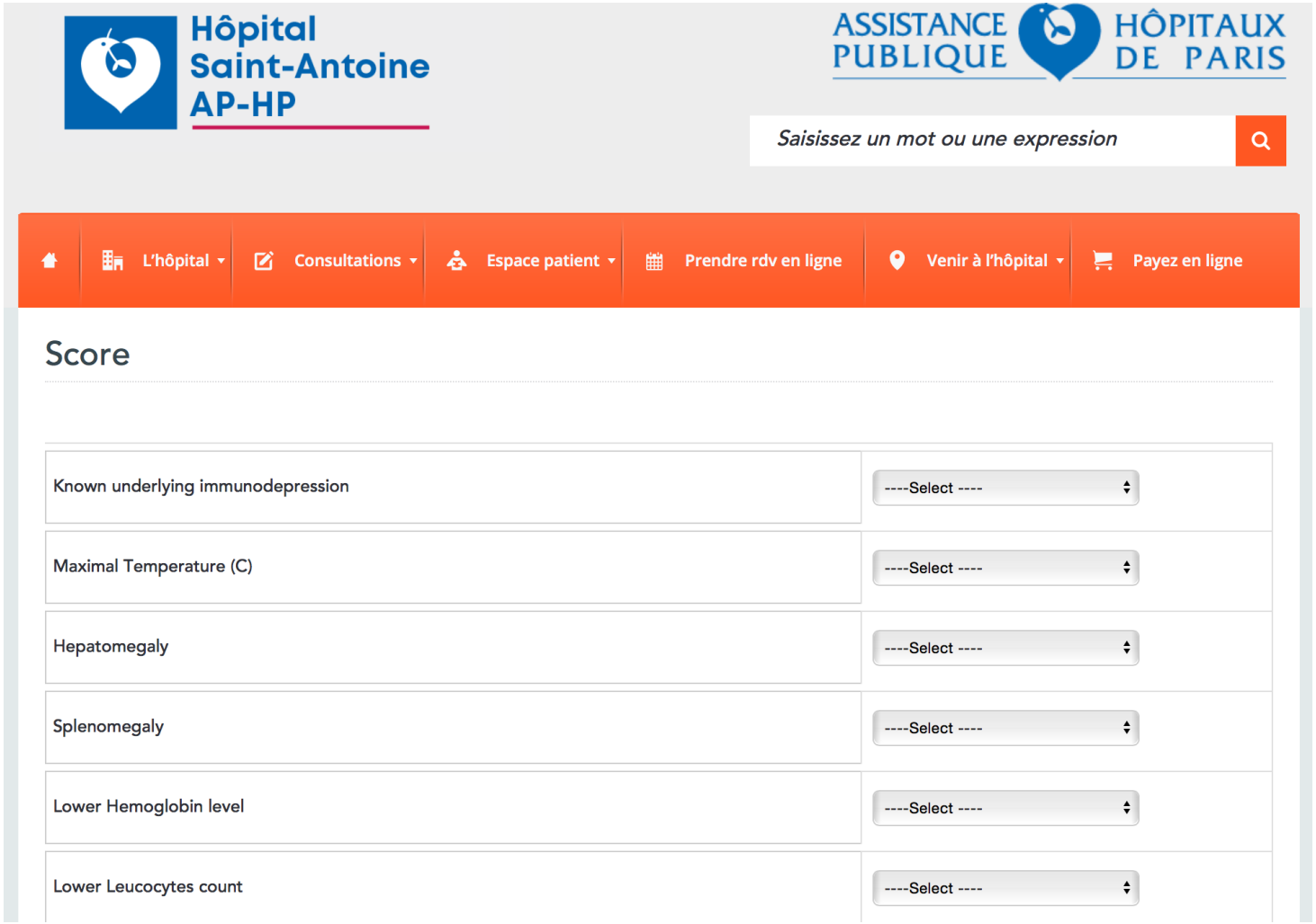
Table 1 - Summary of evidence for tocilizumab in COVID-19

Study Title (location)	Methodology	Population	Outcome assessed	Efficacy data	Reference
Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia (China) [16]	Retrospective observational analysis of chart data. Intervention: tocilizumab	Patients (n=29) were stratified into three groups according to degree of severity: mild (15 cases), severe (9 cases) and critical (5 cases).	To analyse the clinical characteristics of 2019 novel coronavirus (2019-nCoV) pneumonia and to investigate the correlation between serum inflammatory cytokines and severity of the disease.	There were statistically significant differences in the expression levels of interleukin-2 receptor (IL-2R) and IL-6 in the serum of the three groups ($P<0.05$), among which the critical group was higher than the severe group and the severe group was higher than the mild group. The authors claim that the increased expression of IL-2R and IL-6 in serum is expected to predict the severity of the 2019-nCoV pneumonia and the prognosis of patients. However, patient numbers in this study are small. No criteria were provided to define severity in COVID-19. Baseline and change in IL-6 levels were not presented in the publication. No a priori definition was provided which defined magnitude or range of IL-6 to be measured. The study has not been peer-reviewed.	Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. [16]
Effective Treatment of Severe COVID-19 Patients with Tocilizumab (China) [17]	Retrospective observational analysis of chart data. Intervention: tocilizumab 400mg once as an IV infusion. (Note: n =3/21 had a second dose within 12 hours) All patients were treated with standard of care prior to initiation of tocilizumab which included lopinavir, methylprednisolone, other supportive therapies and oxygen therapy.	Patients (n=20) diagnosed as severe or critical COVID-19. Severity was defined if any of the following conditions was met: (1) respiratory rate ≥ 30 breaths/min; (2) SpO2 ≤ 93% while breathing room air; (3) PaO2/FiO2 ≤ 300 mmHg. A critical case was diagnosed if any of: (1) respiratory failure which requiring mechanical ventilation; (2) shock; (3) combined with other organ failure, need to be admitted to ICU	To retrospectively analyse the changes of clinical manifestations, CT scans, and laboratory examinations.	Preliminary data was reported from a small study demonstrated that 15 of the 20 patients reduced their oxygen therapy and one patient did not require oxygen therapy following treatment with tocilizumab. The body temperature of all patients returned to normal on the first day after receiving tocilizumab and remained stable then after. The authors report that inflammatory markers including CRP, lymphocytes all normalised or decreased significantly. In total nineteen patients (90.5%) have been discharged on average 13.5 days after the treatment with tocilizumab. The study has not been peer-reviewed. The study sample is small. Patients were also being treated with other therapies during the study including lopinavir which may have contributed to the positive outcomes. It is noted that based on these results, China recently updated its COVID-19 treatment guidelines, approving the use of tocilizumab to treat patients with severe or critical disease	Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective Treatment of Severe Covid-19 Patients with Tocilizumab. ChinaXiv [Internet]. 2020 Mar 5 [cited 2020 Mar 16]; Available from: https://www.ser.es/wp-content/uploads/2020/03/TCZ-and-COVID-19.pdf [17]

Technical Appendix 2:H Score

The H score generates a probability for the presence of secondary haemophagocytic lymphohistiocytosis (sHLH). HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator which is available at http://saintantoine.aphp.fr/score/

HScore for secondary HLH, by clinical parameter



1. Immunsüpresyon
2. Sıcaklık
3. Hepatomegali
4. Splenomegali
5. Hb
6. Düşük lökosit sayısı
7. Düşük trombosit
8. Yüksek ferritin
9. Yüksek trigliserid
10. Yüksek AST/ALT
11. Hemofagositoz

IL-6 Testi ve Tocilizumab

1. IL-6 testi kimlere yapılmalı?
2. Tocilizumab ne zaman verilmeli
    - 3x > IL-6 veya >300 (üst sınır 9)
    - Artış olması
    - Başka parametrelerle birlikte

Yararı Olmadığı Düşünülen İlaçlar

Ribavirin
Interferonlar
Oseltamivir: nörominidazı kullanmıyor
Baloxavir

COVID-19 Treatment: A Review of Early and Emerging Options

Erin K. McCreary, PharmD, BCPS, BCIDP[1,#] and Jason M. Pogue, PharmD, BCPS, BCIDP[2] on behalf of the Society of Infectious Diseases Pharmacists

1. Department of Pharmacy, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
2. Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI, USA