Fondazione theBRIDGE SCIENZA TRA CLINICA E SOCIETÀ

COVID-19
Il virus ignorante

LA PRATICA CLINICA

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Covid -19, primi mesi: la scelta terapeutica

Since the beginning of the COVID-19 outbreak, a growing body of information on therapeutic strategies has emerged, mainly based on **preliminary experience** on **retrospective studies** or **small case series**. Antivirals, antimalarials, corticosteroids, biotechnological and small molecules, convalescent plasma and anticoagulants are among the drugs proposed for the treatment or in tested for COVID-19.

RAPID RISK ASSESSMENT

Coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – seventh update

25 March 2020

RAPID RISK ASSESSMENT

Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update

8 April 2020

Clinical management of COVID-19

Interim guidance
27 May 2020

World Health Organization

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19

Scientific brief

19 April 2020

World Health Organization

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19

Scientific brief

19 April 2020

World Health Organization

Handbook of COVID-19 Prevention and Treatment

The First Affiliated Hospital, Zhejiang University School of Medicine
Compiled According to Clinical Experience

马云公益基金会 Jack Ma Foundation | 浙江大学 | Alibaba Cloud | AliHealth 阿里健康

parola guida: limitations

This assessment is undertaken based on information available to ECDC at the time of publication. There is **substantial uncertainty** regarding the epidemiological characteristics of COVID-19. There is **limited** epidemiological and clinical information on the cases of COVID-19 identified so far (e.g. efficiency of different modes of transmission, proportion of mild and asymptomatic cases, transmission during incubation and recovery period, **effectiveness of treatment regimes**, risk factors for severe illness other than age, effective preventive measures). **Given these limitations**, ECDC will revise the current risk assessment as soon as more information becomes available.

Covid -19, primi mesi: la scelta terapeutica

Since the beginning of the COVID-19 outbreak, a growing body of information on therapeutic strategies has emerged, mainly based on **preliminary experience** on **retrospective studies** or **small case series**. Antivirals, antimalarials, corticosteroids, biotechnological and small molecules, convalescent plasma and anticoagulants are among the drugs proposed for the treatment or in tested for COVID-19.

Corriere del mezzogiorno
25 marzo 2020

EMERGENZA COVID-19

Coronavirus, cura Ascierto-Pascale: a Napoli torna a casa la prima paziente trattata col Tocilizumab

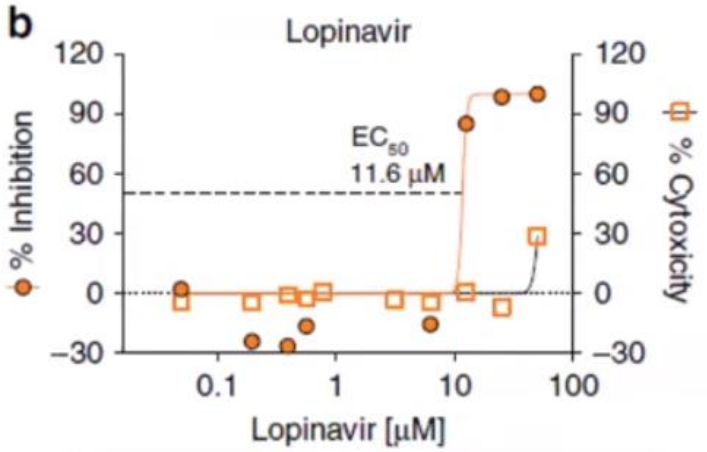
L'oncologo promotore dello studio Aifa: «Un altro segnale incoraggiante, andiamo avanti»

Farmaci utilizzati all'inizio della epidemia

- **Farmaci antiretrovirali**
  - Lopinavir
  - Darunavir
- **Altri antivirali**
  - Remdesivir
  - Ribavirina
  - Favipiravir
- **Altri farmaci ad azione antivirale**
  - Clorochina
  - Idrossiclorochina
- **Farmaci immunomodulanti**
  - Corticosteroidi
  - Anti-IL6R (Tocilizumab, ecc)
  - Anti-IL1R (Anakinra, ecc)
  - Plasma iperimmune
- **Altri farmaci**
  - Eparine a basso peso molecolare o Eparina non frazionata

Lopinavir/ritonavir

- **Inhibit SARS-CoV-2 serine proteases?**
- **Modest evidence of in vitro activity[1]**
- **Retrospective case-control series suggest benefit in SARS[2,3]**
- **RCT in patients with severe COVID-19 showed no clinical benefi4[3]**
  - Possible benefit if started early in disease (prior to day12?)



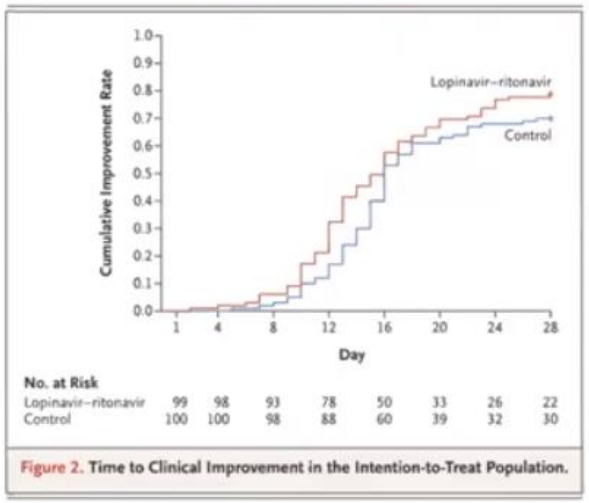
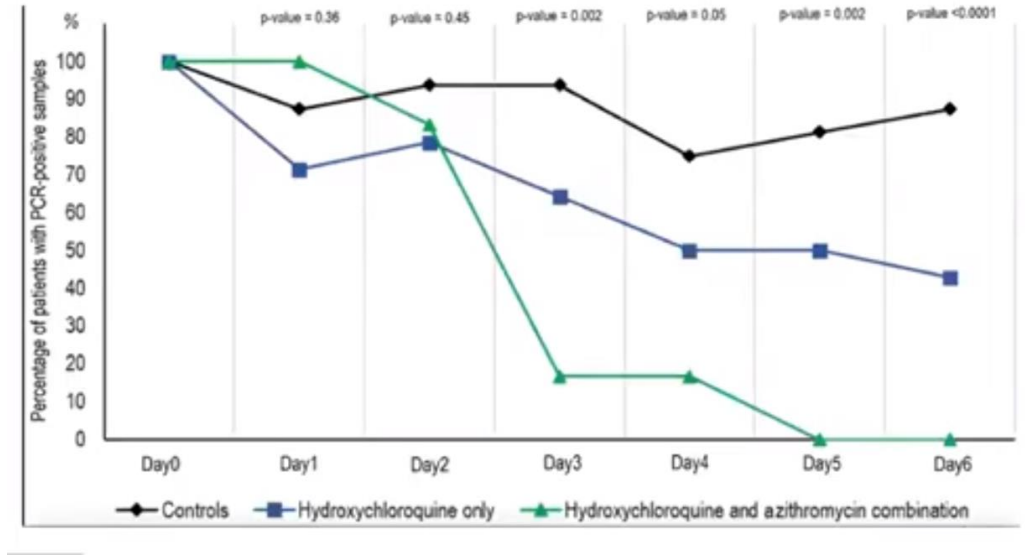


Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

[1]Sheahan TP et al Nat Commun 2020; [2]Chu CM et al Thorax 2004; [3]Chan KS et al Hong Kong Med J 2003; [4]Cao B et al N Engl J Med 2'20

Hydroxychloroquine

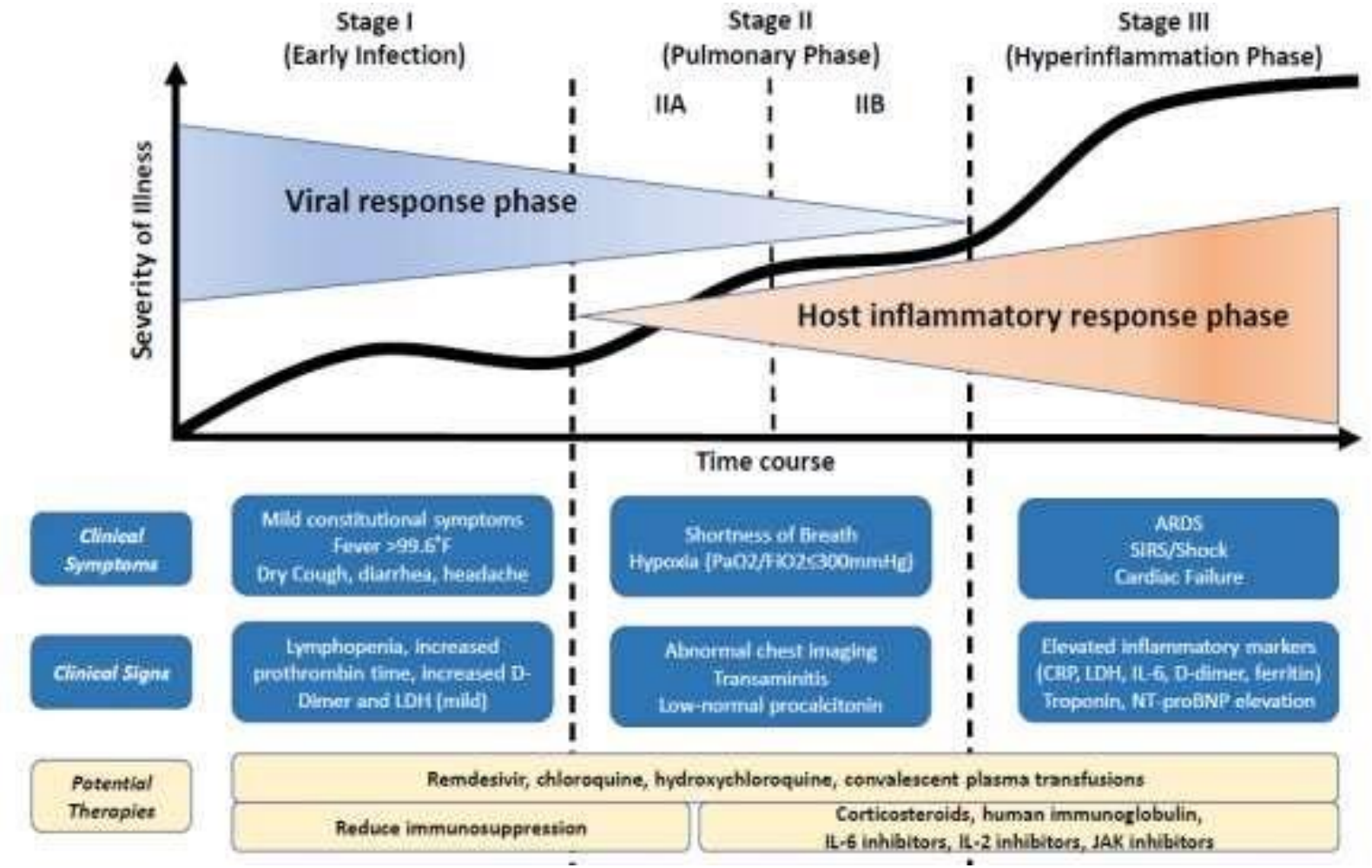
- **Two potential modes of action**
  - **Antiviral (inhibits acidification of endosomal vesicles)**
  - **Anti-inflammatory**
- **in vitro evidence for antiviral activity[1]**
- **Mixed results from small clinical trials[2,3]**
- **One trial suggests faster reduction of SARS-CoV-2 shedding from oropharynx[4]**



[1]Liu J et al Cell Discovery 2020; [2]Cortegiani A et al J Crit Care 2020; [3]Chan Z et al medRxiv 2020; [4] Gautret P et al Int J Antimicrob Agents 2020

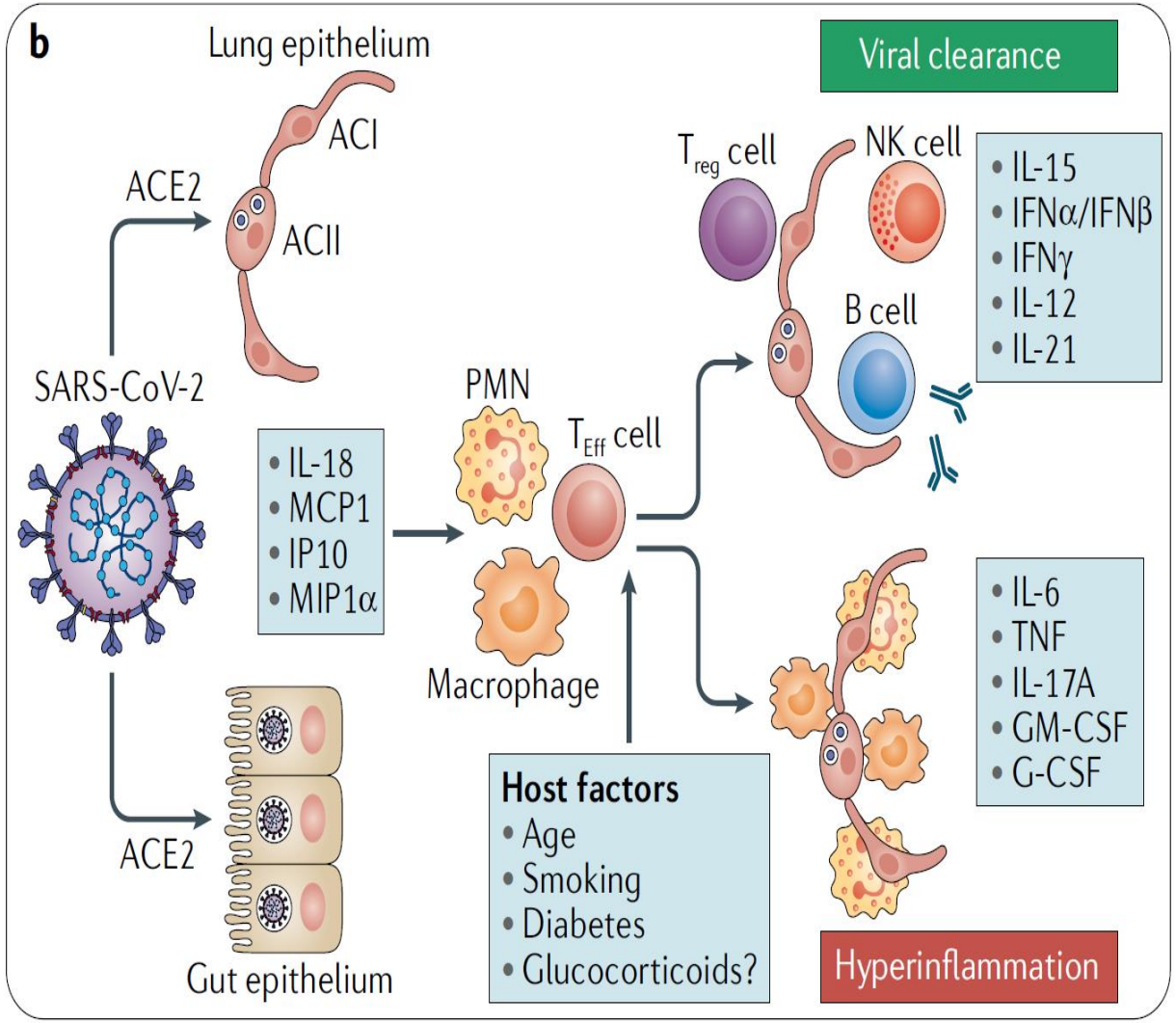
Esperienza frustrante …ma qualcosa abbiamo imparato

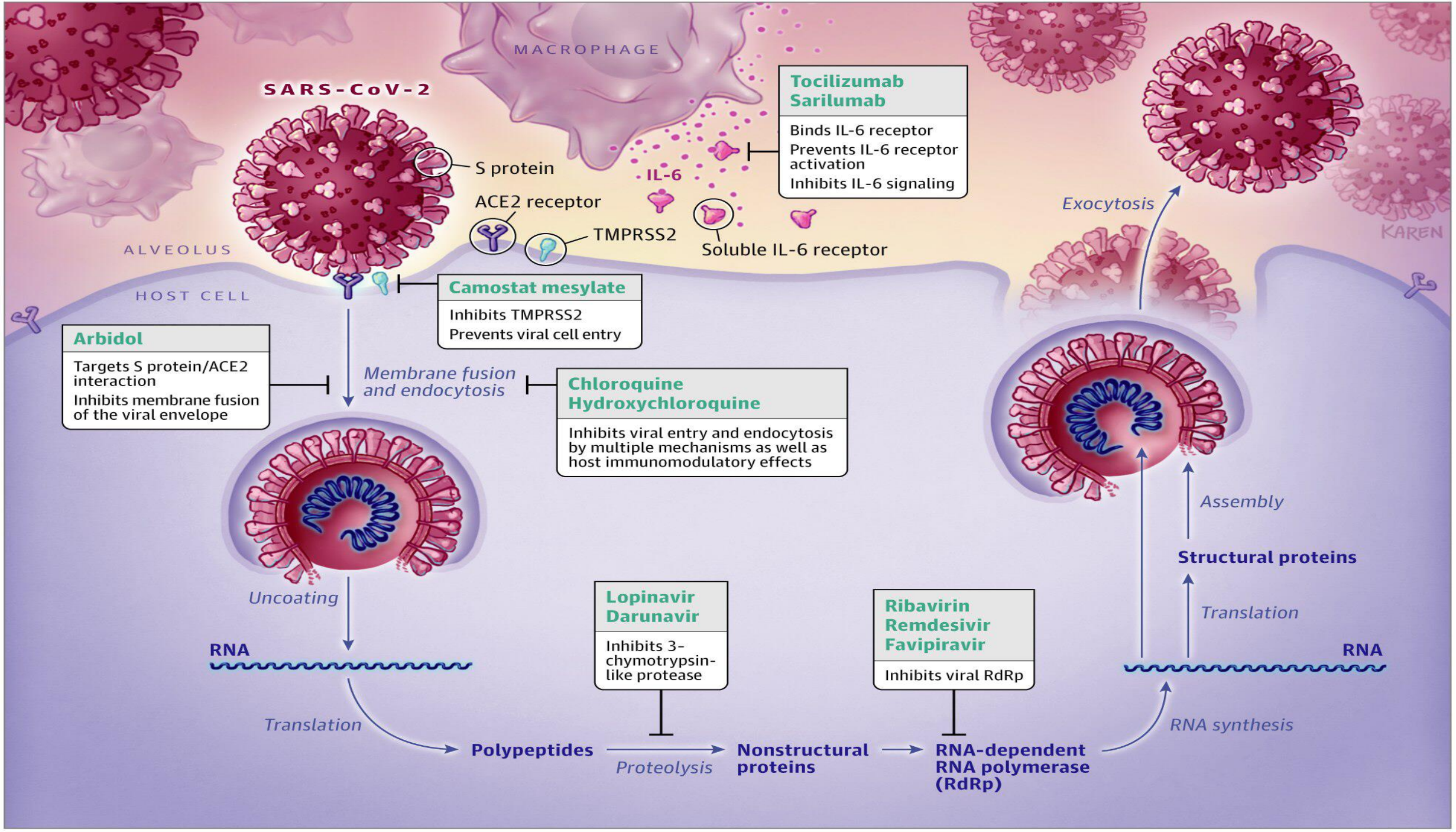
Proposta di stadiazione della malattia



Siddiqi HK et al, *Journal of Heart and Lung Transplantation 2020*

Cytokine pathogenesis of COVID-19

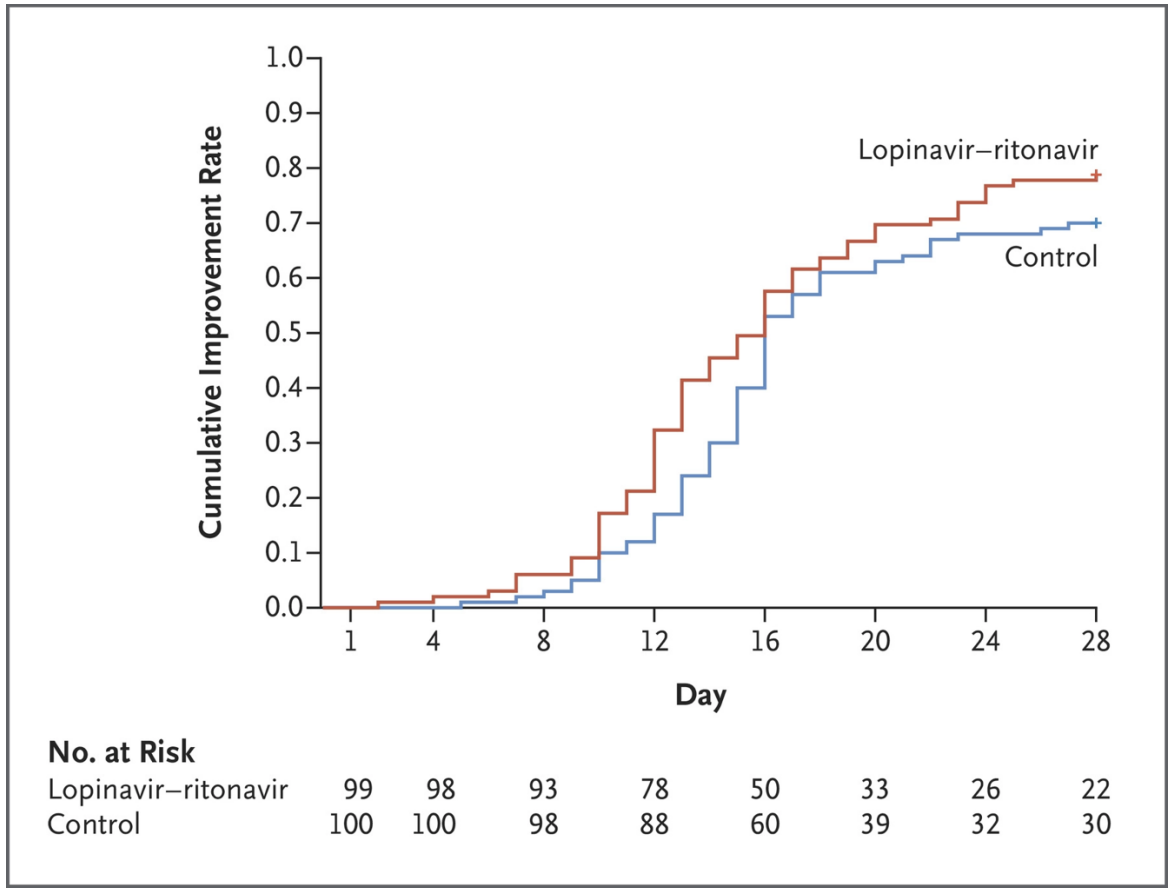



MACROPHAGE
SARS-CoV-2
S protein
ACE2 receptor
TMPRSS2
IL-6
Soluble IL-6 receptor
Tocilizumab
Sarilumab
Binds IL-6 receptor
Prevents IL-6 receptor activation
Inhibits IL-6 signaling
ALVEOLUS
HOST CELL
Camostat mesylate
Inhibits TMPRSS2
Prevents viral cell entry
Arbidol
Targets S protein/ACE2 interaction
Inhibits membrane fusion of the viral envelope
Membrane fusion and endocytosis
Chloroquine
Hydroxychloroquine
Inhibits viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects
Exocytosis
KAREN
Uncoating
RNA
Translation
Lopinavir
Darunavir
Inhibits 3-chymotrypsin-like protease
Ribavirin
Remdesivir
Favipiravir
Inhibits viral RdRp
Polypeptides
Proteolysis
Nonstructural proteins
RNA-dependent RNA polymerase (RdRp)
RNA synthesis
RNA
Translation
Structural proteins
Assembly

abbiamo cominciato a capire…
quello che probabilmente non funziona

ORIGINAL ARTICLE

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



Cao B et al. *NEJM 2020*

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

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

lacking. Clinical trials (for example, ChiCTR2000029539) have been initiated to test HIV protease inhibitors such as lopinavir and ritonavir in patients infected with 2019-nCoV. Lopinavir and ritonavir were initially hypothesized to inhibit the 3-chymotrypsin-like protease of SARS and MERS, and appeared to be associated with improved clinical outcomes of patients with SARS in a non-randomized open-label trial[2]. However, it is debatable whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of 2019-nCoV. HIV protease belongs to the aspartic protease family, whereas the two coronavirus proteases are from the cysteine protease family. Furthermore, HIV protease inhibitors were specifically optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer, but this C2-symmetric pocket is absent in coronavirus proteases. If HIV protease inhibitors

Idrossiclorochina

Dati osservazionali – New York City

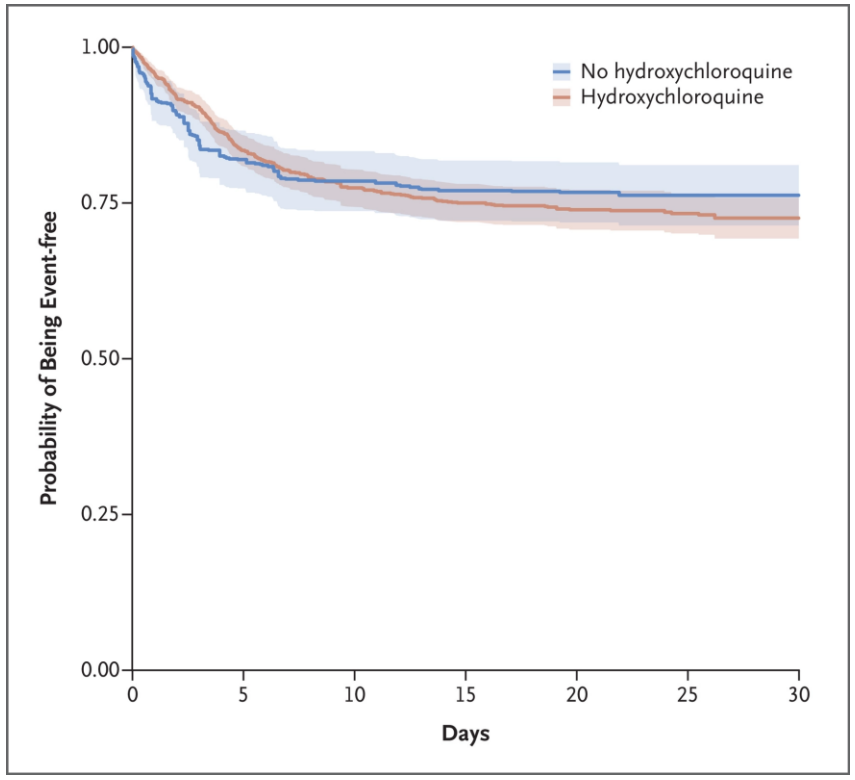


Table 2. Associations between Hydroxychloroquine Use and the Composite End Point of Intubation or Death in the Crude Analysis, Multivariable Analysis, and Propensity-Score Analyses.

Analysis	Intubation or Death
No. of events/no. of patients at risk (%)	
Hydroxychloroquine	262/811 (32.3)
No hydroxychloroquine	84/565 (14.9)
Crude analysis — hazard ratio (95% CI)	2.37 (1.84–3.02)
Multivariable analysis — hazard ratio (95% CI)*	1.00 (0.76–1.32)
Propensity-score analyses — hazard ratio (95% CI)	
With inverse probability weighting†	1.04 (0.82–1.32)
With matching‡	0.98 (0.73–1.31)
Adjusted for propensity score§	0.97 (0.74–1.28)

Geleris J et al. *N Eng J Med 2020*

DOI: 10.1002/jmv.26407

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Early administration of lopinavir/ritonavir plus hydroxychloroquine does not alter the clinical course of SARS-CoV-2 infection: A retrospective cohort study

Andrea Giacomelli MD[1,2] | Gabriele Pagani MD[1,2] | Anna L. Ridolfo MD[1] | Letizia Oreni BIT[2] | Federico Conti MD[1,2] | Laura Pezzati MD[1,2] | Lucia Bradanini MD[1,2] | Giacomo Casalini MD[1,2] | Cinzia Bassoli MD[1,2] | Valentina Morena MD[1,2] | Simone Passerini MD[1] | Giuliano Rizzardini MD[1,3] | Chiara Cogliati MD[4] | Elisa Ceriani MD[4] | Riccardo Colombo MD[5] | Stefano Rusconi MD[1,2] | Cristina Gervasoni MD[1] | Dario Cattaneo PharmD, PhD[6] | Spinello Antinori MD[1,2] | Massimo Galli MD[1,2]

Comment

Expression of concern: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Important scientific questions have been raised about data reported in the paper by Mandeep Mehra et al—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis[1]—published in *The Lancet* on May 22, 2020. Although an independent audit of the provenance and validity of the data has been commissioned by the authors not affiliated with Surgisphere and is ongoing, with results expected very shortly, we are issuing an Expression of Concern to alert readers to the fact that serious scientific questions have been brought to our attention. We will update this notice as soon as we have further information.

Published Online June 2, 2020 https://doi.org/10.1016/S0140-6736(20)31290-3

The Lancet Editors

The Lancet, London EC2Y 5AS, UK

1 Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020; published online May 22. https://doi.org/10.1016/S0140-6736(20)31180-6.

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

	Control group (n=81 144)	Chloroquine (n=1868)	Chloroquine with macrolide* (n=3783)	Hydroxychloroquine (n=3016)	Hydroxychloroquine with macrolide* (n=6221)
Age, years	53·6 (17·6)	55·1 (18·0)	54·9 (17·7)	55·1 (17·9)	55·2 (17·7)
BMI, kg/m²	27·4 (5·4)	27·8 (6·1)	28·2 (5·8)	28·4 (5·9)	28·5 (5·9)
Sex					
Female	37 716 (46·5%)	845 (45·2%)	1718 (45·4%)	1388 (46·0%)	2759 (44·3%)
Male	43 428 (53·5%)	1023 (54·8%)	2065 (54·6%)	1628 (54·0%)	3462 (55·7%)
Comorbidities					
Coronary artery disease	10 076 (12·4%)	284 (15·2%)	515 (13·6%)	421 (14·0%)	841 (13·5%)
Congestive heart failure	1949 (2·4%)	50 (2·7%)	103 (2·7%)	78 (2·6%)	188 (3·0%)
Arrhythmia	2861 (3·5%)	63 (3·4%)	126 (3·3%)	108 (3·6%)	223 (3·6%)
Diabetes	11 058 (13·6%)	258 (13·8%)	584 (15·4%)	447 (14·8%)	913 (14·7%)
Hypertension	21 437 (26·4%)	560 (30·0%)	1095 (28·9%)	891 (29·5%)	1827 (29·4%)
Hyperlipidaemia	25 538 (31·5%)	607 (32·5%)	1164 (30·8%)	941 (31·2%)	1948 (31·3%)
COPD	2647 (3·3%)	55 (2·9%)	144 (3·8%)	111 (3·7%)	220 (3·5%)
Current smoker	7884 (9·7%)	190 (10·2%)	428 (11·3%)	342 (11·3%)	644 (10·4%)
Former smoker	14 049 (17·3%)	321 (17·2%)	648 (17·1%)	509 (16·9%)	1026 (16·5%)
Immunocompromised	2416 (3·0%)	53 (2·8%)	122 (3·2%)	90 (3·0%)	187 (3·0%)
Outcomes					
De-novo ventricular arrhythmia	226 (0·3%)	81 (4·3%)	246 (6·5%)	184 (6·1%)	502 (8·1%)
Non-ICU length of stay, days	9·1 (6·4)	8·8 (6·2)	9·0 (6·6)	8·9 (6·2)	9·1 (6·7)
ICU length of stay, days	2·6 (5·0)	4·3 (6·8)	4·9 (8·1)	4·3 (6·8)	4·7 (7·8)
Total length of stay, days	11·7 (8·4)	13·2 (9·1)	13·8 (11·0)	13·2 (9·3)	13·8 (10·7)
Mechanical ventilation	6278 (7·7%)	403 (21·6%)	814 (21·5%)	616 (20·4%)	1243 (20·0%)
Mortality	7530 (9·3%)	307 (16·4%)	839 (22·2%)	543 (18·0%)	1479 (23·8%)
Ventilator or mortality	10 703 (13·2%)	531 (28·4%)	1288 (34·0%)	877 (29·1%)	2120 (34·1%)

Lancet 2020

tocilizumab

- ***Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia***
- COVACTA trial **did not meet** its primary endpoint of **improved clinical status** in patients with COVID-19 associated pneumonia, or the key secondary endpoint of **reduced patient mortality**
- The study is the first global, randomised, double-blind, placebo-controlled phase III trial investigating Actemra/RoActemra in this setting

Basel, 29 July

Farmaci utilizzati all'inizio della epidemia

- **Farmaci antiretrovirali**
  - ~~Lopinavir~~
  - ~~Darunavir~~
- **Altri antivirali**
  - Remdesivir
  - ~~Ribavirina~~
  - Favipiravir ???
- **Altri farmaci ad azione antivirale**
  - ~~Clorochina~~
  - ~~Idrossiclorochina~~
- **Farmaci immunomodulanti**
  - Corticosteroidi
  - ~~Anti-IL6R (Tocilizumab, ecc)~~
  - Anti-IL1R (Anakinra, ecc) ???
  - Plasma iperimmune ???
- **Altri farmaci**
  - Eparine a basso peso molecolare o Eparina non frazionata

…e quello che, forse, almeno un po’ funziona

REMDESIVIR

- RNA polymerase inhibitor with in vitro activity against Ebola, SARS, MERS and SARS CoV-2

Sheahan TP et al Nat Commun 2020; Wang M et al Cell Res 2020

- Compassionate Use of Remdesivir for Patients with Severe Covid-19: 53 pts
  - Clinical improvement was observed in 36 of 53 patients (68%)

No. of Patients in Oxygen-Support Group at Baseline (%)

No. of Patients in Oxygen-Support Group after Treatment (%)	Category on ordinal scale	Invasive (N=34)	Noninvasive (N=7)	Low-flow oxygen (N=10)	Ambient air (N=2)
		5	4	3	2
Death	6	6 (18)	1 (14)	0	0
Invasive	5	9 (26)	1 (14)	0	0
Noninvasive	4	3 (9)	0	0	0
Low-flow oxygen	3	0	0	0	0
Ambient air	2	8 (24)	0	0	0
Discharged	1	8 (24)	5 (71)	10 (100)	2 (100)
Improvement		**19 (56)**	**5 (71)**	**10 (100)**	**2 (100)**

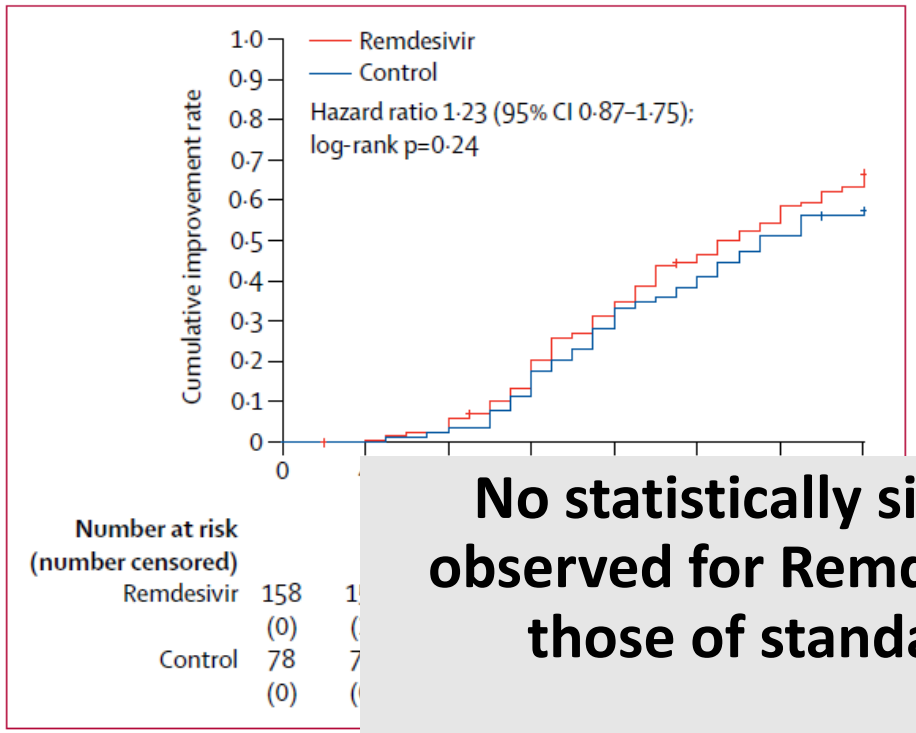
Category on ordinal scale

Grein et al NEJM 2020

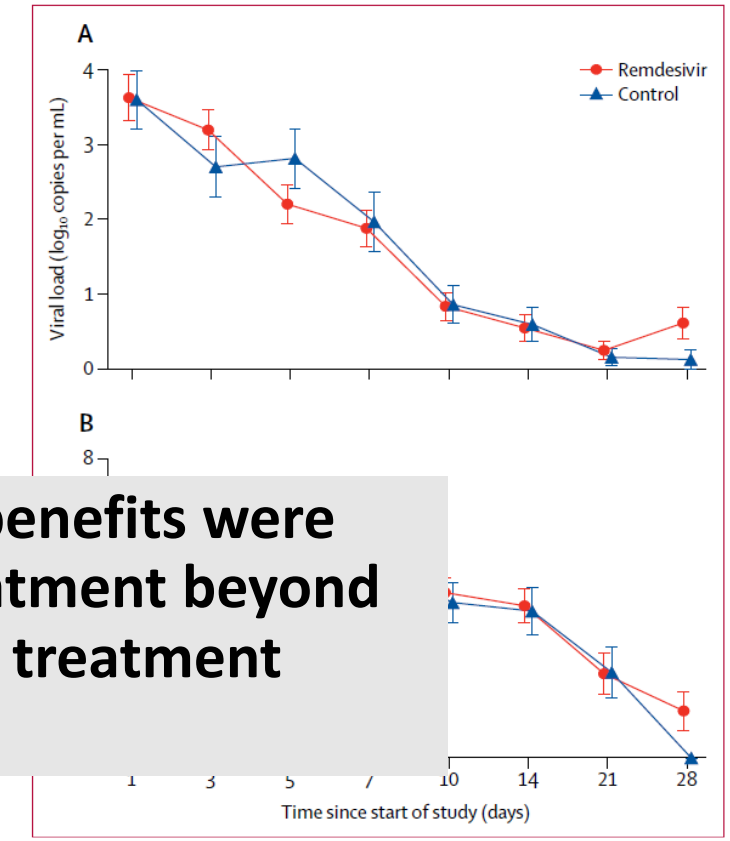
Remdesivir in adults with severe COVID-19:
a randomized double-blind, placebo-controlled, multicentre trial

- **237 of the intended 453 patients admitted to hospital for severe COVID-19 were randomized within 12 days of symptom onset to receive iv remdesivir (n=158) or placebo n=79). Concomitant use of lopinavir/ritonavir, interferons, corticosteroids permitted**

Time to clinical improvement in the intention-to-treat population



Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)



No statistically significant benefits were observed for Remdesivir treatment beyond those of standard of care treatment

Wang Y et al Lancet Infect Dis 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

CONCLUSIONS

Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

NIH randomized, placebo-controlled trial of remdesivir

NIH news release

- Interim analysis of nearly 1100 patients hospitalized with COVID-19 and lung involvement
- Median time to recovery (that is, no longer requiring oxigen or hospitalization) was 31% faster with remdesivir than placebo (11 vs 15 days)
- The mortality rate was 8% with remdesivir and 11.6% with placebo (p=0,059)

May 01, 2020

FDA issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., Kristen M. Marks, M.D., Raffaele Bruno, M.D., Rocio Montejano, M.D., Christoph D. Spinner, M.D., Massimo Galli, M.D., Mi-Young Ahn, M.D., Ronald G. Nahass, M.D., Yao-Shen Chen, M.D., Devi SenGupta, M.D., Robert H. Hyland, D.Phil., Anu O. Osinusi, M.D., Huyen Cao, M.D., Christiana Blair, M.S., Xuelian Wei, Ph.D., Anuj Gaggar, M.D., Ph.D., Diana M. Brainard, M.D., William J. Towner, M.D., Jose Muñoz, M.D., Kathleen M. Mullane, D.O., Pharm.D., Francisco M. Marty, M.D., Karen T. Tashima, M.D., George Diaz, M.D., and Aruna Subramanian, M.D., for the GS-US-540-5773 Investigators*

CONCLUSIONS

In patients with severe Covid-19 not requiring mechanical ventilation, our trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. With no placebo control, however, the magnitude of benefit cannot be determined. (Funded by Gilead Sciences; GS-US-540-5773 ClinicalTrials.gov number, NCT04292899.)

Research

JAMA | Original Investigation

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19
A Randomized Clinical Trial

Christoph D. Spinner, MD; Robert L. Gottlieb, MD, PhD; Gerard J. Criner, MD; José Ramón Arribas López, MD; Anna Maria Cattelan, MD; Alex Soriano Viladomiu, MD; Onyema Ogbuagu, MD; Prashant Malhotra, MD; Kathleen M. Mullane, DO; Antonella Castagna, MD; Louis Yi Ann Chai, MD; Meta Roestenberg, MD; Owen Tak Yin Tsang, MD; Enos Bernasconi, MD; Paul Le Turnier, MD; Shan-Chwen Chang, MD; Devi SenGupta, MD; Robert H. Hyland, DPhil; Anu O. Osinusi, MD; Huyen Cao, MD; Christiana Blair, MS; Hongyuan Wang, PhD; Anuj Gaggar, MD, PhD; Diana M. Brainard, MD; Mark J. McPhail, MD; Sanjay Bhagani, MD; Mi Young Ahn, MD; Arun J. Sanyal, MD; Gregory Huhn, MD; Francisco M. Marty, MD; for the GS-US-540-5774 Investigators

CONCLUSIONS AND RELEVANCE Among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, but the difference was of uncertain clinical importance.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04292730

JAMA. 2020;324(11):1048-1057. doi:10.1001/jama.2020.16349
Published online August 21, 2020.

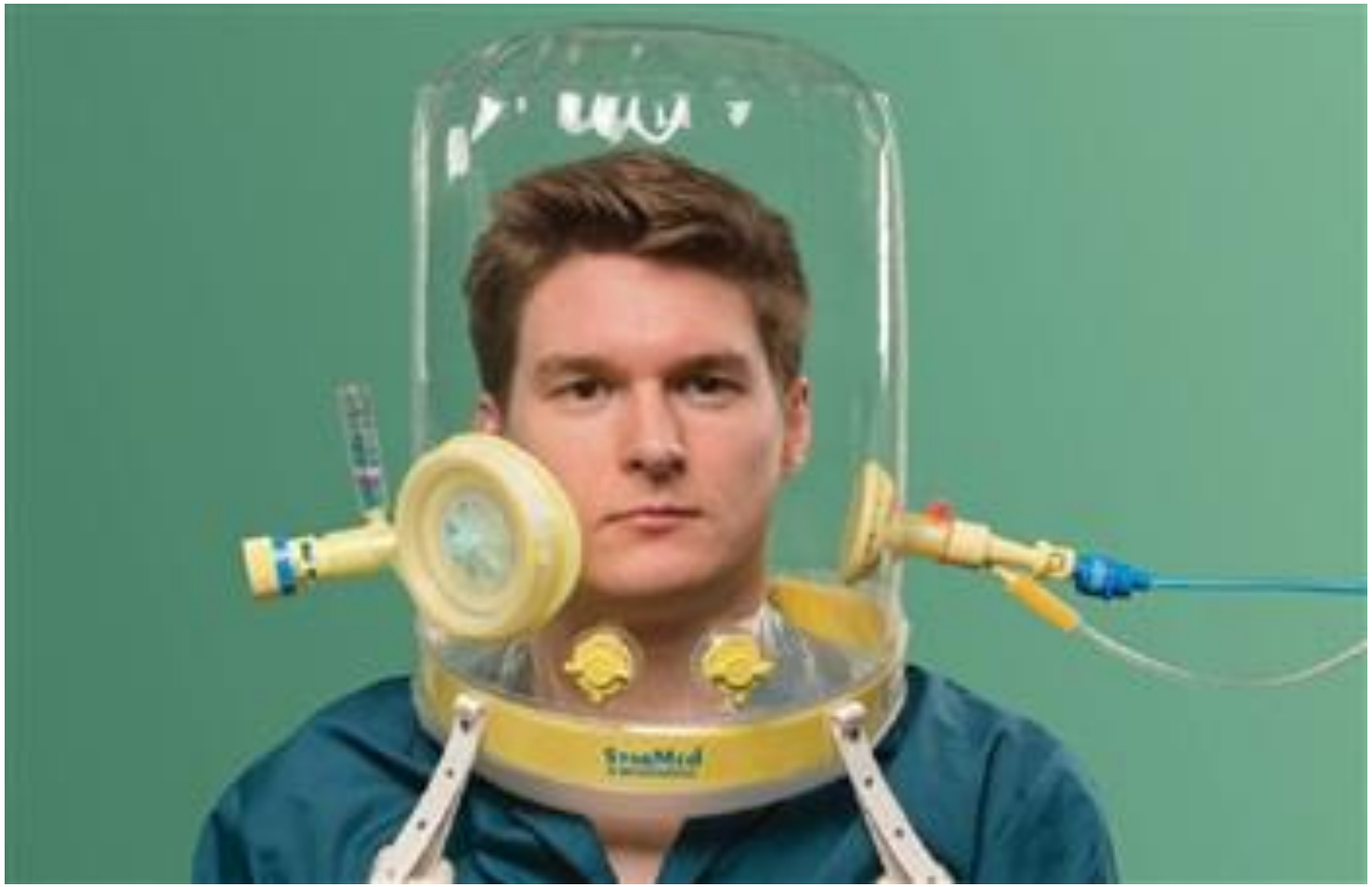
Convalescent plasma

- **Plasma collected from patients who have recovered from COVID-19 may contain antibodies to neutralize and suppress SARS-CoV-2**
- **Convalescent plasma has shown some benefit in treatment of avian (H1N5) and H1N1influenza, SARS and MERS**
- **Uncontrolled pilot study (5 patients with COVID-19 and ARDS) suggested possible benefit. Symptoms improved in all patients and no AEs were reported.[1]**
- **In a case series of 10 severelly ill patients with COVID-19, patients were given antiviral therapy and one dose of convalescent plasma. Symptoms improved in all patients and no serious Aes were observed.[2]**
- **Clinical trials planned/underway**

[1]Shen C et al JAMA 2020; [2]Duan K et al PNAS 2020

… e, da ultimo, quello che probabilmente funziona

SUPPORTO VENTILATORIO



FR
SatO2
Ega
PaO2/FiO2

Venturi ‘s mask

HFNC

PaO2/FiO2 > a 400

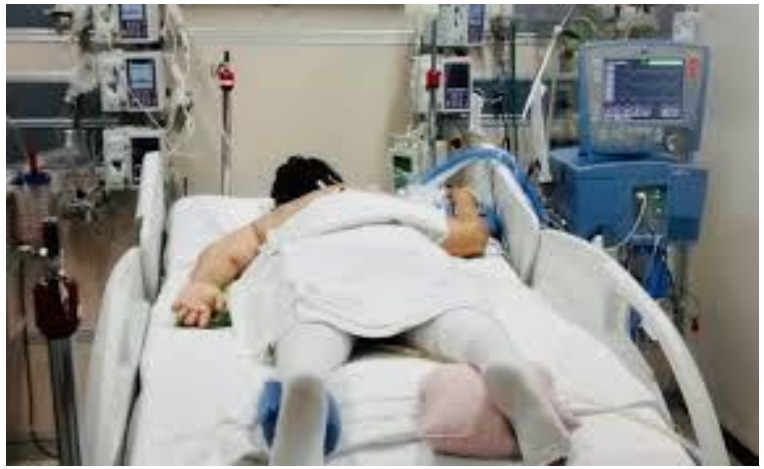
PaO2/FiO2<400 >300 IRA di grado lieve

PaO2/FiO2 <300 > 200 IRA di grado medio

PaO2/FiO2 <200> 100 IRA di grado moderato

PaO2/Fio2 < 100 IRA di grado severo

C-PAP / BiPAP



Mechanical ventilation

il cortisone

On the use of corticosteroids for 2019-nCoV pneumonia

In their Comment about the use of corticosteroids to treat 2019 novel coronavirus (2019-nCoV) lung injury, Clark Russell and colleagues[1] summarise the available clinical evidence on corticosteroid to treat patients with severe human coronavirus infections (severe acute respiratory syndrome [SARS] coronavirus and Middle East respiratory syndrome coronavirus), and other severe respiratory virus infections. In accordance with current WHO guidance,[2] Russell and colleagues[1] recommend that corticosteroids should not be used in 2019-nCoV-induced lung injury or shock, except in the setting of a clinical trial. The Comment[1] contributes to a better understanding of corticosteroid treatment in viral pneumonia. However, as a team of front-line physicians from China, we have a different perspective.

As mentioned by the authors,[1] the studies referred to in the paper were mostly observational studies. In clinical settings, physicians tend to use corticosteroids in the most critically ill patients. Therefore, selection bias and confounders in observational studies might contribute to any observed increased mortality in patient groups treated with corticosteroids. Although attempts were made to adjust for confounding factors in the studies, conclusive inference should not be made. Also, we question the interpretation of the systematic review about effective treatments for SARS.[3] Russell and colleagues state that "four studies provided conclusive data, all indicating harm".[1] These four studies were not definitive and only showed evidence of possible harm, whereas the results of 25 other studies were inconclusive, leading the original authors to state that the totality of data are inconclusive, and because of methodological limitations, it was not possible to make any recommendation. Inconclusive clinical evidence should not be a reason for abandoning corticosteroid use in 2019-nCoV pneumonia.

Moreover, there are studies supporting the use of corticosteroids at low-to-moderate dose in patients with coronavirus infection. For example, in a retrospective study of 401 patients with SARS,[4] proper use of corticosteroids was found to reduce mortality and shorten the length of stay in hospital for critically ill patients with SARS without causing secondary infection and other complications. Relevant research has also been done for other virus-associated respiratory diseases, such as influenza-associated pneumonia. For example, in a prospective cohort study enrolling 2141 patients with influenza A (H1N1)pdm09 viral pneumonia from 407 hospitals in China,[5] low-to-moderate dose of corticosteroids (25–150 mg/day methylprednisolone or equivalent) reduced mortality in patients with oxygen index lower than 300 mm Hg. Besides, a systematic review[6] suggested corticosteroids could reduce mortality and the need for mechanical ventilation in patients with severe community-acquired pneumonia.

Because of methodological limitations in the available evidence, the use of corticosteroids remains controversial. We acknowledge the potential risks associated with high-dose corticosteroids in treating 2019-nCoV pneumonia, such as secondary infections, long-term complications, and prolonged virus shedding. However, in critically ill patients, the overwhelming inflammation and cytokine-related lung injury might cause rapidly progressive pneumonia. Given the inconclusive evidence and urgent clinical demand, physicians from the Chinese Thoracic Society have developed an expert consensus statement on the use of corticosteroids in 2019-nCoV pneumonia.[7] All members of the expert panel participated in treating patients with 2019-nCoV pneumonia. The expert consensus statement is based both on the available published scientific literature and relevant research by panel members, and it was brought together through e-mail correspondence and online meetings.

According to the expert consensus statement, the following basic principles should be followed when using corticosteroids: (1) the benefits and harms should be carefully weighed before using corticosteroids; (2) corticosteroids should be used prudently in critically ill patients with 2019-nCoV pneumonia; (3) for patients with hypoxaemia due to underlying diseases or who regularly use corticosteroids for chronic diseases, further use of corticosteroids should be cautious; and (4) the dosage should be low-to-moderate (≤0·5–1 mg/kg per day methylprednisolone or equivalent) and the duration should be short (≤7 days).

Corticosteroid treatment is a double-edged sword. In line with the expert consensus, we oppose liberal use of corticosteroids and recommend short courses of corticosteroids at low-to-moderate dose, used prudently, for critically ill patients with 2019-nCoV pneumonia. Existing evidence is inconclusive, and even systematic reviews and meta analyses on this topic reach differing conclusions. Therefore, in line with Russell and colleagues,[1] we believe that there is a need for well designed randomised controlled trials in the future to promote a more solid foundation for treatment recommendations.

We declare no competing interests. JZ, YH, RD, and BC are members of the panel that created the expert consensus statement on the use of corticosteroids in patients with 2019-nCoV pneumonia. We thank Zhenshun Cheng, Yang Jin, Min Zhou, Jing Zhang, and Jieming Qu for contributing to the development of the expert consensus on the use of corticosteroids in patients with 2019-nCoV pneumonia. We extend great thanks to Peter W Horby and Frederick G Hayden for assistance in writing this Correspondence.

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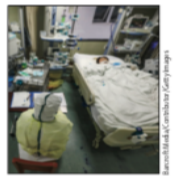

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For the Chinese translation see Online for appendix

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)

Anticoagulants

Disseminated intravascular coagulation (DIC) is frequently reported also in the mild and early stages of the disease [38], and it is strongly associated with a significantly higher mortality (71.4% of non-survivors—0.6% of survivors) [39]. Although the dysregulation of the haemostatic system is well documented in sepsis, SARS-CoV-2 is probably more prone to induce DIC, also thanks to the hyperimmune host response [40]. According to our experience, heparin is recommended at the initial dose of 50 UI/Kg or 25 UI/Kg in patients with bleeding or platelet count < 50xl 09/L with aPPT being 40–60 s as a target of anticoagulation maintenance dosage.

…quindi a che punto siamo?

Curing COVID-19

As the COVID-19 pandemic moves into its 10th month, greater patient survival suggests that treatment of severe disease has improved. How much of this improvement is due to better supportive care and how much to pharmaceuticals is a matter of debate. Given the huge effort that the biomedical community has put into finding drugs to treat COVID-19, with thousands of trials completed and ongoing, it's worth taking stock of the evidence for what has worked and what has not.

The hunt for COVID-19 treatments has become extraordinarily politicised, and no more so than with the aminoquinoline drugs chloroquine and hydroxychloroquine. Early observational studies suggested a beneficial effect of treatment with these cheap drugs, leading to acclamation by US President Trump. However, randomised controlled trials (RCTs) in hospitalised patients have shown no effect of hydroxychloroquine in reducing mortality. One RCT hinted at an effect when used as post-exposure prophylaxis, but this was not statistically significant. Unless new, high-quality evidence emerges, the aminoquinolines appear to have no future in the management of COVID-19. Remdesivir, an antiviral, was also the subject of White House fanfare. The US Government has attempted to corner the market for this costly drug but results of clinical trials are ambiguous. One review concluded that remdesivir may reduce time to clinical improvement and decrease mortality but had no effect on need for invasive ventilation or length of hospital stay. A subsequent RCT found no effect on mortality. Although approved to treat COVID-19 in the USA and Europe, conclusive evidence to support remdesivir is lacking. For other antivirals, there is no good evidence for efficacy of favipiravir, although it has been approved in Russia, and the lopinavir/ritonavir combination showed no clinical benefit in the UK RECOVERY RCT.

Immunomodulators to treat COVID-19 are being widely tested in clinical trials. Among the front-runners, evidence to support use of tocilizumab, a monoclonal antibody against interleukin-6 receptors, comes largely from observational studies. Roche, the manufacturer, has announced that the drug did not improve clinical status in a phase 3 RCT among patients with severe COVID-19-associated pneumonia. Similarly, good quality evidence on the use of convalescent plasma is still awaited. Large RCTs such as RECOVERY, which includes tocilizumab and convalescent plasma groups, should provide answers. Immunomodulators that do work are the corticosteroids. In the dexamethasone group of RECOVERY, deaths were reduced by 35% in ventilated patients and by 20% among those receiving oxygen only compared with those in the standard care group. An RCT of dexamethasone done in Brazil further supports the beneficial effect of the drug. The REMAP-CAP RCT of hydrocortisone—another corticosteroid—versus placebo in patients with severe COVID-19 showed a 93% improvement in the intervention group in days when organ support was not needed. Based on these findings, WHO guidelines recommend corticosteroids in patients with severe and critical COVID-19.

Is targeted treatment reducing deaths as the disease continues to sweep around the world? Where there has been a resurgence of COVID-19 cases to levels at least as high as when the pandemic first struck in the spring, such as in the USA, France, and Spain, it has not been followed by a comparable increase in deaths, nor of people requiring admission to hospital. Thus, treatment alone cannot be responsible for saving lives. Possible explanations for the recent disparity in cases and deaths include more widespread testing, meaning that the number of cases being detected is closer to the true burden of infection, whereas the accuracy of counting deaths remains unchanged; lower viral load at the point of transmission, and hence less severe disease, because of non-pharmaceutical measures such as mask wearing; and changes in the distribution of cases towards younger age groups. Data from England show that until recently cases have been fairly evenly distributed across all ages from 20 years upwards, but by the last 2 weeks of August cases in people aged 20–39 were about ten times the number in those aged 70 or more. Risk of COVID-19 death in young people is tiny compared with the elderly. However, cases in the young might yet spill over into older people, and the long-term consequences of non-fatal disease are unknown.

Whatever the reasons for apparent declining mortality, the impact of drug treatments on the COVID-19 pandemic is still limited. The massive research effort needs to bear fruit with a broader range of effective therapies. ■ *The Lancet Infectious Diseases*

Published Online
September 10, 2020
https://doi.org/10.1016/S1473-3099(20)30706-4

For the **meta-analysis on the effect of hydroxychloroquine** see *Clin Microb Infect* 2020; published online Aug 26. https://doi.org/10.1016/j.cmi.2020.08.022

For the **trial of hydroxychloroquine as prophylaxis** see *N Engl J Med* 2020; **383**: 517–25

For the **review of remdesivir** see *BMJ* 2020; **370**: m2924

For **remdesivir RCT** see *JAMA* 2020; published online Aug 21. doi:10.1001/jama.2020.16349

For more on the **RECOVERY trial** see https://www.recoverytrial.net/

For the **trial on dexamethasone** see *JAMA* 2020; published online Sept 2. doi:10.1001/jama.2020.17021

For the **REMAP-CAP trial** see https://www.remapcap.org/

For **WHO guidelines on corticosteroid use** see https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

For **cases and deaths by age group in England** see https://www.gov.uk/government/publications/national-covid-19-surveillance-reports

Farmaci da utilizzare nella terapia di COVID-19 (Indicazioni IDSA e CDC)

- **Farmaci antiretrovirali**
  - ~~Lopinavir/ritonavir~~
  - ~~Darunavir~~
- **Altri antivirali**
  - **Remdesivir**
  - ~~Ribavirina~~
  - Favipiravir ???
- **Altri farmaci ad azione antivirale**
  - ~~Clorochina~~
  - ~~Idrossiclorochina~~

- **Farmaci immunomodulanti**
  - **Corticosteroidi**
  - Anti-IL1R (Anakinra, ecc)
  - **Plasma iperimmune**
  - Anti-IL6R (Tocilizumab, ecc)
- **Altri farmaci**
  - **Eparine a basso peso molecolare o Eparina non frazionata**

Solo all'interno di studi clinici controllati

Remdesivir LG IDSA (Sep, 2020)

- **Recommendation 9: In hospitalized patients with severe* COVID-19 (SpO2 ≤94% on room air; on supplemental oxygen, mechanical ventilation, or ECMO, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)**

  Remark: For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.

- **Recommendation 10: In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)**

  Remark: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.

- **Recommendation 11: In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, IDSA suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)**

Desametazone LG IDSA (Sep, 2020)

- **Recommendation 4: Among hospitalized critically ill patients* with COVID-19, the IDSA guideline panel recommends dexamethasone rather than no dexamethasone. (Strong recommendation, Moderate certainty of evidence)**

  Dexamethasone 6 mg IV or PO for 10 days (or until discharge)

- **Recommendation 5: Among hospitalized patients with severe**, but non-critical, COVID-19 the IDSA guideline panel suggests dexamethasone rather than no dexamethasone. (Conditional recommendation, Moderate certainty of evidence)**

  Dexamethasone 6 mg IV or PO for 10 days (or until discharge)

- **Recommendation 6: Among hospitalized patients with non-severe*** COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)**

**Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock.*

***Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen.*

****Non-severe illness is defined as patient with a SpO2 > 94% not requiring supplemental oxygen.*

Terapia anticoagulante – LG CDC

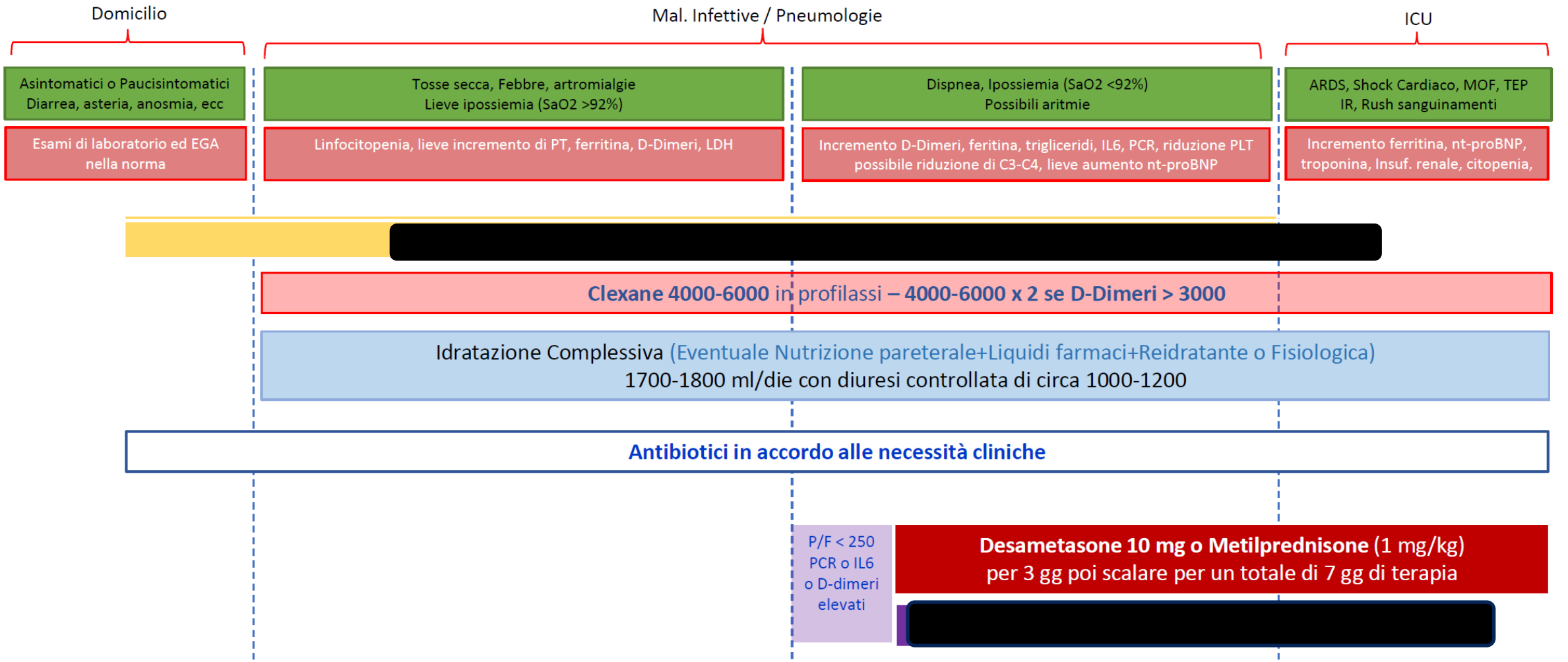
Chronic Anticoagulant and Antiplatelet Therapy:

- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 **(AIII)**.

Venous Thromboembolism Prophylaxis and Screening:

- For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications **(AIII)**.
- Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults **(AIII)**. A diagnosis of COVID-19 should not influence a pediatrician's recommendations about VTE prophylaxis in hospitalized children **(BIII)**. Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.
- Reported incidence of VTE in hospitalized patients with COVID-19 varies. There are currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial **(BIII)**.
- Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis **(AIII)**. Using Food and Drug Administration-approved regimens, extended VTE prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19 (see text for details on defining at-risk patients) **(BI)**.

Schema terapeutico COVID-19



Grazie per l’attenzione