Literatur Review – mit Conclusion – updates since 15.3.20

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Breakthrough: Chloroquine Phosphate Has Shown Apparent Efficacy in Treatment of COVID-19 Associated Pneumonia in Clinical Studies

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Abstract
The coronavirus disease 2019 (COVID-19) virus is spreading rapidly, and scientists are endeavoring to discover drugs for its efficacious treatment in China. Chloroquine phosphate, an old drug for treatment of malaria, is shown to have apparent efficacy and acceptable safety against COVID-19 associated pneumonia in multicenter clinical trials conducted in China. The drug is recommended to be included in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future.

Keywords: 2019-nCoV; COVID-19; SARS-CoV-2; chloroquine; pneumonia.

Features, Evaluation and Treatment Coronavirus (COVID-19)

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2020 Mar 8. Affiliations

Excerpt
According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded. Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012. In a timeline that reaches the present day, an epidemic of cases with unexplained low respiratory infections detected in Wuhan, the largest metropolitan area in China's Hubei province, was first reported to the WHO Country Office in China, on December 31, 2019. Published literature can trace the beginning of symptomatic individuals back to the beginning of December 2019. As they were unable to identify the causative agent, these first cases were classified as "pneumonia of unknown etiology." The Chinese Center for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation program. The etiology of this illness is now attributed to a novel virus belonging to the coronavirus (CoV) family, COVID-19. On February 11, 2020, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, announced that the disease caused by this new CoV was a "COVID-19," which is the acronym of "coronavirus disease 2019". In the past twenty years, two additional coronavirus epidemics have occurred. SARS-CoV provoked a large-scale epidemic beginning in China and involving two dozen countries with approximately 8000 cases and 800 deaths, and the MERS-CoV that began in Saudi Arabia and has approximately 2,500 cases and 800 deaths and still causes as sporadic cases. This new virus seems to be very contagious and has quickly spread globally. In a meeting on January 30, 2020, per the International Health Regulations (IHR, 2005), the outbreak was declared by the WHO a Public Health Emergency of International Concern (PHEIC) as it had spread to 18 countries with four countries reporting human-to-human transmission. An additional landmark occurred on February 26, 2020, as the first case of the disease, not imported from China, was recorded in the United States. Initially, the new virus was called 2019-nCoV. Subsequently, the task of experts of the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus as it is very similar to the one that caused the SARS outbreak (SARS-CoVs). The **CoVs** have become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species. For reasons yet to be explained, these viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS. Interestingly, these latter viruses have probably originated from bats and then moving into other mammalian hosts — the Himalayan palm civet for SARS-CoV, and the dromedary camel for MERS-CoV — before jumping to humans. The dynamics of SARS-Cov-2 are currently unknown, but there is speculation that it also has an animal origin. The potential for these viruses to grow to become a pandemic worldwide seems to be a serious public health risk. Concerning COVID-19, the WHO raised the threat to the CoV epidemic to the "very high" level, on February 28, 2020. Probably, the effects of the epidemic caused by the new CoV has

yet to emerge as the situation is quickly evolving. World governments are at work to establish countermeasures to stem possible devastating effects. Health organizations coordinate information flows and issues directives and guidelines to best mitigate the impact of the threat. At the same time, scientists around the world work tirelessly, and information about the **transmission mechanisms**, the clinical spectrum of disease, new diagnostics, and prevention and **therapeutic strategies** are rapidly developing. Many uncertainties remain with regard to both the virus-host interaction and the evolution of the epidemic, with specific reference to the times when the epidemic will reach its peak. At the moment, the therapeutic strategies to deal with the infection are only supportive, and prevention aimed at reducing transmission in the community is our best weapon. Aggressive isolation measures in China have led to a progressive reduction of cases in the last few days. In Italy, in geographic regions of the north of the peninsula, political and health authorities are making incredible efforts to contain a shock wave that is severely testing the health system. In the midst of the crisis, the authors have chosen to use the "Statpearls" platform because, within the PubMed scenario, it represents a unique tool that may allow them to make updates in real-time. The aim, therefore, is to collect information and scientific evidence and to provide an overview of the topic that will be continuously updated.

Drug Treatment Options for the 2019-new Coronavirus (2019-nCoV)

Hongzhou Lu [1] [2] [3]

Abstract
As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (2019-nCoV) have been reported in 25 provinces (districts and cities) in China. At present, there is no vaccine or antiviral treatment for human and animal coronavirus, so that identifying the drug treatment options as soon as possible is critical for the response to the 2019-nCoV outbreak. Three general methods, which include existing broad-spectrum antiviral drugs using standard assays, screening of a chemical library containing many existing compounds or databases, and the redevelopment of new specific drugs based on the genome and biophysical understanding of individual coronaviruses, are used to discover the potential **antiviral treatment of human pathogen coronavirus**. Lopinavir /Ritonavir, Nucleoside analogues, Neuraminidase inhibitors, Remdesivir, peptide (EK1), arbidol, RNA synthesis inhibitors (such as TDF, 3TC), anti-inflammatory drugs (such as hormones and other molecules), Chinese traditional medicine, such ShuFengJieDu Capsules and Lianhuaqingwen Capsule, could be the drug treatment options for 2019-nCoV. However, the efficacy and safety of these drugs for 2019- nCoV still need to be further confirmed by clinical experiments.
Keywords: 2019-nCoV; Coronaviruses; pneumonia.

Potential Interventions for Novel Coronavirus in China: A Systematic Review

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Abstract
An outbreak of a novel coronavirus (COVID-19 or 2019-CoV) infection has posed significant threats to international health and the economy. In the absence of treatment for this virus, there is an urgent need to find alternative methods to control the spread of disease. Here, we have conducted an online search for all treatment options related to coronavirus infections as well as some RNA-virus infection and we have found that general treatments, coronavirus-specific treatments, and antiviral treatments should be useful in fighting COVID-19. We suggest that the nutritional status of each infected patient should be evaluated before the administration of general treatments and the current children's RNA-virus vaccines including influenza vaccine should be immunized for uninfected people and health care workers. In addition, convalescent plasma should be given to COVID-19 patients if it is available. In conclusion, we suggest that all the potential interventions be implemented to control the emerging COVID-19 if the infection is uncontrollable.

Keywords: 2019-CoV; COVID-19; MERS; SARS; coronavirus; potential interventions.

Learning From the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV

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Abstract
With the current trajectory of the 2019-nCoV outbreak unknown, public health and medicinal measures will both be needed to contain spreading of the virus and to optimize patient outcomes. Although little is known

about the virus, an examination of the genome sequence shows strong homology with its better-studied cousin, SARS-CoV. The spike protein used for host cell infection shows key nonsynonymous mutations that might hamper the efficacy of previously developed therapeutics but remains a viable target for the development of biologics and macrocyclic peptides. Other key drug targets, including RNA-dependent RNA polymerase and coronavirus main proteinase (3CLpro), share a strikingly high (>95 %) homology to SARS-CoV. Herein, we suggest four potential drug candidates (an ACE2-based peptide, remdesivir, 3CLpro-1 and a novel vinylsulfone protease inhibitor) that could be used to treat patients suffering with the 2019-nCoV. We also summarize previous efforts into drugging these targets and hope to help in the development of broad-spectrum anti-coronaviral agents for future epidemics.

Keywords: 2019-nCoV; 3CLpro; RdRp; SARS; antiviral agents; coronavirus; spike proteins.

SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

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Abstract
The recent emergence of the novel, pathogenic SARS-coronavirus 2 (SARS-CoV-2) in China and its rapid national and international spread pose a global health emergency. Cell entry of coronaviruses depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. Unravelling which cellular factors are used by SARS-CoV-2 for entry might provide insights into viral transmission and reveal therapeutic targets. Here, we demonstrate that SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. A TMPRSS2 inhibitor approved for clinical use blocked entry and might constitute a treatment option. Finally, we show that the sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry. Our results reveal important commonalities between SARS-CoV-2 and SARS-CoV infection and identify a potential target for antiviral intervention.

Keywords: ACE2; COVID-19; SARS-CoV-2; TMPRSS2; coronavirus; entry; neutralization; priming; spike.

Therapeutic Strategies in an Outbreak Scenario to Treat the Novel Coronavirus Originating in Wuhan, China

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Abstract
A novel coronavirus (2019-nCoV) originating in Wuhan, China presents a potential respiratory viral pandemic to the world population. Current efforts are focused on containment and quarantine of infected individuals. Ultimately, the outbreak could be controlled with a protective vaccine to prevent 2019-nCoV infection. While vaccine research should be pursued intensely, there exists today no therapy to treat 2019-nCoV upon infection, despite an urgent need to find options to help these patients and preclude potential death. Herein, I review the potential options to treat 2019-nCoV in patients, with an emphasis on the necessity for speed and timeliness in developing new and effective therapies in this outbreak. I consider the options of drug repurposing, developing neutralizing monoclonal antibody therapy, and an oligonucleotide strategy targeting the viral RNA genome, emphasizing the promise and pitfalls of these approaches. Finally, I advocate for the fastest strategy to develop a treatment now, which could be resistant to any mutations the virus may have in the future. The proposal is a biologic that blocks 2019-nCoV entry using a soluble version of the viral receptor, angiotensin-converting enzyme 2 (ACE2), fused to an immunoglobulin Fc domain (ACE2-Fc), providing a neutralizing antibody with maximal breath to avoid any viral escape, while also helping to recruit the immune system to build lasting immunity. The ACE2-Fc therapy would also supplement decreased ACE2 levels in the lungs during infection, thereby directly treating acute respiratory distress pathophysiology as a third mechanism of action. The sequence of the ACE2-Fc protein is provided to investigators, allowing its possible use in recombinant protein expression systems to start producing drug today to treat patients under compassionate use, while formal clinical trials are later undertaken. Such a treatment could help infected patients before a protective vaccine is developed and widely available in the coming months to year(s).

Keywords: coronavirus; Wuhan; neutralizing antibody; ACE2; outbreak; 2019-nCoV

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Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases

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Cynthia Liu,* Qiongqiong Zhou, Yingzhu Li, Linda V. Garner, Steve P. Watkins, Linda J. Carter, Jeffrey Smoot, Anne C. Gregg, Angela D. Daniels, Susan Jervey and Dana Albaiu

Since the outbreak of the novel coronavirus disease COVID-19, caused by the SARS-CoV-2 virus, this disease has spread rapidly around the globe. Considering the potential threat of a pandemic, scientists and physicians have been racing to understand this new virus and the pathophysiology of this disease to uncover possible treatment regimens and discover effective therapeutic agents and vaccines. To support the current research and development, CAS has produced a special report to provide an overview of published scientific information with an emphasis on patents in the CAS content collection. It highlights antiviral strategies involving small molecules and biologics targeting complex molecular interactions involved in coronavirus infection and replication. The drug-repurposing effort documented herein focuses primarily on agents known to be effective against other RNA viruses including SARS-CoV and MERS-CoV. The patent analysis of coronavirus-related biologics includes therapeutic antibodies, cytokines, and nucleic acid-based therapies targeting virus gene expression as well as various types of vaccines. More than 500 patents disclose methodologies of these four biologics with the potential for treating and preventing coronavirus infections, which may be applicable to COVID-19. The information included in this report provides a strong intellectual groundwork for the ongoing development of therapeutic agents and vaccines.

BACKGROUND

The outbreak of the novel coronavirus disease, COVID-19, caused by the new coronavirus 2019-nCoV that is now officially designated as severe acute respiratory syndrome-related coronavirus SARS-CoV-2, represents a pandemic threat to global public health.[1,2] Although the epicenter of the COVID-19 outbreak in December of 2019 was located in Wuhan, China, this disease has spread to more than 100 countries (Figure 1) with over 100000 confirmed cases and over 3,800 confirmed deaths worldwide (Figure 2) as of March 9, 2020.[3] In addition, millions of people's lives have been affected as a result of mandatory isolations/quarantines. The ripple effect of the COVID-19 outbreak could potentially bring major challenges to worldwide health systems and have far-reaching consequences on the global economy if the spread of the virus is not effectively controlled.[1,2,4]

Coronaviruses (CoVs) are relatively large viruses containing a single-stranded positive-sense RNA genome encapsulated within a membrane envelope. The viral membrane is studded with glycoprotein spikes that give coronaviruses their crown-like appearance (Figure 3). While coronaviruses infect both humans and animals, certain types of animals such as bats that host the largest variety of coronaviruses appear to be immune to coronavirus-induced illness.[5] There are four classes of coronaviruses designated as alpha, beta, gamma, and delta. The beta-coronavirus class includes severe acute respiratory syndrome (SARS) virus (SARS-CoV), Middle East respiratory syndrome (MERS) virus (MERS-CoV), and the COVID-19 causative agent SARS-CoV-2. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 attacks the lower respiratory system to cause viral pneumonia, but it may also affect the gastrointestinal system, heart, kidney, liver, and central nervous system leading to multiple organ failure.[6,7] Current information indicates that SARS-CoV-2 is more transmissible/contagious than SARS-CoV.[8]

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Table 3. Key Protein Targets and Related Patents in the CAS Content Collection and Potential Drug Candidates in CAS REGISTRY of Chemical Substances

target	no. of patents	no. of potential drug candidates
3CLpro	49	2178
PLpro	4	189
RdRp	26	570
S protein	46	333
ACE2	5	97
AT2	2	38

disclose preparation of the nucleotide analog drug remdesivir that was later developed as a therapeutic agent for Ebola and Marburg virus infections (Patent US20170071964). Because of its promising results in at least two COVID-19 patients, remdesivir has now entered into phase III clinical trials.

Patent application WO2013049382 discloses both structures and syntheses of compounds from various structure classes (peptidyl aldehydes, peptidyl α-ketoamides, peptidyl bisulfite salts, and peptidyl heterocycles), as well as certain formulation compositions, developed to inhibit viral 3C protease or 3C-like protease (i.e., 3CLpro).

Patent application WO2018042343 presents both preparation methods and biological assay results for compounds capable of inhibiting the SARS virus proteases. These compounds appeared to exhibit good enzyme-inhibiting activity ($pIC_{50} \approx 7$

Table 4. Existing Drugs with Therapeutic Potentials for COVID-19 (Drug Repurposing)

drug candidate	CAS RN	target	possible mechanism of action on COVID-19	disease indication
baricitinib[35]	1187594-09-7	JAK kinase	a JAK inhibitor that may interfere with the inflammatory processes	approved drug for rheumatoid arthritis
lopinavir[19a]	192725-17-0	viral proteases: 3CLpro or PLpro	protease inhibitors that may inhibit the viral proteases: 3CLpro or PLpro	lopinavir and ritonavir are approved drug combination for HIV infection
ritonavir[19,37c]	155213-67-5			
darunavir[33]	206361-99-1			approved drug for HIV infection
favipiravir (favilavir)[29,36]	259793-96-9	RdRp	a purine nucleoside that acts as an alternate substrate leading to inaccurate viral RNA synthesis	viral infections
remdesivir[19,29,32a]	1809249-37-3		a nucleotide analogue that may block viral nucleotide synthesis to stop viral replication	Ebola virus infection
ribavirin[16,29−31a]	36791-04-5			RSV infection, hepatitis C, some viral hemorrhagic fevers
galidesivir[34b]	249503-25-1			hepatitis C, Ebola virus, Marburg virus
BCX-4430 (salt form of galidesivir)[34b]	222631-44-9			hepatitis C, Ebola virus, Marburg virus
Arbidol[22,33a]	131707-23-8	S protein/ ACE2[d]	an inhibitor that may disrupt the binding of viral envelope protein to host cells and prevent viral entry to the target cell	influenza antiviral drug
chloroquine[29,32]	54-05-7	endosome/ ACE2	a drug that can elevate endosomal pH and interfere with ACE2 glycosylation	malarial parasite infection
nitazoxanide[29]	55981-09-4	N/A	a drug that may inhibit viral protein expression	various helminthic, protozoal, and viral infection-caused diarrhea

[a]Drugs under clinical trials for treating COVID-19 (repurposing). [b]Drugs under clinical trials for other virus-induced diseases. [c]Ritonavir is a pharmacokinetic profile enhancer that may potentiate the effects of other protease inhibitors due to its ability to attenuate the degradation of those drugs by the liver enzyme CYP3A4 and thus is used in combination with antiviral Lopinavir.[37] [d]An inhibitor of viral entry to host cells. Its direct action on S protein and ACE2 is yet to be confirmed.

Table 5. Selected Patents Associated with Potential Drugs (Repurposing) for COVID-19 or Small Molecules for Treatment of SARS or MERS

COVID-19: combining antiviral and anti-inflammatory treatments

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Both coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) are characterised by an overexuberant inflammatory response and, for SARS, viral load is not correlated with the worsening of symptoms.[1,2] In our previous Correspondence to *The Lancet*,[3] we described how BenevolentAI's proprietary artificial intelligence (AI)-derived knowledge graph,[4] queried by a suite of algorithms, enabled identification of a target and a potential therapeutic against SARS coronavirus 2 (SARS-CoV-2; the causative organism in COVID-19). We identified a group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells (appendix). The drug targets are members of the numb-associated kinase (NAK) family—including AAK1 and GAK—the inhibition of which has been shown to reduce viral infection in vitro.[5,6] Baricitinib was identified as a NAK inhibitor, with a particularly high affinity for AAK1, a pivotal regulator of clathrin-mediated endocytosis. We suggested that this drug could be of use in countering SARS-CoV-2 infections, subject to appropriate clinical testing.

To take this work further in a short timescale, a necessity when dealing with a new human pathogen, we re-examined the affinity and selectivity of all the approved drugs in our knowledge graph to identify those with both antiviral and anti-inflammatory properties. Such drugs are predicted to be of particular importance in the treatment of severe cases of COVID-19, when the host inflammatory response becomes a major cause of lung damage and subsequent mortality. Comparison of the properties of the three best candidates are shown in the table. Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. All three are powerful anti-inflammatories that, as JAK-STAT signalling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon-γ) typically observed in people with COVID-19.[7] Although the three candidates have similar JAK inhibitor potencies, a high affinity for AAK1 suggests baricitinib is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile.[7] The most significant side-effect seen over 4214 patient-years in the clinical trial programmes used for European Medicines Agency registration was a small increase in upper respiratory tract infections (similar to that observed with methotrexate), but the incidence of serious infections (eg, herpes zoster) over

See Online for appendix

	Baricitinib	Ruxolitinib	Fedratinib
Daily dose, mg	2–10	25	600
Affinity and efficacy: K_d or IC_{50}, nM*			
AAK1†			
Cell free	17	100	32
Cell	34	700	960
GAK†			
Cell free	136	120	1
Cell	272	840	30
BIKE†			
Cell free	40	210	32
Cell	80	1470	960
JAK1			
Cell free	6	3	20
Cell	12	20	600
JAK2			
Cell free	6	3	3
Cell	11	21	100
JAK3			
Cell free	>400	2	79
Cell	>800	14	2370
TYK2			
Cell free	53	1	20
Cell	106	7	600
Pharmacokinetics			
Plasma protein binding	50%	97%	95%
C_{max} (unbound), nM	103‡	117	170
Safety: tolerated dose	≤10 mg/day	≤20 mg twice daily	≤400 mg/day

See regulatory approval documents for further information on these drugs. K_d=dissociation constant. IC_{50}=half-maximal inhibitory concentration. C_{max}=maximum serum concentration. *All values are IC_{50} except the cell free values for AAK1, GAK, and BIKE; "cell free" values indicate inhibitory activity against purified protein in biochemical assay; "cell" values indicate enzyme-inhibitory activity inside a cell. †In the absence of direct measurements of drug inhibition in cells, the predicted cell affinity and efficacy values are derived from the ratio of each compound for their primary target; for example, for baricitinib, K_d_AAK1(cell)=(IC$_{50}$_AAK1(cell)/IC$_{50}$_AAK1(cell free))×K_d_AAK1(cell free). ‡At a 10 mg dose.

Table: Properties of three antiviral and anti-inflammatory candidate drugs

52 weeks' dosing was small (3·2 per 100 patient-years), and similar to placebo.[7] Use of this agent in patients with COVID-19 over 7–14 days, for example, suggests side-effects would be trivial.

Other AI-algorithm-predicted NAK inhibitors include a combination of the oncology drugs sunitinib and erlotinib, shown to reduce the infectivity of a wide range of viruses, including hepatitis C virus, dengue virus, Ebola virus, and respiratory syncytial virus.[5,6] However, sunitinib and erlotinib would be difficult for patients to tolerate at the doses required to inhibit AAK1 and GAK. By contrast, at therapeutic doses used for the treatment of patients with rheumatoid arthritis, the free plasma concentrations of baricitinib are predicted to be sufficient to inhibit AAK1, and potentially GAK, in cell-based assays.

The predicted inhibition of clathrin-mediated endocytosis by baricitinib is unlikely to be observed with other anti-arthritic drugs or JAK inhibitors. Our analysis of the closely related JAK inhibitors ruxolitinib and fedratinib (table) illustrates that the predicted unbound plasma exposure required to inhibit the enzymes needed for clathrin-mediated endocytosis greatly exceeds the currently tolerated exposures used therapeutically. These drugs are, therefore, unlikely to reduce viral infectivity at tolerated doses, although they might reduce the host inflammatory response through JAK inhibition. Intriguingly, another JAK inhibitor, tofacitinib, shows no detectable inhibition of AAK1. The high affinity of baricitinib for NAKs, its anti-inflammatory properties, and its ability to ameliorate associated chronic inflammation in interferonopathies,[8] together with its advantageous pharmacokinetic properties, appear to make it a special case among the approved drugs.

In addition, the potential for combination therapy with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. Furthermore, there is the potential for combining baricitinib with the direct-acting antivirals (lopinavir or ritonavir and remdesivir) currently being used in the COVID-19 outbreak, since it has a minimal interaction with the relevant CYP drug-metabolising enzymes. Combinations of baricitinib with these direct-acting antivirals could reduce viral infectivity, viral replication, and the aberrant host inflammatory response. This work demonstrates that the use of an AI-driven knowledge graph can facilitate rapid drug development.

JS is editor-in-chief of *Oncogene*. JS has previously sat on a number of scientific advisory boards, including BenevolentAI, and consults with Lansdowne partners and Vitruvian; he now sits on the Board of Directors for BB Biotech Healthcare Trust and chairs Xerion Healthcare. All other authors are employees of BenevolentAI. Events in relation to the COVID-19 outbreak are evolving rapidly, and we make our initial thoughts available in this Comment in good faith and to assist in the global response. Our early investigations and suggestions require further detailed work and analysis and should not be relied on as constituting any kind of medical or other advice or recommendation.

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SARS-CoV-2 – Bindung an die Wirtszelle – 24.3.20

Die Forscher schließen, dass der neue Virus SARS-CoV-2 genauso wie SARS auch TMPRSS2 nutzt, um über das Spike-Protein an Wirtszellen zu binden und in sie einzudringen. Camostat-Mesylat, ein Inhibitor von TMPRSS2, kann somit die Infektion der Lungenzellen mit SARS-CoV-2 inhibieren.
SARS-Antikörper stören auch SARS-CoV-2, wenn auch weniger effektiv.
Die Forscher fanden neben diesem potenziellen Wirkstoff allerdings eine weitere relevante Unterstützung gegen SARS-CoV-2. Frühere Arbeiten zeigten bereits, dass genesene SARS-Patienten einen Antikörper gegen das virale Spike-Protein entwickelten. Ob diese Antikörper auch gegen das neue SARS-CoV-2 helfen konnten, untersuchte das Team nun in seiner Zellstudie. Tatsächlich fanden sie, dass das Serum von Patienten, die nach einer Infektion mit dem älteren SARS-Virus genesen waren, konzentrationsabhängig sowohl SARS-Viren als auch SARS-CoV-2 dabei hemmten, neue Zellen zu infizieren. Bei dem neueren SARS-CoV-2 geschah diese Hemmwirkung allerdings mit geringerer Effizienz. Aus Kaninchen gewonnene Sera gegen SARS-Spike-Protein hemmten SARS-Viren und mit geringerer Effizienz auch SARS-CoV-2.
Das Team schließt, dass Antikörper gegen SARS-Viren, speziell gegen das Spike-Protein der SARS-Viren, auch die Infektion durch SARS-CoV-2 zumindest reduzieren können.
Zwei schnelle Chancen gegen SARS-CoV-2: Impfstoff auf SARS-Basis, Hemmstoff aus Pankreatitis
Damit bietet diese Arbeit zwei mögliche Waffen gegen das neue Virus. Einmal einen Hemmstoff, Camostat-Mesylat, gegen die Bindung des Virus an die Wirtszellen, und schließlich einen, wenn auch nicht optimalen, Impfstoff auf Basis des SARS-Virus. In diesem Kontext besonders relevant: Camostat-Mesylat ist in Japan zur Behandlung von Menschen zugelassen – allerdings zur Behandlung einer Pankreatitis. Der Off-Label-Einsatz wäre demnach bei Patienten mit SARS-CoV-2-Infektion möglich.

Daten zur Inkubationszeit – Manifestation des Infektes:

- Wissenschaftler analysierten die Daten von 181 bestätigten COVID-19-Fällen
- Ziel der Studie war es, die Inkubationszeit von COVID-19 einzuschätzen
- Sie kamen zu folgenden Ergebnissen:
  - Weniger als 2,5 % entwickelten ihre Symptome innerhalb von 2,2 Tagen
  - Bei 50 % machten sich die Symptome innerhalb von 5,1 Tagen bemerkbar
  - 97,5 % bildeten innerhalb von 11,5 Tagen Symptome aus

Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0)

DGP – Basierend auf den dort gewonnenen Erfahrungen aus dem aktuellen Ausbruch seit Dezember 2019 veröffentlichte ein Team des Peking Union Medical College Hospital nun eine Empfehlung für die Vorgehensweise rund um Diagnose und klinische Behandlung von SARS-CoV-2-Infektionen. Auszüge aus dieser Publikation zu Untersuchung und supportiver Behandlung berichten wir hier als Checkliste.
Das Team des Peking Union Medical College Hospital hat auf den Erfahrungen aus China in Kooperation mit weiteren Autoren ein Protokoll entwickelt, um Diagnose und Management von SARS-CoV-2-Infektionen zu standardisieren. Teile dieser Publikation zu Untersuchung und supportiver Behandlung vor allem in der Klinik berichten wir hier als Checkliste. Details dieser Liste sollten allerdings anhand der neuesten Erkenntnisse laufend aktualisiert werden.
Diagnostische Kriterien

Supportive epidemiologische Historie (z. B. Kontakt zu infizierter Person)
Klinische Manifestation
Fieber, normale oder niedrige Werte weißer Blutkörperchen, reduzierte Lymphozytenzahl zu Beginn
Im Frühstadium zeigt die radiologische Untersuchung charakteristische kleine Schattenflecken und interstitielle Veränderungen, besonders prominent in den extrapulmonaren Bändern.
Fortgeschrittene Stadien zeigen beidseitig ground-glass opacities (milchige Schatten) und Infiltrationen.

Diagnose

SARS-CoV-2 Nukleinsäuren positiv in Sputum, Pharynx-Abstrich und Sekret des unteren respiratorischen Trakts
Real-time reverse Transkriptase–Polymerase-Kettenreaktion (rRT-PCR)
Für Patienten mit akutem Fieber (>37,5 °C innerhalb von 72 Stunden) und unauffälliger Bildgebung, wenn die absolute Zahl peripherer Lymphozyten geringer als 0,8 × 109/l wird, oder die Zahl von CD4+ und CD8+ T-Zellen deutlich abnimmt, sollte die Isolierung und enge Beobachtung zu Hause durchgeführt werden, selbst wenn der erste SARS-CoV-2-Test negativ ausfiel. Eine Wiederholung des Tests sollte nach 24 h angedacht werden. Ebenso kann ein CT angefertigt werden, wenn nötig.

Screening bei Aufnahme
Tag 1: Immer
Nukleinsäure-Test von Sputum oder naso-/oropharyngealen Abstrichen
Großes Blutbild, Urintest, Analyse der arteriellen Blutgase
Leber- und Nierenfunktion, C-reaktives Protein (CRP), Procalcitonin (PCT), Kreatinkinase plus Myoglobin, Koagulation
Thorax-CT

Tag 1: Wenn angebracht
Inflammatorische Zytokine: Interleukine IL-6, IL-10 und Tumornekrosefaktor (TNF)-α
TB Lymphozyten Untergruppen (z. B. CD4+, CD8+) und Komplement
Siehe Li et al. 2003 (Chin Med J, Engl.), Tai-sheng et al. 2003 (Chin J Lab Med), Taoran G et al. 2020 (Chin J Internal Med)

Weitere Untersuchungen bei bestätigter Infektion

Tage 2–3 nach Aufnahme
Röntgenaufnahmen der Brust oder CT, weitere Aufnahmen je nach Erkrankungsstatus, nicht länger als 5 Tage später
Tage 3, 5. und 7 und bei Entlassung je nach Erkrankungsstatus
Großes Blutbild, Leber- und Nierenfunktion, Kreatinkinase plus Myoglobin, Koagulation, CRP, PCT, TB Lymphozyten Untergruppen (z. B. CD4+, CD8+)

Wiederholung an Tagen 5–7, wenn möglich
PCT, TB Lymphozyten Untergruppen (z. B. CD4+, CD8+)
Siehe Li et al. 2003 (Chin Med J, Engl.), Tai-sheng et al. 2003 (Chin J Lab Med), Taoran G et al. 2020 (Chin J Internal Med)

Bei Entlassung
Großes Blutbild
Röntgenbild der Brust
Leber- und Nierenfunktion
Alle auffälligen Ergebnisse bei Aufnahme

Behandlungselemente bei COVID-19

Supportive Behandlung
Elektrolyten
Flüssigkeit
Vitalwerte?
Sauerstoffsättigung?
Sauerstoffbehandlung
Sauerstofffraktion jeweils angepasst an Sättigung
Hypoxämie?
→ Sauerstofftherapie
Sättigung mind. 90 % (Männer und nicht schwangere Frauen)
Sättigung zwischen 92–95 % (schwangere Frauen)
Milde Hypoxämie?
→ Nasenkanüle mit 5 l/min
Stärkerer Sauerstoffmangel?

→ Höherer Durchfluss mit 20 l, graduell ansteigend bis zu 50–60 l/min

Die Autoren empfehlen nicht invasive Ventilation nur für Patienten, die dies tolerieren, und Intubierung nur durch erfahrenes Personal mit Schutzkleidung.
Li und seine Kollegen empfehlen zudem eine protektive Beatmungsstrategie für ein akutes respiratorisches Distresssyndrom (akutes Lungenversagen, ARDS). Für Patienten mit besonders schwerem ARDS raten sie zu extrakorporaler Membranoxygenierung (ECMO) oder Bauchlage.

Antivirale Behandlung
Li und Kollegen betonen, dass bislang unklar ist, ob existierende antivirale Therapien gegen SARS-CoV-2 anschlagen, schlagen aber vor, Lopinavir/Ritonavir, wenn angebracht, in der Menge von zwei Tabletten zweimal täglich für 14 Tage zu geben.

Glukokortikoid-Behandlung
Schwer erkrankte Patienten können, schreiben die Ärzte, in frühem Stadium beispielsweise intravenös Methylprednisolon 40–80 mg erhalten (einmal täglich für 5 Tage). Die Behandlung kann je nach klinischem Zustand und radiologischer Manifestation angepasst werden.

Intravenöses Immunglobulin
Frühe intravenöse Infusion mit humanem Immunoglobulin empfehlen Li und Kollegen für Patienten in kritischem Zustand, je nach ihrer klinischen Verfassung in Dosierungen zwischen 0,25–0,5 g/(kg/Tag) für 3–5 Tage.

Antibakterielle Therapie
Wenn eine bakterielle Infektion auf Basis klinischer und bildgebender Daten vermutet wird, können Patienten mit milder Erkrankung oral antibiotisch gegen CAP (ambulant erworbene Pneumonie) behandelt werden. Vorgeschlagen werden beispielsweise Cephalosporine oder Fluoroquinolone. Bei schwer erkrankten Patienten sollten alle möglichen Pathogene abgedeckt werden, wenn nötig.

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Medikamentöse Therapieformen -27.3.20, cit. Amboss

Bisher ist keine nachweislich wirksame Therapieform etabliert, daher stets experimentell; ein Einsatz kann unter Nutzen-Risiko-Abwägung in Einzelfällen erwogen werden [121][97][59]

Übersicht aktuell erprobter Wirkstoffe

1. Therapieversuche mit vielen Substanzen, klinische Studien laufend, es werden auch verschiedene Kombinationsregime getestet!
    1. Hervorgehoben erscheinen die am intensivsten untersuchten Wirkstoffe
2. Wirkstoff(-gruppen), Substanzen und mögliche therapeutische Zielstrukturen [122][123]
    1. Inhibition der Adhäsion und Invasion
        1. Camostat [46] (Protease-Inhibitor)
    2. Inhibition der Fusion
        1. Chloroquin/Hydroxychloroquin , zusätzlich oder als alternativ führender Mechanismus immunsuppressive Effekte [124][125][126][127]
            1. Intensiv erprobt wird die Kombination mit Azithromycin [128]
                1. Azithromycin wird auch zum Einsatz als Immunmodulans bei COVID-19-Pneumonie diskutiert, Zithromax
        2. Umifenovir [129]
    3. Protease-Inhibition
        1. Lopinavir/Ritonavir [130][131][24]
        2. Darunavir/Ritonavir (ggf. in Kombination mit Umifenovir)
        3. Remdesivir [132][133]
    4. RNA-Polymerase-Inhibitoren bzw. Nukleotidanaloga
        1. Favipiravir [134]
        2. Remdesivir [133][135]
        3. Baloxavirmarboxil [136]
    5. Antikörpertherapie und Biologicals [22]

1. Tocilizumab [137][138], insb. in der Phase des ARDS bei erhöhtem IL-6 und CRP Roactemra Inj.Lsg, 4St 1380.- *Interleukin-Inhibitor*
2. Rekombinantes ACE2 (rhACE2, APN01) [47][139]

6. Passive Immunisierung durch Serumtherapie: Form der Impfung, bei genügend hoher Anzahl Immunisierter und Serumspenden im Verlauf als Option für eine breitere Anwendung, bspw. bei Risikogruppen [140]

3. Interaktionen der genannten Medikamente: Zahlreich, bei erwogenem Einsatz zu beachten (Fachinfo!) bzw. gemäß Übersicht der University of Liverpool! [141]
   1. Siehe auch
      1. Risikokonstellationen einer verlängerten QT-Zeit
      2. Torsade de pointes - Klinisches Management

Für die Wirksamkeit der Medikamente ist wahrscheinlich der Zeitpunkt des Einsatzes im Krankheitsverlauf entscheidend – während in die Virusinvasion und -replikation eingreifende Medikamente (z.B. Remdesivir, Hydroxychloroquin) so früh wie möglich appliziert werden müssten, könnten andere Ansätze, die auf die Kontrolle der dysregulierten Immunantwort bei schweren Verläufen abzielen (z.B. Tocilizumab), auch in späteren Phasen des Krankheitsverlaufes sinnvoll eingesetzt werden!

Favipiravir

Wikipedia: Favipiravir ist Guanin-Analogon[3] und ein Inhibitor der viralen RNA-abhängigen RNA-Polymerase von verschiedenen Viren,[4] nicht jedoch von zellulären Polymerasen. Weiterhin erhöht es die Mutationsrate bei der Replikation des Influenzavirus[5] und des Ebolavirus.[6] Favipiravir ist ein Prodrug, das heißt, es wird im Stoffwechsel durch die HGPRT in Favipiravir-ribofuranosyl-5'-monophosphat (FRMP) und Favipiravir-ribofuranosyl-5'-triphosphat (FRTP) überführt,[7][8] wobei FRTP die wirksame Form von Favipiravir bei der Hemmung der RNA-abhängigen RNA-Polymerase ist.[2]

Favipiravir ist unter anderem wirksam gegen das Influenzavirus, das Maul-und-Klauenseuche-Virus, verschiedene Flaviviren (das West-Nil-Virus, das Gelbfieber-Virus), Arenaviren, Bunyaviren und Alphaviren,[2] manche Enteroviren,[9] das Nipahvirus,[10] Noroviren,[11] das Ebolavirus,[12] das Lassa-Virus,[11] das Tollwutvirus[13][14] und das Rifttalfieber-Virus.[15] Es wirkt auch gegen das Zika-Virus, aber schlechter als MK-608.[16]

Im Februar 2020 wurde Favipiravir in China in einer ersten nicht randomisierten Doppelblindstudie an 80 Patienten als antivirale Therapie gegen das Coronavirus SARS-CoV-2 getestet.[21][22] In einer weiteren Studie, in der Favipiravir gegen das virostatische Präparat *Arbidol* (Umifenovir) an jeweils rund 120 Patienten verglichen wurde, zeigte Favipiravir eine signifikante Verbesserung. Die Ergebnisse dieser Studie werden jedoch bezweifelt.[23] Favipiravir hat zuvor im Februar 2020 in China die Zulassung zu klinischen Tests zur Evaluierung der Wirksamkeit bei COVID-19 erhalten.[24]

Avigan (Favipiravir) gehört zu den Arzneimitteln, für die das Bundesministerium für Gesundheit die zentrale Beschaffung zur Behandlung infizierter und schwer erkrankter COVID-19 Patienten in Deutschland eingeleitet hat. Da es sich bei einer Covid-19-Therapie um einen individuellen Heilversuch ohne klinischen Wirksamkeitsnachweis handele, solle der Einsatz vorrangig bei schweren Verlaufsformen patientenindividuell erwogen werden.[25]

WHO launches global megatrial of the four most promising coronavirus treatments – 22.3.20

Remdesivir: shuts down viral replication by inhibiting akey viral enzyme, the RNA-dependent RNApolymerase.
chloroquine/hydroychloroquine: drug works by decreasing the acidity in endosomes, compartment inside cells that they use to ingest outside marerial and that some viruses can coopt to enter a cell. Doses needed are usually high and could dause serious toxicities.
Main entryway for SARS-CoV2 is a different one, using ist socalled spike protein to attach to a receptor on the surface of human cells.
combination of two HIV drugs – lopinavir u. ritonavir and this combination with interferon-beta: first used in Saudi Arabia for MERS patients. Interferone given late in the disease it could easily lead to worse tissue damage.

The influenca drug f**avipiravir** may be added to the trial
Design ist not double-blind, we have to balance scientific rigor against speed.

Executive Summary Covid19 v2 – Stellungnahme zur COVID19 Krise

Zusammenfassung einiger quantitativer Perspektiven, 31.3.20
Beiglböck M., Grohs Ph., Hermisson J., Nordborg M. u. Schachermayer W.
https://www.oesterreich.gv.at

Robert Koch Institut: Coronavirus SARS-CoV-2
https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Steckbrief.html

The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. - 13.4.20
Academic Journal
(English) By: Caly L; Druce JD; Catton MG; Jans DA; Wagstaff KM, Antiviral Research [Antiviral Res], ISSN: 1872-9096, 2020 Apr 03, pp. 104787; Publisher: Elsevier; PMID: 32251768;

Although several clinical trials are now underway to test possible therapies, the worldwide response to the **COVID-19** outbreak has been largely limited to monitoring/containment. We report here that Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity in vitro, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 hours post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Ivermectin therefore warrants further investigation for possible benefits in humans.

Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro.
Academic Journal
(English) By: Choy KT; Yin-Lam Wong A; Kaewpreedee P; Sia SF; Chen D; Yan Hui KP; Wing Chu DK; Wai Chan MC; Pak-Hang Cheung P; Huang X; Peiris M; Yen HL, Antiviral Research [Antiviral Res], ISSN: 1872-9096, 2020 Apr 03, pp. 104786; Publisher: Elsevier; PMID: 32251767;

An escalating pandemic by the novel SARS-CoV-2 virus is impacting global health and effective therapeutic options are urgently needed. We evaluated the in vitro antiviral effect of compounds that were previously reported to inhibit coronavirus **replication** and compounds that are currently under evaluation in clinical trials for SARS-CoV-2 patients. We report the antiviral effect of remdesivir, lopinavir, homorringtonine, and emetine against SARS-CoV-2 virus in Vero E6 cells with the estimated 50% effective concentration at 23.15 μM, 26.63 μM, 2.55 μM and 0.46 μM, respectively. Ribavirin or favipiravir that are currently evaluated under clinical trials showed no inhibition at 100 μM. Synergy between remdesivir and emetine was observed, and remdesivir at 6.25 μM in combination with emetine at 0.195 μM may achieve 64.9% inhibition in viral yield. Combinational therapy may help to reduce the effective concentration of compounds below the therapeutic plasma concentrations and provide better clinical benefits.

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths.
Academic Journal
(English) By: Grant WB; Lahore H; McDonnell SL; Baggerly CA; French CB; Aliano JL; Bhattoa HP, Nutrients [Nutrients], ISSN: 2072-6643, 2020 Apr 02; Vol. 12 (4); Publisher: MDPI Publishing; PMID: 32252338;

The world is in the grip of the **COVID-19** pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and **COVID-19**, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral **replication** rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of **COVID-19** includes that the

outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or **COVID-19** consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with **COVID-19**, higher vitamin D3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.

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How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1.

Editorial & Opinion
(English) By: Conti P; Gallenga CE; Tetè G; Caraffa A; Ronconi G; Younes A; Toniato E; Ross R; Kritas SK, Journal Of Biological Regulators And Homeostatic Agents [J Biol Regul Homeost Agents], ISSN: 0393-974X, 2020 Mar 31; Vol. 34 (2); Publisher: Biolife; PMID: 32228825;

SARS-CoV-2, also referred to as CoV-19, is an RNA virus which can cause severe acute respiratory diseases (**COVID-19**), with serious infection of the lower respiratory tract followed by bronchitis, pneumonia and fibrosis. The severity of the disease depends on the efficiency of the immune system which, if it is weak, cannot stem the infection and its symptoms. The new CoV-19 spreads in the population at a rate of 0.8-3% more than normal flu and mostly affects men, since immune genes are more expressed on the X chromosome. If CoV-19 would spread with a higher incidence rate (over 10%), and affect the people who live in closed communities such as islands, it would cause many more deaths. Moreover, people from the poorest classes are most at risk because of lack of health care and should be given more assistance by the competent authorities. To avoid the aggravation of CoV-19 infection, and the collapse of the health system, individuals should remain at home in quarantine for a period of approximately one month in order to limit viral transmission. In the case of a pandemic, the severe shortage of respirators and protective clothing, due to the enormous demand and insufficient production, could lead the CoV-19 to kill a large number of individuals. At present, there is no drug capable of treating CoV-19 flu, the only therapeutic remedies are those aimed at the side effects caused by the virus, such as inflammation and pulmonary fibrosis, recognized as the first causes of death. One of the **COVID-19** treatments involves inhaling a mixture of gaseous hydrogen and oxygen, obtaining better results than with oxygen alone. It was also noted that individuals vaccinated for viral and/or bacterial infectious diseases were less likely to become infected. In addition, germicidal UV radiation "breaks down" the oxygen O2 which then aggregate into O3 (ozone) molecules creating the ozone layer, capable of inhibiting viral **replication** and improving lung respiration. All these precautions should be taken into consideration to lower the risk of infection by CoV-19. New anti-viral therapies with new drugs should also be taken into consideration. For example, microbes are known to bind TLR, inducing IL-1, a pleiotropic cytokine, highly inflammatory, mediator of fever and fibrosis. Therefore, drugs that suppress IL-1 or IL-1R, also used for the treatment of rheumatoid arthritis are to be taken into consideration to treat **COVID-19**. We strongly believe that all these devices described above can lead to greater survival and. therefore, reduction in mortality in patients infected with CoV-19.

Novel coronavirus 2019 (COVID-19): Emergence and implications for emergency care

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Abstract
A novel coronavirus (COVID-19) causing acute illness with severe symptoms has been isolated in Wuhan, Hubei Province, China. Since its emergence, cases have been found worldwide, reminiscent of severe acute respiratory syndrome andMiddle East respiratory syndrome outbreaks over the past 2 decades. Current understanding of this epidemic remains limited due to its rapid development and available data. While occurrence outside mainland China remains low, the likelihood of increasing cases globally continues to rise. Given this potential, it is imperative that emergency clinicians understand the preliminary data behind the dynamics of this disease, recognize possible presentations

of patients, and understand proposed treatment modalities.
KEYWORDS: global health, infectious disease, public health

Endothelial cell infection and endotheliitis in COVID-19

Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies S Zinkernagel, et al.
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Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood.
SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells.
Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus is currently unknown. Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro.

Here we demonstrate endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19 (further case details are provided in the appendix).
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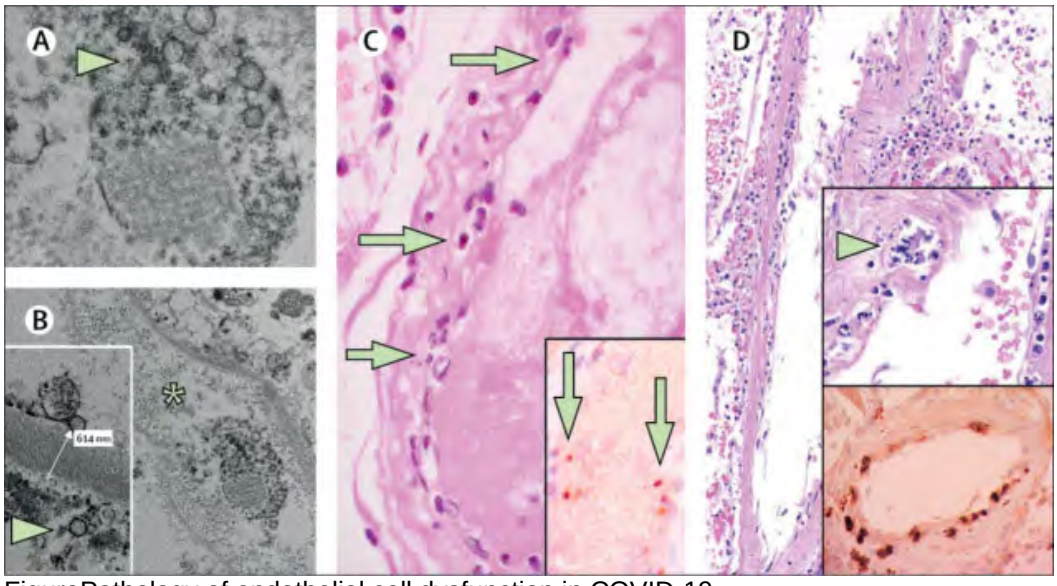
Patient 1 was a male renal transplant recipient, aged 71 years, with coronary artery disease and arterial hypertension. The patient's condition deteriorated following COVID-19 diagnosis, and he required mechanical ventilation. Multisystem organ failure occurred, and the patient died on day 8.
Post-mortem analysis of the transplanted kidney by electron microscopy revealed viral inclusion structures in endothelial cells (figure A, B). In histological analyses, we found an accumulation of inflammatory cells associated with endothelium, as well as apoptotic bodies, in the heart, the small bowel (figure C) and lung (figure D). An accumulation of mononuclear cells was found in the lung, and most small lung vessels appeared congested.



FigurePathology of endothelial cell dysfunction in COVID-19

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Patient 2 was a woman, aged 58 years, with diabetes, arterial hypertension, and obesity. She developed progressive respiratory failure due to COVID-19 and subsequently developed multi-organ failure and needed renal replacement therapy. On day 16, mesenteric ischaemia prompted removal of necrotic small intestine. Circulatory failure occurred in the setting of right heart failure consequent to an ST-segment elevation myocardial infarction, and cardiac arrest resulted in death. Post-mortem histology revealed lymphocytic endotheliitis in lung, heart, kidney, and liver as well as liver cell necrosis. We found histological evidence of myocardial infarction but no sign of lymphocytic myocarditis. Histology of the small intestine showed endotheliitis (endothelialitis) of the submucosal vessels.
Patient 3 was a man, aged 69 years, with hypertension who developed respiratory failure as a result of COVID-19 and required mechanical ventilation. Echocardiography showed reduced left ventricular ejection fraction. Circulatory collapse ensued with mesenteric ischaemia, and small intestine resection was performed, but the patient survived. Histology of the small intestine resection revealed prominent endotheliitis of the submucosal vessels and apoptotic bodies (figure C).
We found evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation. Although the virus uses ACE2 receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, thereby causing lung injury, the ACE2 receptor is also widely expressed on endothelial cells, which traverse multiple organs.

Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis (figure D).
The vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homoeostasis.

Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and a pro-coagulant state.

Our findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. COVID-19-endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilise the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins.
This strategy could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity, and established cardiovascular disease, all of which are associated with adverse outcomes in COVID-19.
ZV and AJF contributed equally as first authors, and RAS, FR, and HM contributed equally as last authors. AJF reports fees from Alnylam, Amgen, AstraZeneca, Fresenius, Imedos Systems, Novartis, Pfizer, Roche, Vifor, and Zoll, unrelated to this Correspondence. MRM reports consulting relationships with Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, NupulseCV, FineHeart, Leviticus, Baim Institute for Clinical Research, Riovant, and Triple Gene, unrelated to this Correspondence. FR has been paid for the time spent as a committee member for clinical trials, advisory boards, other forms of consulting and lectures or presentations. These payments were made directly to the University of Zurich and no personal payments were received in relation to these trials or other activities. All other authors declare no competing interests.

Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans

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Abstract:
SARS-CoV-2 has rapidly spread across the United States, causing extensive morbidity and mortality, though the histopathologic basis of severe disease cases has yet to be studied in detail. Over the past century, autopsy has contributed significantly to our understanding of numerous disease processes, but for several reasons, autopsy reports following deaths related to SARSCoV-2 have thus far been limited across the globe. We report on the relevant cardiopulmonary findings in the first series of autopsies in the United States, with the cause of death being due to SARS-CoV-2 infection. These cases identify key pathologic states potentially contributing to severe disease and decompensation in these patients.

Introduction:
The first confirmed case of SARS-CoV-2 infection in the United States was reported on January 20, 2020. Since that time, the virus has spread across the country, with several cities within the United States becoming epicenters of the pandemic. As of March 31, 2020 the Louisiana Department of Health reported a total of 5,237 COVID-19 cases with 1,355 hospitalizations, and 239 COVID-19 related deaths statewide. A total of 1,834 of the 5,239 COVID-19 cases and 101 of the 239 deaths have occurred in the city of New Orleans – the highest rate of death per capita in the United States. University Medical Center in New Orleans, built following Hurricane Katrina, is equipped with an autopsy suite meeting the modern standards recommended by the CDC for performance of autopsy on COVID-19 positive patients. We report here on the cardiopulmonary findings of the first four autopsies of a series of twelve performed on patients within the United States, with relevant implications for the treatment of severe cases.

Brief Clinical Summary:
The four decedents included male and female patients, ages 44-76. All were African American, and had a history of obesity class 2-3, and hypertension controlled by medication. Three of the patients had insulin-dependent type II diabetes, two had known chronic kidney disease (stages 2 and 3), and one was taking methotrexate.
In all cases the clinical course consisted of approximately three days of mild cough and fever to 101-102° F., with sudden respiratory decompensation just prior to arrival in the emergency department. Chest radiographs revealed bilateral ground-glass opacities, consistent with acute respiratory distress syndrome (ARDS) which worsened over the hospital course. The patients were intubated and brought to the ICU. Treatment in the ICU included vancomycin, azithromycin, and aefepime for all patients, with one patient receiving dexamethasone. All of the patients tested positive for SARS-CoV-2 (by 2019 Novel Coronavirus Real Time RT-PCR). Notable laboratory findings were the development of elevated ferritin, fibrinogen, PT, and within 24 hours of death, an increased neutrophil count with relative lymphopenia. Glucose and AST became slightly elevated above normal, and creatinine increased above baseline for all patients. D-dimers drawn near the time of death in two patients were markedly elevated (1200-2900 ng/mL). (A detailed description of ante-mortem laboratory findings can be found in **Table S1** in the Supplementary Appendix). When the patients continued to deteriorate despite support, the families elected to withdraw care. In each case, consent for autopsy was given, and nonrestricted by the next of kin. Studies performed outside of routine autopsy were determined to be exempt by the IRB at Tulane University.

Gross Findings:
Gross examination of the lungs at the time of autopsy revealed the tracheae to be of normal caliber and mildly erythematous. All of the lungs were heavy, the left ranging from 680g to 1030g , normal (583 +/-216); right ranging from 800g to 1050g, normal (663+/-239). They contained the usual lobes and fissures, with exception to one decedent with prior partial lobectomy on the right The pulmonary arteries at the hilum of each of the lungs were free of thromboemboli. The bronchi revealed thick, white mucous in the lungs of one patient, and pink froth in the airways of the other three. Mild to moderate serosanguinous pericardial and pleural effusions were also present. The parenchyma of each of the lungs was diffusely edematous and firm, consistent with the clinical diagnosis of ARDS. Notably, regions of dark-colored hemorrhage with focal demarcation could be identified throughout the peripheral parenchyma in the lungs of all but one of the decedents (**Figure 1A**). On cut sections, the areas identified as hemorrhagic on the external surface showed frank hemorrhage. After fixation, the cut surfaces of the lung tissue showed alternating areas of tan-grey consolidation with patchy areas of hemorrhage that ranged

from 3-6 cm in maximal diameter. In some cases, small, firm thrombi were present in sections of the peripheral parenchyma (**Figure 1C**). Only in the case of the patient on immunosuppression was there focal consolidation - the remainder of the lungs showed no evidence of lobar infiltrate, abscess, or definitive gross inflammatory process.
Examination of the heart was performed in three cases, with the hearts ranging in size from 430g to 550g (normal: 365g +/-71). The most significant gross findings were cardiomegaly, and right ventricular dilatation. In one case, massive dilatation could be seen, in which the right ventricular cavity measured 3.6cm in diameter, while the left ventricle measured 3.4cm in greatest diameter (**Figure 1B**). The cut surface of the myocardium was firm, red-brown, and free of significant lesions in all cases, and the coronary arteries showed no significant stenosis or acute thrombus formation.

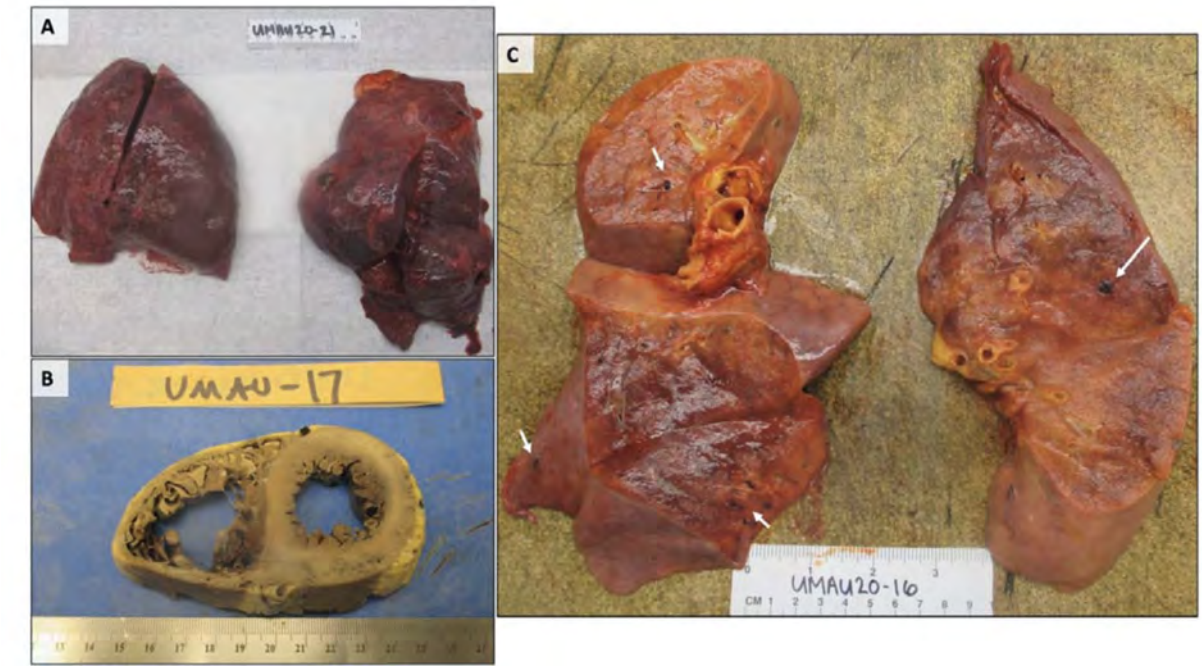

FIGURE 1: Gross Findings of the Lungs and Heart. A) Lungs with bilateral pulmonary edema and patches of dark hemorrhage, and **B)** A heart showing extreme right ventricular dilatation, with straightening of the interventricular septum. **C)** Cut sections of lung showing thrombi present within peripheral small vessels (white arrows).

Microscopic Findings:
Pulmonary. The lungs were extensively sampled across central and peripheral regions of each lobe bilaterally. Histologic examination of the lungs showed bilateral diffuse alveolar damage with a comparatively mild-to-moderate lymphocytic infiltrate, composed of a mixture of CD4+ and CD8+ lymphocytes (**Figure 2**), located predominantly in the interstitial spaces and around larger bronchioles. CD4+ lymphocytes could be seen in aggregates around small vessels, some of which appeared to contain platelets and small thrombi. In all but one case, foci of hemorrhage were present. Desquamated type 2-pneumocytes with apparent viral cytopathic effect consisting of cytomegaly, and enlarged nuclei with bright, eosinophilic nucleoli, were present within alveolar spaces (**Figure 3**). The largest of these cells frequently contained an eccentric clearing of the cytoplasm with small vesicles discernible at higher power, likely representing viral inclusions. Scattered hyaline membranes could be seen, as well as fibrin deposition, highlighted by trichrome stains (**Figure 2**), consistent with diffuse alveolar damage. The alveolar capillaries were notably thickened, with surrounding edema, and fibrin thrombi were present within the capillaries and small vessels. A notable finding was the presence of CD61+ megakaryocytes (**Figure 2**), possibly representing resident pulmonary megakaryocytes, with significant nuclear hyperchromasia and atypia. These cells were located within alveolar capillaries, and could be seen in association with, and actively producing platelets (**Figure 2**). The fibrin and platelets present within small vessels also appeared to aggregate inflammatory cells, with entrapment of numerous neutrophils. Only in the case of the patient on immunosuppression was there evidence of a focal acute inflammatory infiltrate possibly consistent with secondary infection. The neutrophils in this case, however, were partially degenerated and entrapped in fibers, possibly

representing neutrophil extracellular traps (**Figure 3**),1,2 and were present in association with clusters of CD4+ mononuclear cells. No significant neutrophilic infiltrate was identified within airways or the interstitium to suggest secondary infection in other cases.

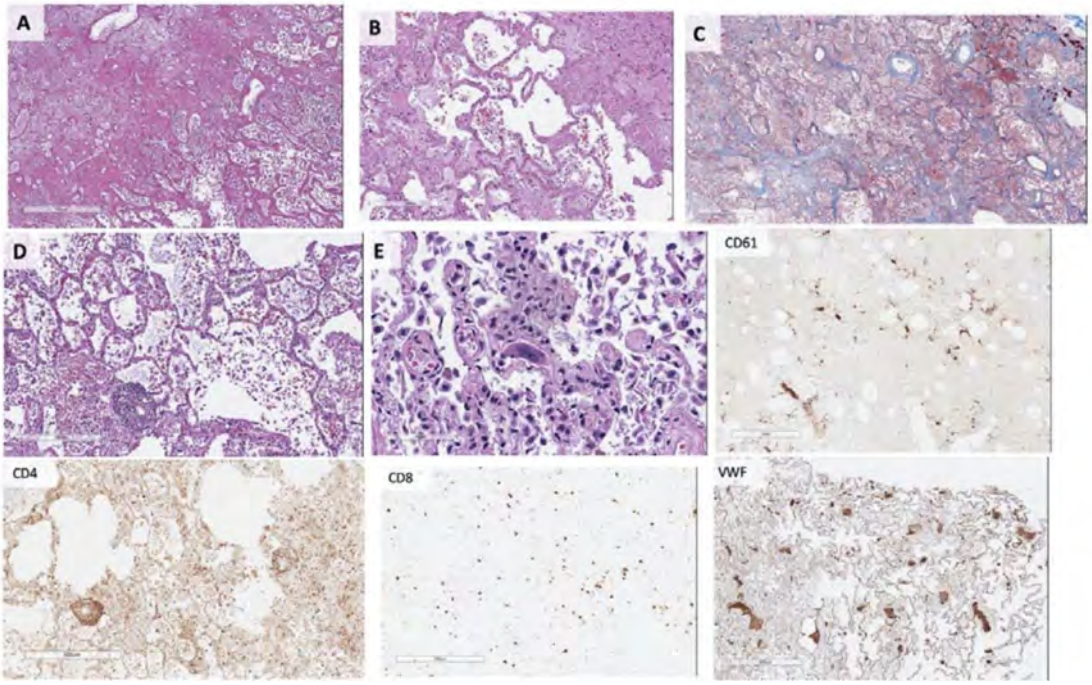

FIGURE 2: Pulmonary Microscopic Findings. All patients demonstrated extensive diffuse alveolar damage. **A)** Hyaline membranes and hemorrhage (H&E), with **B)** Fibrin thrombi present within distended small vessels and capillaries, and **C)** Extensive extracellular fibrin deposition highlighted in blue by Masson-Trichrome stain. **D)** Perivascular aggregations of lymphocytes, which were positive for CD4 immunostain, with only scattered CD8 positive cells present. **E)** Numerous megakaryocytes were present within the small vessels and alveolar capillaries, highlighted by CD61 and Von Willebrand Factor immunostains.

Cardiac. The sections of myocardium did not show any large or confluent areas of myocyte necrosis. The cardiac histopathology was remarkable, however, for scattered individual cell myocyte necrosis in each heart examined. In rare areas, lymphocytes were adjacent to, but not surrounding degenerating myocytes. Whether this may represent an early manifestation of a viral myocarditis is not certain, but there was no significant brisk lymphocytic inflammatory infiltrate consistent with the typical pattern of viral myocarditis. This may be consistent with a recent paper by Chen et al. that hypothesizes that pericytes may be infected by the SARS-CoV-2 virus and cause capillary endothelial cell/microvascular dysfunction which may cause individual cell necrosis.3 There was no obvious viral cytopathic effect by light microscopy, but direct viral infection of myocytes cannot be entirely ruled out in this limited examination.

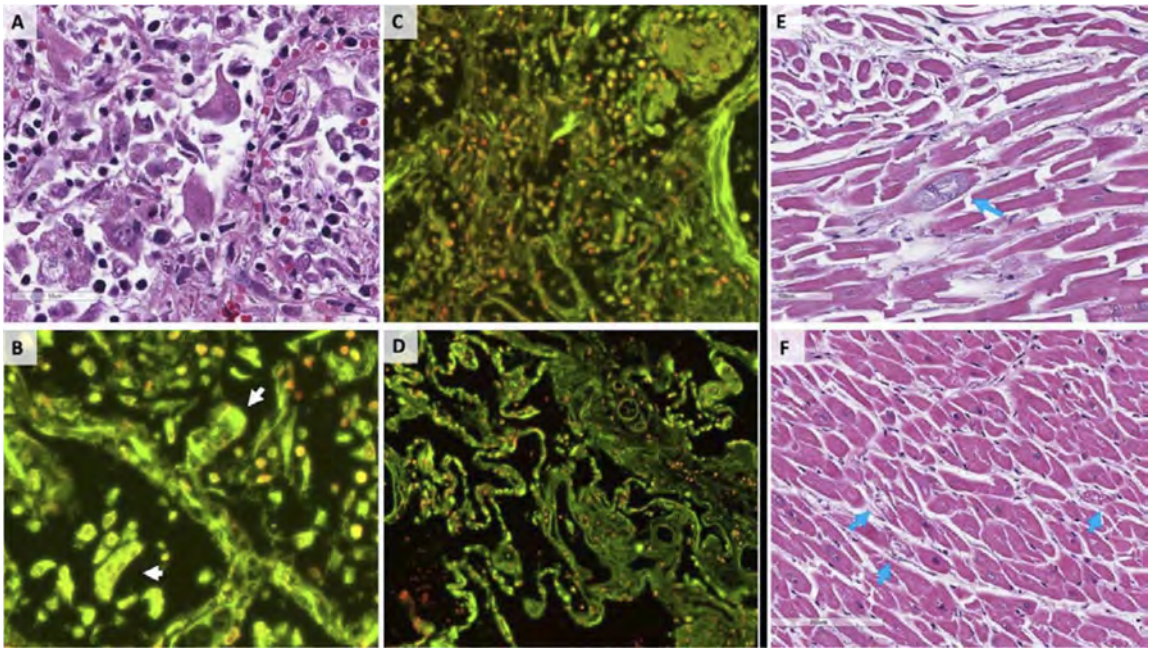

FIGURE 3: SARS-CoV-2 cytopathic effects. A) H&E stain of several enlarged pneumocytes within a damaged alveolus, having enlarged nuclei, prominent nucleoli, and cytologic atypia. **B)** Relative distribution of dsDNA (red) versus RNA (green) in tissue sections via DRAQ5 and SYTO RNASelect fluorescent staining (see **Supplementary Methods** for staining details). Virally infected cells in alveolar spaces show multinucleation and grouping as evidenced by DNA stain, and abundant RNA present within the cytoplasm (white arrows), **C)** Entrapment of immune cells, including degeneration neutrophils, within fibrin, and strands of extracellular material with weak DNA staining, and **D)** Control lung tissue obtained at autopsy for non-pulmonary cause of death prior to the SARS-CoV-2 pandemic. **E)** and **F)** H&E stains of cardiac myocytes with focal degeneration (blue arrows).

Discussion:
The dominant process in all cases was consistent with diffuse alveolar damage, with a mild to moderate mononuclear response consisting of notable CD4+ aggregates around thrombosed small vessels, and significant associated hemorrhage. Important additional mechanisms that may have contributed to death in this initial series of autopsies include a thrombotic microangiopathy that was restricted to the lungs. This process may involve activation of megakaryocytes, possibly those native to the lung, with platelet aggregation and platelet-rich clot formation, in addition to fibrin deposition. Small vessel thrombus formation in the lung periphery was in many cases associated with foci of alveolar hemorrhage. In one case, extensive fibrin and early organization was present, with degenerated neutrophils within the alveoli possibly representing neutrophil extracellular traps.1,2 On RNA imaging, we were able to visualize multinucleated cells within alveolar spaces, containing abundant RNA, likely representing virally infected cells. These may represent the multinucleated cells previously described from a single report of post-mortem biopsy from a decedent in China.4 Cardiac findings were significant for a lack of myocarditis, and the rise in BNP observed in at least one of our cases was likely due to acute right ventricular dilatation. The underlying cause of scattered atypical myocyte degeneration remains uncertain. There is prior evidence of viral infection causing activation of both maladaptive cytokine pathways, and platelet response, and our findings suggest that these immune functions may be related to severe forms of Covid-19. In response to systemic and pulmonary viral infections of H1N1 influenza and dengue, megakaryocytes have been known to respond by overexpressing IFITM3, and producing platelets with the same over-expression 5 In addition, platelets and megakaryocytes may have receptors for viruses6–9, some of which have been specifically activated in H1N1 influenza, often in association with lymphopenia10–12 There is even some evidence that the earlier SARS-CoV directly infected megakaryocytes, and that platelets function was affected in damaged lungs of those with severe SARS.14 We do not currently have evidence of direct infection of megakaryocytes by SARS-CoV-2, but the abundance of these cells in the lungs at autopsy is likely related to the abundance of small, sometimes platelet-rich thrombi, and foci of hemorrhage.
A notable finding was the lack of significant secondary infection in all of our cases. While all of the

patients received antibiotic therapy throughout their hospital courses, the lack of significant bacterial or fungal infection suggests that this is not the main cause of their decline. We also note that two of our patients were younger than those commonly thought to be ask risk for death due to Covid-19, and without immunosuppressive therapy, though with obesity, hypertension, and diabetes - comorbidities often present in our patient population, and in the population of many cities with Covid-19 on the rise. Based on our findings, we believe that effective therapy for these patients should not only target the viral pathogen, but also the thrombotic and microangiopathic effects of the virus, and possibly a maladaptive immune response to viral infection.

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We would first like to acknowledge our patients and their families, who in a time of loss have sought to help others understand this disease. We are also grateful for the support of the Department of Pathology at LSU Health Sciences Center, and for the hard work of the University Medical Center staff - in particular, Nicole Bichsel, for her invaluable role as autopsy assistant. Finally, we would like to acknowledge Dr. Paula L. Bockenstedt, Associate Professor of Hematology at the University of Michigan, for her expertise and guidance in this work.

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Clinical characteristics of 82 death cases with COVID-19

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Abstract
Background: A recently developing pneumonia caused by SARS-CoV-2 was originated in Wuhan, China, and has quickly spread across the world. We reported the clinical characteristics of 82 death cases with COVID-19 in a single center.
Methods: Clinical data on 82 death cases laboratory-confirmed as SARS-CoV-2 infection were obtained from a Wuhan local hospital's electronic medical records according to previously designed standardized data collection forms.
Results: All patients were local residents of Wuhan, and the great proportion of them were diagnosed as severe illness when admitted. Most of the death cases were male (65.9%). More than half of dead patients were older than 60 years (80.5%) and the median age was 72.5 years. The bulk of death cases had comorbidity (76.8%), including hypertension (56.1%), heart disease (20.7%), diabetes (18.3%), cerebrovascular disease (12.2%), and cancer (7.3%). Respiratory failure remained the leading cause of death (69.5%), following by sepsis syndrome/MOF (28.0%), cardiac failure (14.6%), hemorrhage (6.1%), and renal failure (3.7%). Furthermore, respiratory, cardiac, hemorrhage, hepatic, and renal damage were found in 100%, 89%, 80.5%, 78.0%, and 31.7% of patients, respectively. On the admission, lymphopenia (89.2%), neutrophilia (74.3%), and thrombocytopenia (24.3%) were usually observed. Most patients had a high neutrophil-to-lymphocyte ratio of >5 (94.5%), high systemic immune-inflammation index of >500 (89.2%), increased C-reactive protein level (100%), lactate dehydrogenase (93.2%), and D-dimer (97.1%). A high level of IL-6 (>10 pg/ml) was observed in all detected patients. Median time from initial symptom to death was 15 days (IQR 11-20), and a significant association between aspartate aminotransferase (p=0.002), alanine aminotransferase (p=0.037) and time from initial symptom to death were interestingly observed.
Conclusion: Older males with comorbidities are more likely to develop severe disease, even die from SARS-CoV-2 infection. Respiratory failure is the main cause of COVID-19, but either virus itself or cytokine release storm mediated damage to other organ including cardiac, renal, hepatic, and hemorrhage should be taken seriously as well.
Key words: COVID-2019; SARS-CoV-2; transmission; death; pneumonia; cytokine storm
Funding: No founding.

Research in context
Evidence before this study
As the seventh member of enveloped RNA coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV)-2 causes a cluster of severe respiratory disease which is similar to another two fatal coronavirus infection caused by

SARS-CoV and Middle Eastern respiratory syndrome coronavirus (MERS-CoV). Through searching PubMed and the China National knowledge infrastructure databases up to February 20, 2020, no published article focusing on hospitalized dead patients was identified.

Added value of this study

We conducted a single-center investigation involving 82 hospitalized death patients with COVID-19 and focused on their epidemiological and clinical characteristics. 66 of 82 (80.5%) of patients were older than 60 years and the median age was 72.5 years. The bulk of death cases had comorbidity (76.8%). Respiratory failure remained the leading cause of death, following by sepsis syndrome/MOF, cardiac failure, hemorrhage, and renal failure. Most patients had a high neutrophil-to-lymphocyte
ratio, high systemic immune-inflammation index, and increased levels of proinflammatory cytokines.

Implications of all the available evidence

SARS-CoV-2 causes a cluster of severe respiratory illness which is similar to another two fatal coronavirus infection caused by SARS-CoV and MERS-CoV. Death is more likely to occur in older male patients with comorbidity. Infected patients might develop acute respiratory distress and respiratory failure which was the leading cause of death, but damages of other organs and systems, including cardiac, hemorrhage, hepatic, and renal also contribute to the death. These damages might be attributable to indirect cytokines storm initiated by immune system and direct attack from SARS-CoV-2 itself.

Introduction

In December 2019, the first acute respiratory disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2, and recently officially named as Corona Virus Disease 2019 (COVID-19) by World Health Organization (WHO) occurred in Wuhan, China.1,2 Person-to-person transmission has been identified through respiratory droplets or likely feces.3-5 By February 14, 2020, more than
60,000 confirmed cases and close to 2,000 dead cases have been documented in China, with hundreds of imported patients found in other countries.4-7 Generally, the incubation period of COVID-19 was 3 to 7 days. Fever, cough, and fatigue were the most common symptoms.1 Approximately 20-30% of cases would develop severe illness, and some need further intervention in intensive care unit
(ICU) .8,9 Organ dysfunction including acute respiratory distress syndrome (ARDS), shock, acute cardiac injury, and acute renal injury, can happen in severe cases with COVID-19.1,8,9 It has been reported that critical ill patients were more likely to be older, had underlying diseases, and were more likely to have a symptom of dyspnea.9 Oxygen therapy, mechanical ventilation, intravenous antibiotics and antiviral therapy were usually applied in clinical management, but presently there were no effective drugs for improving the clinical outcome of COVID-19, especially for severe cases.1,8,9

ARDS, a rapidly progressive disease, is the main cause of death for the patients infected with previously recognized corona virus infection such as SARS-CoV and Middle Eastern respiratory syndrome coronavirus (MERS-CoV).10,11 In this context, it was initially considered that lung is the most commonly damaged organ by SARS-CoV-2 infection since human airway epithelia express angiotensin converting enzyme 2 (ACE2), a host cell receptor for SARS-CoV-2 infection.12,13 However, increasing clinical cases indicated cardiac, renal and even digestive organ damage in
the patients with COVID-19,9 which is consistent with the findings that kidney, colon and the other tissues also express ACE2 besides airway epithelia.14,15 The above clinical phenomenon and basic research suggest more complicated pathogenesis of COVID-19. Hence, analyzing clinical characteristics of death cases with COVID-19 is urgently needed to improve the outcome of infected patients.

Methods

Data collection

We retrospectively collected epidemiological and clinical features of laboratory-confirmed COVID-19 dead patients from January 11, 2020 to February 10, 2020 in the Renmin Hospital, Wuhan University. The confirmed diagnosis of COVID-19 was defined as a positive result by using real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) detection for routine nasal and pharyngeal swab
specimens. This study received approval from the Research Ethics Committee of the Renmin Hospital of Wuhan University, Wuhan, China (approval number: WDRY2020-K038). The Research Ethics Committee waived the requirement informed consent before the study started because of the urgent need to collect epidemiological and clinical data. We analyzed all the data anonymously. The clinical features, including clinical symptoms, signs, laboratory analyses, radiological findings, treatment, and outcome, were obtained from the hospital's electronic medical records according to previously designed standardized data collection forms. Laboratory analyses included complete blood count, liver function, renal function, electrolytes test, coagulation function, C-reactive protein, lactate
dehydrogenase, myocardial enzymes, procalcitonin, and status of other virus infection. Radiological analyses comprised of X-ray and computed tomography. The date of onset of symptoms, initial diagnosis of COVID-19, and death were recorded accurately. The incubation period was defined as the time from the contact of transmission origin to the onset of different symptoms and signs. Onset survival time was defined as the period between the onset of different symptoms and signs and

the time of death. To increase the accuracy of collected data, two researchers independently reviewed the data collection forms. We also directly communicated with patients or their family members to ascertain the epidemiological and symptom data.

Inflammation markers

Inflammation markers were calculated using specific parameters of blood tests. Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the lymphocyte count. Systematic inflammatory index (SII) was defined as platelet count × neutrophil count/ lymphocyte count (/μL). Interleukin (IL)-6 was detected using Human Cytokine Standard Assays panel (ET Healthcare, Inc., Shanghai, China) and the Bio-Plex 200 system (Bio-Rad, Hercules, CA, USA)
according to the manufacturer's instructions.

Statistical analysis

Descriptive analyses were used to determine the patients' epidemiological and clinical features. Continuous variables were presented as median and interquartile range (IQR), and categorical variables were expressed as the percentages in different categories. The Chi-squared test or Fisher's exact test was adopted for category variables. The association between the different clinical variables and the time from initial symptom to death was evaluated using Spearman's rank correlation coefficient. Statistical analyses in this study were performed with use of STATA 15.0 software
(Stata Corporation, College Station, TX, USA). A two-sided p value less than 0.05 was considered statistically significant.

Results

From January 11, 2020 to February 10, 2020, a total of 1,334 patients with a diagnosis of laboratory-confirmed COVID-19 were recorded in the Renmin Hospital, Wuhan University, while 6.2% (82/1334) of patients with this disease were dead. In the same period, the rate of mortality for all causes and non-COVID-19 in this hospital, were 2.3% (162/7119) and 1.4% (80/5785), respectively. The mortality rate of COVID-19 was higher than that of non- COVID-19 ($p<0.001$). The epidemiological features and underlying diseases were shown in table 1. All patients were local residents of Wuhan, and only 2 patients acknowledged a contact with the patients confirmed as SARS-CoV-2 infection. All the patients denied a history of contact with wildlife or Huanan seafood market visit. The great proportion
of them were diagnosed as severe illness when admitted (77/82). Median incubation time was 7 days (IQR 5.0-10.0). Most of the death cases were male (65.9%), older than 60 years (80.5%) and the median age was 72.5 years (IQR 65.0-80.0). The bulk of death cases had comorbidity (75.6%), including hypertension (56.1%), heart disease (20.7%), diabetes (18.3%), cerebrovascular disease (12.2%), and cancer (7.3%). 30 out of 82 dead patients (30.5%) had 2 or more underlying diseases.

We analyzed the causes of mortality of patients with laboratory-confirmed SARS-CoV-2 infection (table 2). Respiratory failure remained the leading cause of death (69.5%), following by sepsis syndrome/multiple organ dysfunction syndrome (MOF) (28.0%), cardiac failure (14.6%), hemorrhage (6.1%), and renal failure (3.7%). Furthermore, respiratory, cardiac, hemorrhage, hepatic, and renal damage were found in 100%, 89%, 80.5%, 78.0%, and 31.7% of patients, respectively. A majority of
patients (75.6%) had 3 or more damaged organs or systems following the infection with SARS-CoV-2.

As shown in table 3, fever (78.0%), cough (64.6%), and shortness of breath (63.4%) were the main common symptom. Diarrhea was observed in 12.2% of patients. All patients had bilateral involvement of chest radiographs. On the admission, lymphopenia (89.2%), neutrophilia (74.3%), and thrombocytopenia (24.3%) were usually observed. All the patients had increased C-reactive protein level (100%), and most patients had a high NLR >5.0 (94.5%), SII index of >500 (89.2%), lactate
dehydrogenase (93.2%), D-dimer (97.1%), cardiac troponin I (86.7%), and procalcitonin (81.2%). Insufficient cell immunity with reduced CD3+ (93.1%), CD8+ (98.3%), CD6+CD56+ (100%) cell count, and high level of circulating IL-6 (100%) were observed in patients. Furthermore, in the last 24 hours of the death, lymphopenia (73.7%), neutrophilia (100%), and thrombocytopenia (63.2%) were continuously present. Increased C-reactive protein level, high NLR, increased lactate dehydrogenase, and increased D-dimer were found in all patients. The incidence of neutrophilia was increased from
74.3% to 100%, and the incidence of lymphopenia was reduced from 89.2% to 73.7%. The incidence of high creatinine and blood urea nitrogen were increased from 15.3% to 45.0%, and 48.6% to 85.0%, respectively. High level of IL-6 (>10U/L) remained in all detected patients. More than half had a pH value of less than 7.35 (52.9%), and a pO2 value of less than 60 mmHg (70.6%) (table 4). As shown in table 3, a total of 14 patients (17.1%) were treated in ICU. Patients received oxygen therapy (100%), mechanical ventilation (40.2%), including 4 invasive mechanical ventilation (4.8%). All patients received intravenous of antibiotics and anti-virus medications, and systematic corticosteroids were used in 29 patients (35.3%). The median time from initial symptom to death was 15 days (IQR 15-20) and a significant association between aspartate aminotransferase ($p=0.002$), alanine minotransferase ($p=0.037$) and time from initial symptom to death were interestingly observed (figure 1A-C).

Discussion

To our knowledge, this is the first study to describe the clinical characteristics of dead patients with COVID-19. The mortality of 6.2% from current study was lower than that of SARS infection in 2003. However, the mortality rate from this center is a little bit higher than previously reported.9 We speculated the reason might be that fewer patients in our study were transferred to the ICU in time when their condition rapidly worsened. On the other hand, limited death cases, less than 15 patients were included in their cohort,8,9 while much more death cases were included in the present study.

Our study firstly focused on the epidemiological characteristics of dead patients with COVID-19. Several factors were responsible for the death of these patients included in this study. A majority of patients were older than 60 years in our study, and a borderline significant association between age and time from initial symptom to death were interestingly observed. These results are consistent with that older age was more likely occurred in critically ill patients.16 Moreover, we found underlying diseases such as hypertension, heart disease and diabetes were very common in our death cases,

and 30.5% of patients had 2 or more comorbidities. These features are consistent with previous report that patients with underlying diseases more likely developed to severe illness.9 Cancer patients is comprised of 7.3% in our cohort, much higher than cancer morbidity, suggest that cancer patients more likely develop to severe disease, even death. These results are consistent with the findings from a national wide analysis in China.17 Immune deficiency to virus infection seems to be the common features in older males with comorbidities. We further analyzed the cause of death case with COVID-19 and found that respiratory failure remained the leading cause of death. It has been reported that the binding receptor for SARS-CoV-2, ACE2 is mainly expressed in blood vessels and lung alveolar type II (AT2) epithelial cells,13 Similar to the SARS-CoV and MERS-CoV, SARS-CoV-2 can directly attack ACE2-expressing cells.13 Indeed, pathological findings indicated that infected lungs with SARS-CoV-2 present as ARDS, pulmonary edema with hyaline membrane formation, evident desquamation of pneumocytes.18 Therefore, our finding that respiratory failure is the leading cause of

death, is consistent with the underlying pathological mechanism of COVID-19. Besides respiratory failure, cardiac failure, hemorrhage, renal failure and even MOF were also recognized as the cause of death by COVID-19 in our study. Laboratory findings also revealed cardiac, hepatic, and renal damage in some of patients. We also observed a significant association between aspartate aminotransferase, alanine aminotransferase and time from initial symptom to death. These clinical phenomena could be explained by virus itself attack and cytokine release storm (CRS) mediated tissue damage. First, ACE2 expression is also found in the kidney, heart, and liver etc, therefore SARS-CoV-2 could invade the cells of above tissues, reproduce and damage these organ.14,15 Second, virus infection and subsequent tissue damage either in the lung or other target organ could elicit immune cells to produce pro-inflammatory cytokines, namely CRS, ultimately injury the tissue and cause target organ failure.

Obviously, increased amounts of cytokines, including IL-1β, IL-6, and monocyte chemotactic protein-1 (MCP-1), are associated with severe lung injury in patients infected with SARS-CoV and MERS-CoV.19,20 A recent study showed high levels of IL-1β, interferon γ-induced protein 10 , and MCP-1 occurred in serum of patients infected with SARS-CoV-2, which probably leaded to the activation of T-helper-1 cell response1. In the present report, high level of IL-6 of more than10U/L and C-reactive protein were detected in all patients, even in the last 24 hours prior to death. We also depicted the immune status of COVID-19 patients with severe illness. Most of patients in our study presented as neutrophilia and lymphopenia on admission, specifically reduced CD3+, CD4+, and CD8+ T-cell counts were observed in some patients. A high NLR was also observed on the admission and 24 hours before the death. These results, consistent with the previous findings found in the patients with

severe illness, suggest perturbation of immune system contribute the pathogenesis of SARS-CoV-2. These observations could be also explained why older males with comorbidities likely succumb to COVID-19. Our study has some limitations. Firstly, some patients did not receive timely supportive interventions such as admission to ICU, because increasing number of severe patients occurred in a short period. However, present data could partially be scenario where COVID-19 patients progress in a natural pathophysiology rather than outcome from intervention by treatment. Secondly, consecutive detection of cytokines was lacking, which fail to truly monitor the severity of CRS. Thirdly, organ damage could originate from a history of medication including nonsteroidal anti-inflammatory

drugs, antibiotics, and traditional Chinese medicine which are associated with renal or liver injury.21,22 In our study, all patients received intravenous of antibiotics and anti-virus drugs.

Overall, from the point of view of the causes of death, we presented the clinical characteristics of patients with COVID-19. Lung injury begins with an insult to the lung epithelium mainly attacked by SARS-CoV-2 itself because of ACE2 expressed in the lungs, which leads to most common respiratory failure. Other organs or tissues, more or less, are potentially damaged through direct attack from SARS-CoV-2. In addition, damages of multiple systems including the lungs, might originate with

systemic damage due to CRS following SARS-CoV-2 infection. Considering the pandemic potential and moderate threaten of COVID-19 for population with multiple underlying diseases, further studies are required to focus on pathology and pathophysiology of tissue injury caused by SARS-CoV-2 infection, especially on the activation process of immune response and cytokines storm.

Contributors

JW, BZ and QS had the idea for and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. BiZh, YZ and YQ contributed to writing of the report. BZ contributed to critical revision of the report. JW and BiZh contributed to the statistical analysis. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Declaration of interests

All authors declare no competing interests.

Data sharing

The data that support the findings of this study are available from the corresponding author on reasonable request. Participant data without names and identifiers will be made available after approval from the corresponding author and National Health Commission. After publication of study findings, the data will be available for others to request. The research team will provide an email address for communication once the data are approved to be shared with others. The proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the
reasonability to request for our data. The corresponding author will make a decision based on these materials. Additional materials may also be required during the process.

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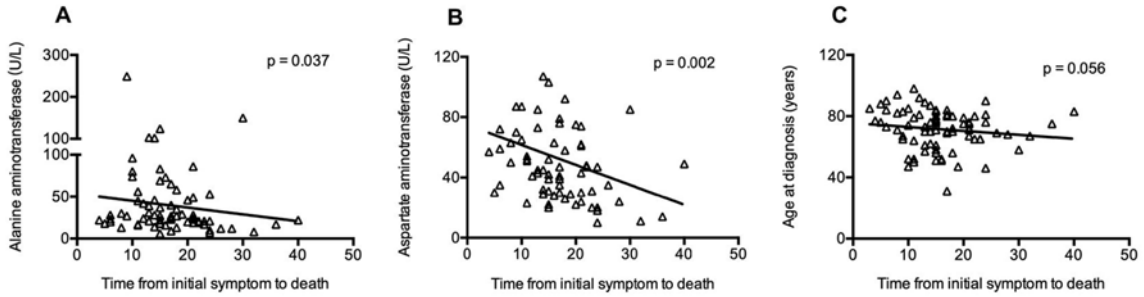

Figure legends

Figure 1: The association between clinical features and time from initial symptom to death

(A)Alanine aminotransferase (B) Aspartate aminotransferase (C) Age

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Table 1. Clinical features of dead patients with COVID-19

Clinical features	
Age, years	72.5 (65.0-80.0)
Age group	
≤40 years	2/82 (2.4)
40-50 years	4/82 (4.9)
50-60 years	10/82 (12.2)
60-70 years	20/82 (24.4)
70-80 years	26/82 (31.7)
>80 years	20/82 (24.4)
Sex	
Male	54/82 (65.9)
Female	28/82 (34.1)
Local residents of Wuhan	82/82 (100)
Severe pneumonia	77/82 (93.9)
Median incubation time (range), days	7/82 (5-10)
Comorbidity	
All	62/82 (76.8)
Hypertension	46/82 (56.1)
Diabetes	15/82 (18.3)
Chronic obstructive pulmonary disease	12/82 (14.6)
Heart disease	17/82 (20.7)
Cerebrovascular	10/82 (12.2)
Liver disease	2/82 (2.4)
Renal insufficiency	4/82 (4.9)
Infection	5/82 (6.1)
Cancer	6/82 (7.3)
Surgery	3/82 (3.7)
Disease with reduced immunity	14/82 (17.1)

Number of comorbidity diseases
0 19/82 (23.2)
1 25/82 (30.5)
2 18/82 (22.0)
≥3 7/82 (8.5)
Data are presented as median (IQR), n/N (%), where N represents the total number of patients with COVID-19

Table 2. Causes of death of patients with COVID-19
Causes of death and injured organs or systems
Causes of mortality
Respiratory 57/82 (69.5)
Sepsis/MOF 23/82 (28.0)
Cardiac 12/82 (14.6)
Hemorrhage 5/82 (6.1)
Renal 3/82 (3.7)
Gastrointestinal 2/82 (2.4)
Diabetic ketoacidosis 2/82 (2.4)
Hepatic 1/82 (1.2)
Damaged organs or systems
Respiratory 82/82 (100)
Cardiac 73/82 (89.0)
Hemorrhage 66/82 (80.5)
Hepatic 64/82 (78.0)
Renal 26/82 (31.7)
Gastrointestinal 5/82 (6.1)
Number of damaged organs or systems
1 8/82 (9.8)
2 3/82 (3.7)
3 9/82 (11.0)
4 41/82 (50.0)
≥5 21/82 (25.6)
Data are presented as n/N (%), where N represents the total number of patients with COVID-19.

Table 3. Initial symptoms, laboratory analyses, radiological findings, treatment, and survival time of dead patients with COVID-19
Initial clinical features, symptoms, laboratory analyses, treatment, and survival time
Initial symptoms
Fever 64/82 (78.0)
Temperature, oC 38.8 (38.0-39.0)
Fatigue 38/82 (46.3)
Cough 53/82 (64.6)
Nasal congestion 1/82 (1.2)
Sore throat 4/82 (4.9)
Diarrhea 10/82 (12.2)
Vomiting 2/82 (2.3)
Chest tightness 36/82 (43.9)
Shortness of breath 52/82 (63.4)
Consciousness problem 17/82 (20.7)
Complete blood count
Neutrophil count, × 109/L 6.8 (4.5-11.5)
Neutrophil count <1.8 × 109/L 2/74 (2.7)
Neutrophil count >6.3 × 109/L 55/74 (74.3)
Lymphocyte count, × 109/L 0.5 (0.3-0.8)
Lymphocyte count <1.0 × 109/L 66/74 (89.2)
Monocyte count, × 109/L 0.3 (0.2-0.5)
Platelet count, × 109/L 148.5 (102.0-206.0)
Platelet count <100 × 109/L 18/74 (24.3)
Platelet count >400 × 109/L 10/74 (13.5)

Neutrophil-to-lymphocyte ratio 14.4 (7.1-25.8)
Neutrophil-to-lymphocyte ratio >5 69/73 (94.5)
Platelet-to-lymphocyte ratio 235.0 (259.0-442.0)
Platelet-to-lymphocyte ratio >200 55/74 (74.3)
Systemic immune-inflammation index 1966.1 (923.1-3206.5)
Systemic immune-inflammation index >500 66/74 (89.2)
Oxygen saturation, median (range), % 77.0 (65.5-85.0)
Oxygen saturation <94% 27/28 (96.4)
Blood biochemical analysis
C-reactive protein level, U/L 11.7 (63.3-186.6)
C-reactive protein level >10U/L 58/58 (100.0)
Alanine aminotransferase, U/L 26.0 (18.5-47.5)
Alanine aminotransferase >40U/L 22/72 (30.6)
Aspartate aminotransferase, U/L 72.0 (30.0-71.0)
Aspartate aminotransferase >40U/L 44/72 (61.1)
Total bilirubin, mmol/L 13.6 (10.0-22.9)
Total bilirubin >20.5mmol/L 22/72 (30.6)
Albumin, g/L 33.1 (30.3-36.9)
Albumin <40g/L 56/72 (77.8)
Potassium, mmol/L 4.1 (3.7-4.4)
Potassium >5.5mmol/L 16/72 (22.2)
Sodium, mmol/L 141 (138.0-144.5)
Blood urea nitrogen, mmol/L 8.6 (6.0-14.8)
Blood urea nitrogen >8.8mmol/L 35/72 (48.6)
Creatinine, μmol/L 78.0 (56.0-111.0)
Creatinine >133μmol/L 11/72 (15.3)
Creatine kinase, U/L 107.5 (56-336.5)
Creatine kinase >200 U/L 25/72 (34.7)
Myoglobin, μg/L 124.9 (71.1-392.3)
Myoglobin >110μg/L 42/70 (60.0)
Lactate dehydrogenase, U/L 515.0 (365.0-755.0)
Lactate dehydrogenase >250 U/L 68/73 (93.2)
Creatine kinase-MB, ng/ml 2.6 (1.2-5.3)
Creatine kinase-MB >5ng/ml 21/70 (30.0)
NT-pro B-type natriuretic peptide, pg/ml 122.0 (106.0-140.0)
Cardiac troponin T, pg/ml 0.1 (0.1-0.7)
Cardiac troponin T >0.04pg/ml 52/60 (86.7)
Procalcitonin, ng/ml 0.3 (0.1-1.1)
Procalcitonin >0.1 ng/ml 56/69 (81.2)
Prothrombin time, s 13.2 (12.3-14.3)
Activated partial thromboplastin time, s 29.4 (22.5-63.2)
D-dimer, mg/L 5.1 (2.2-21.5)
D-dimer >0.55mg/L 66/68 (97.1)
Cell immunity, × 109/L
CD3+ cell count 245.0 (45.6-67.8)
CD3+ cell count <723 × 109/L 54/58 (93.1)
CD4+ cell count 32.9 (26.0-42.1)
CD4+ cell count <404 **×** 109/L 34/58 (58.6)
CD8+ cell count 16.5 (10.9-26.5)
CD8+ cell count <220 **×** 109/L 57/58 (98.3)
CD4+/CD8+ 1.9 (1.2-3.0)
CD4+/CD8+>2 28/58 (48.3)
CD19+ cell count 17.7 (10.3-25.5)
CD19+ cell count <80 × 109/L 30/58 (51.7)
CD16+CD56+ cell count 17.2 (11.6-27.5)
CD16+CD56+ cell count <84 × 109/L 58/58 (100)
Humoral immunity, g/L
IgG 7 12.9 (10.8-16.8)
IgG 7 >7g/L 55/56 (98.2)
IgM 0.9 (0.7-1.3)

IgM >0.4g/L 52/56 (92.9)
IgA 2.6 (1.9-3.7)
IgA >0.7g/L 56/56 (100)
IgE 61.5 (26.2-155.5)
IgE >100g/L 23/56 (96.4)
C3 0.9 (0.8-1.1)
C3>0.9g/L 35/56 (62.5)
C4 0.2 (0.2-0.3)
C4>0.1g/L 54/56 (96.4)
Interleukin 6, pg/ml 93.8 (64.5-258.0)
Interleukin 6 >10pg/ml 11/11 (100)
Bilateral involvement of chest radiographs 82/82 (100)
Acquired infection 5/82 (6.1)
Intensive care unit admission 14/82 (17.1)
Treatment with medications
Intravenous of antibiotics 82 (100)
Systematic corticosteroids 29/82 (35.3)
Anti-virus medications 82/82 (100)
Oxygen therapy 82/82 (100)
Mechanical ventilation 33/82 (40.2)
Invasive 4/82 (4.8)
Non-invasive 30/82 (36.6)
Median time from initial symptom to diagnosis, days 7.0 (4.0-10.0)
Median time from initial symptom to admission, days 10.0 (7.0-15.0)
Median time from initial symptom to death, days 15.0 (11.0-20.0)
Data are presented as median (IQR), or n/N (%), where N represents the total number of patients with COVID-19 with available data.
Table 4. Laboratory analyses of dead patients in the last 24 hours of the death
Laboratory analyses
Complete blood count
Neutrophil count, **×** 109/L 12.9 (11.3-26.0)
Neutrophil count >6.3 **×** 109/L 19/19 (100)
Lymphocyte count, **×** 109/L 0.5 (0.4-1.3)
Lymphocyte count <1.0 **×** 109/L 14/19 (73.7)
Monocyte count, **×** 109/L 0.4 (0.3-0.8)
Platelet count, **×** 109/L 77 (62.0-147.0)
Platelet count <100 **×** 109/L 12/19 (63.2)
Neutrophil-to-lymphocyte ratio 19.6 (17.0-33.0)
Neutrophil-to-lymphocyte ratio >5 19/19 (100)
Platelet-to-lymphocyte ratio 77.0 (62.0-147.0)
Platelet-to-lymphocyte ratio >200 7/19 (36.8)
Systemic immune-inflammation index 1861.8 (950.8-3881.8)
Systemic immune-inflammation index >500 74/19 (100)
Blood biochemical analysis
C-reactive protein level, U/L 84.9 (73.5-186.6)
C-reactive protein level >10U/L 13/13 (100)
Alanine aminotransferase, U/L 30.5 (22.0-102.5)
Alanine aminotransferase >40U/L 8/20 (40.0)
Aspartate aminotransferase, U/L 74.5 (35.5-184.0)
Aspartate aminotransferase >40U/L 14/20 (70.0)
Total bilirubin, mmol/L
Albumin, g/L 31 (28.9-32.6)
Albumin <40g/L 18/20 (90.0)
Potassium, mmol/L 4.3 (3.9-4.7)
Sodium, mmol/L 147.0 (143.0-156.0)
Blood urea nitrogen, mmol/L 18.4 (8.5-33.5)
Blood urea nitrogen >8.8mmol/L 17/20 (85.0)
Creatinine, μmol/L 123 (87.5-361.5)
Creatinine >133μmol/L 9/20 (45.0)
Creatine kinase, U/L 258.0 (135.0-535.0)
Creatine kinase >200 U/L 15/21 (71.4)

Myoglobin, µg/L 342.5 (136.2-1000.0)
Myoglobin >110µg/L 13/15 (86.7)
Lactate dehydrogenase, U/L 784 (484.0-1,216.0)
Lactate dehydrogenase >250 U/L 19/19 (100)
Creatine kinase-MB, ng/ml 4.1 (2.7-7.0)
Creatine kinase-MB >5ng/ml 5/15 (33.3)
NT-pro B-type natriuretic peptide, pg/ml 3046.5
(1423.0-14262.0)
NT-pro B-type natriuretic peptide >1800 pg/ml 10/14 (71.4)
Cardiac troponin T, pg/ml 0.7 (0.1-8.7)
Cardiac troponin T >0.04 10/15 (66.7)
Procalcitonin, ng/ml 1.1 (0.4-6.4)
Procalcitonin >0.1 ng/ml 14/16 (87.5)
Prothrombin time, s 17.2 (14.3-26.8)
Prothrombin time >12.1s 13/13 (100)
Activated partial thromboplastin time, s 32.8 (31.3-37.2)
D-dimer, mg/L 42.7 (9.9-74.0)
D-dimer >0.55mg/L 13/13 (100)
Interleukin-6, pg/ml 258.0 (105.6-262.4)
Interleukin-6 >10pg/ml 11 (100)
Arterial gas
PH 7.3 (7.0-7.4)
PH <7.35 9/17 (52.9%)
PH >7.45 4/17 (23.5%)
pO2 47 (40-61)
pO2 <60 mmHg 12/17 (70.6)
pCO2 32.0 (28.0-42.0)
pCO2 <35 mmHg 9/17 (52.9)
pCO2 >50 mmHg 4/17 (23.5)
Data are presented as median (IQR), n/N (%), where N represents the total number of
patients with COVID-19 with available data.

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How doctors can potentially significantly reduce the number of deaths from Covid-19 - Cytokine Storm Syndrome.

We already have medicines for treating **cytokine storm syndrome**, the immune response that's killing many who die of Covid-19.
By Randy Cron and W. Winn Chatham Mar 12, 2020, 3:20pm EDT

It is not yet clear what the death rate of Covid-19 will be, though the best estimate right now is that it is around 1 percent, 10 times more lethal than seasonal flu. Critically important studies emerging from China suggest that for many patients who die of Covid-19, it may be their own immune system, rather than the virus itself, that deals the fatal blow. This is called a cytokine storm. During a cytokine storm, an excessive immune response ravages healthy lung tissue, leading to acute respiratory distress and multi-organ failure. Untreated, cytokine storm syndrome is usually fatal. Patients in other studies who developed cytokine storm syndrome after viral triggers often ironically possessed subtle genetic immune defects resulting in the uncontrolled immune response. Over the past two decades, much has been learned about the diagnosis and treatment of cytokine storm syndromes. On the front lines of the Covid-19 response, it is critical that medical professionals are aware of the syndrome and prepared to identify and treat it. This act of preparation could help to significantly reduce the number of deaths from Covid-19. In treating cytokine storms brought about by other illnesses, like other viral infections and autoimmune diseases, death rates among patients suffering a cytokine storm have been reduced to as low as 27 percent. Until vaccines for the novel coronavirus are available, likely a year or more from now, it is possible that millions of people may become infected around the globe. This is in part due to minimal early symptoms in up to 80 percent of those who

become infected. However, seemingly mild cases of Covid-19 can morph into more severe cases involving the lower lungs and up to 20 percent of symptomatic novel coronavirus infected individuals require hospitalization, with 5 percent overall needing intensive care. Although individuals who are elderly or who have underlying chronic health problems are at a higher risk of mortality, younger previously healthy people have also succumbed to severe Covid-19. Cytokine storm syndromes go by many names, but they share the pathology of an overly active immune response that leads to frequently fatal multi-organ dysfunction syndrome (MODS). The risk factors for why some previously healthy individuals become deathly ill remain unknown. There are likely host factors, including genetic mutations that put individuals at higher risk. Until the risk factors are known, the medical community will need to treat those Covid-19 patients based solely on the severity of their disease.

How to screen for cytokine storm syndrome in sick patients
While novel and repurposed anti-viral therapies are being explored to treat Covid-19, those individuals with cytokine storm syndrome also require treatment of the overly active immune response. In these situations, an overactive immune response can be deadly. All Covid-19 patients sick enough for hospitalization should be given a cheap, quick, and readily available serum ferritin blood test. Indeed, elevated serum ferritin values have recently been reported in Chinese hospitalized patients with Covid-19. This is a good first screening tool for the possibility of a cytokine storm syndrome in sick patients with high fevers. The question then remains how best to treat a cytokine storm syndrome once it is identified. The treating physician is often placed between a rock and a hard place. Corticosteroids can be powerfully broad immunosuppressive agents, and they are inexpensive and readily available throughout the world. However, it can be frightening for a physician to treat a severely ill, infected individual with such powerful and wide-ranging immune suppression.

We already have medicines for treating cytokine storm syndrome triggered by viruses
With the development of biologic therapies for a variety of rheumatic, oncologic, and other conditions, novel approaches to treating the immune response are now available. These highly targeted medicines go after one or a few inflammatory molecules, including cytokines, without the general immune suppression effected by corticosteroids and other relatively non-selective immune suppressants. Recently, a number of specific anti-cytokine approaches have proven effective in treating a variety of cytokine storm syndromes, including those triggered by viruses. These include drugs targeting interleukin-1 (IL-1), IL-6, IL-18, and interferon-gamma. While randomized trials will be needed to confirm which, if any, of these therapeutics will effectively treat Covid-19-infected patients with cytokine storm syndrome, IL-6 blockade has recently been reported to be in use in China with successful outcomes in some individuals receiving this as part of their treatment. While working to prevent future outbreaks of deadly coronavirus infections with vaccine development and discovering new or re-purposed anti-viral medicines to treat the virus, we must also use all the knowledge at our disposal to treat those patients most at risk of dying – including from Covid-19-induced cytokine storms. For this to occur, the medical community must first be aware of the possibility, then make the diagnosis, and finally treat infected individuals with overly active immune responses that are harmful, if not fatal, left untreated. This should help save the lives of those unfortunate individuals at risk of Covid-19 induced cytokine storm syndrome.

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Communication

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Discovering drugs to treat coronavirus disease 2019 (COVID-19)

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SUMMARY The SARS-CoV-2 virus emerged in December 2019 and then spread rapidly worldwide, particularly to China, Japan, and South Korea. Scientists are endeavoring to find antivirals specific to the virus. Several drugs such as chloroquine, arbidol, remdesivir, and favipiravir are currently undergoing clinical studies to test their efficacy and safety in the treatment of coronavirus disease 2019 (COVID-19) in China; some promising results have been achieved thus far. This article summarizes agents with potential efficacy against SARS-CoV-2.

Keywords novel coronavirus, pneumonia, COVID-19, 2019-nCoV, SARS-CoV-2

The virus SARS-CoV-2 (formerly designated 2019-nCoV) emerged in December 2019 and then spread rapidly worldwide, particularly to China, Japan, and South Korea. As of February 21, 2020, a total of 76,288 confirmed cases of coronavirus disease 2019 (COVID-19) and 2,345 deaths have been reported in mainland China (*1*). Scientists are endeavoring to find drugs to treat this disease. Research thus far has revealed more than 30 agents including Western medicines, natural products, and traditional Chinese medicines that may have potential efficacy against COVID-19. Some of these agents have been quickly tested in clinical studies and demonstrated preliminary efficacy against COVID-19. Antivirals including interferon α (IFN-α), lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol have been included in the latest version of the Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia issued by the National Health Commission (NHC) of the People's Republic of China for tentative treatment of COVID-19 (Table 1) (*2*).

The Guidelines have been revised 5 times since first being issued on January 15, 2020; the latest edition (the 6th edition) was issued on February 18, 2020. The fifth edition of the Guidelines recommends antivirals including IFN-α, lopinavir/ritonavir, and ribavirin for treatment of COVID-19 (*3*). Chloroquine phosphate and arbidol are included in the sixth edition of the Guidelines based on the preliminary outcomes of clinical studies (*2*). The specific method for administration of IFN-α is vapor inhalation at a dose of 5 million U (and 2 mL of sterile water for injection) for adults, 2 times/day. The dosage of lopinavir/ritonavir is 400 mg/100 mg for adults, 2 times/day. Ribavirin should be administered *via* intravenous infusion at a dose of 500 mg for adults, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir. Chloroquine phosphate is orally administered at a dose of 500 mg (300 mg for chloroquine) for adults, 2 times/day. Arbidol is orally administered at a dose of 200 mg for adults, 3 times/day. The duration of treatment is no more than 10 days.

IFN-α is a broad-spectrum antiviral that is usually used to treat hepatitis, though it is reported to inhibit SARS-CoV reproduction *in vitro* (*4*). Lopinavir/ritonavir is a medication for the human immunodeficiency virus (HIV) used in combination with other medications to treat adults and children over 14 days of age who are infected with HIV-1 (*5*). Chu *et al.* found that lopinavir/ritonavir has anti-SARS-CoV activity *in vitro* and in clinical studies (*6*). Ribavirin is a nucleoside analogue with a broad-spectrum of antiviral effects. A study compared 111 patients with severe acute respiratory syndrome (SARS) treated with ribavirin monotherapy and 41 patients with SARS treated with lopinavir/ritonavir and ribavirin; patients treated with the combined therapy had a lower risk of acute respiratory distress syndrome (ARDS) and death (*6*). Chloroquine is a widely used antimalarial that was found to be a potential broad-spectrum antiviral in 2006 (*7*). Chloroquine was found to block SARS-CoV-2 infection at low-micromolar concentration, with a half-maximal effective concentration (EC_{50}) of 1.13 μM and a half-cytotoxic concentration (CC_{50}) greater than 100 μM (*8*). Arbidol is an antiviral that can be used to treat influenza virus. A study has revealed that arbidol can effectively inhibit SARS-CoV-2 infection at a concentration of 10-30 μM

Table 1. Antivirals included in the Guidelines (version 6) for treatment of COVID-19

Drug	Dosage	Method of administration	Duration of treatment
IFN-α	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	No more than 10 days
Ribavirin	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500 mg (300 mg for chloroquine) each time, 2 times/day	Oral	No more than 10 days
Arbidol	200 mg each time, 3 times/day	Oral	No more than 10 days

in vitro (*9*).

Besides the drugs above that have been included in the Guidelines, favipiravir is a drug that warrants attention. Favipiravir was approved for treatment of novel influenza on February 15, 2020 in China. This drug is currently undergoing clinic trials in treating COVID-19. Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor. In addition to its anti-influenza virus activity, favipiravir is capable of blocking the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses (*10*). Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity (*11*). Therefore, favipiravir may have potential antiviral action on SARS-CoV-2, which is a RNA virus. On February 14, a clinical trial on favipiravir for the treatment of COVID-19 initiated by the Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen achieved promising results. The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir (*12*). No significant adverse reactions were noted in the favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group (*12*).

Remdesivir is another potential drug for treatment of COVID-19. Remdesivir is a nucleoside analogue and a broad-spectrum antiviral. Animal experiments (*13*) indicated that remdesivir can effectively reduce the viral load in lung tissue of mice infected with MERS-CoV, improve lung function, and alleviate pathological damage to lung tissue. Wang *et al.* found that remdesivir potently blocks SARS-CoV-2 infection at low-micromolar concentrations and has a high selectivity index (half-maximal effective concentration (EC_{50}), 0.77 μM; half-cytotoxic concentration (CC_{50}) > 100 μM; SI > 129.87) (*8*). Holshue *et al.* reported that remdesivir yielded promising results in the treatment of a patient with COVID-19 in the United States (*14*). In order to evaluate the efficacy and safety of the drug in patients with COVID-19, a randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial was launched on February 5, 2020 in China (*15,16*). Patients in the experimental group received a initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days *via* intravenous infusion in addition to routine treatment. Patients in the control group received routine treatment and the same dose of a placebo. The trial is expected to conclude by the end of April 2020.

Studies have also revealed some other drugs may have potential efficacy in treating COVID-19. One is darunavir, which is a second-generation of HIV-1 protease inhibitor. On February 4, 2020, researchers in China announced that darunavir inhibited SARS-CoV-2 infection *in vitro* (*9*). Cell experiments indicated that darunavir significantly inhibited viral replication at a concentration of 300 μM *in vitro* and that its inhibition efficiency was 280-fold that in the untreated group (*9*). Other potential drugs include type II transmembrane serine protease (TMSPSS2) inhibitors and BCR-ABL kinase inhibitor imatinib. Hoffmann *et al.* indicated that SARS-CoV-2 uses the SARS-CoV receptor, ACE2, and the cellular protease TMPRSS2 to enter target cells. A TMPRSS2 inhibitor would block entry and thus constitute a treatment option (*17*). Imatinib has anti-coronal activity primarily because it inhibits the fusion of virions with the endosomal membrane (*18*).

A joint research team of the Shanghai Institute of Materia Medica and Shanghai Tech University performed drug screening in silicon and an enzyme activity test, and they reported 30 agents with potential antiviral activity against SARS-CoV-2 on January 25, 2020 (*19*). These agents are indinavir, saquinavir, lopinavir, carfilzomib, ritonavir, remdesivir, atazanavir, darunavir, tipranavir, fosamprenavir, enzaplatovir, presatovir, abacavir, bortezomib, elvitegravir, maribavir, raltegravir, montelukast, deoxyrhapontin, polydatin, chalcone, disulfiram, carmofur, shikonin, ebselen, tideglusib, PX-12, TDZD-8, cyclosporin A, and cinanserin. The same study also found that Chinese herbal medicines such as Rhizoma Polygoni Cuspidati and Radix Sophorae Tonkinensis may contain active ingredients against SARS-COV-2 (*19*).

As the epidemic spreads, scientists around the world are actively exploring drugs that would be potentially effective in combating COVID-19. Generally, there are

no finally verified antivirals specific to COVID-19 at present. The efficacy and safety of these candidate drugs in the treatment of COVID-19 need to be confirmed in further preclinical and clinical trials.

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EDITORIAL

COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm?

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Abstract
From January 2020, coronavirus disease (COVID-19) originated in China has spread around the world. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The presence of myocarditis, cardiac arrest, and acute heart failure in COVID-19 patients suggests the existence of a relationship between SARS-CoV-2 infection and cardiac disease. The Notch signalling is a major regulator of cardiovascular function and it is also implicated in several biological processes mediating viral infections. In this report we discuss the possibility to target Notch signalling to prevent SARS-CoV-2 infection and interfere with the progression of COVID-19- associated heart and lungs disease.

Keywords Coronavirus disease · COVID-19 · Cardiovascular disease · Angiotensin-converting enzyme 2 · Furin · ADAM17 · Notch

On COVID-19 and the heart

From January 2020, coronavirus disease (COVID-19) has spread fast from China, mainly to Southwest Asia and Europe, especially to Italy, and it is now found everywhere around the world. The disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the seventh member of the coronavirus family which infects humans and to which Middle East Respiratory Syndrome Coronavirus (MERS)-CoV and SARS-CoV also belong [55]. The classical clinical picture of COVID-19 is that of a flu-like syndrome of mild severity in most cases, but in 15% of cases it is complicated by interstitial pneumonia and a variable degree of respiratory failure [40]. The underlying pathological changes, responsible for the respiratory failure, have been characterised in two patients who underwent lung lobotomies for lung adenocarcinoma and were retrospectively found to be COVID-19 positive [6, 48]. Among COVID-19-positive patients, there are those that consult the doctor for heart symptoms, such as palpitations or chest pain rather than respiratory problems [53]. Little is known about a possible relationship between COVID-19 and cardiovascular disease. An early report on 99 patients hospitalised from 1st to 20th January 2020 at Jinyntan Hospital, Wuhan, China, for SARS-CoV-2-related pneumonia, shows that pre-existing cardiovascular disease was present in 40% of them [7]. A second report from the same period of time on 138 patients hospitalised at Zhongnan Hospital of Wuhan University shows that 26% of the patients required cardiologic intensive care. Among these patients, 16.7% developed arrhythmias and 7.2% experienced an acute coronary syndrome in addition to other complications [51]. Furthermore, patients diagnosed with pneumonia due to SARS-CoV-2 infection showed an increase in high-sensitivity cardiac troponin I levels, suggesting myocardial injury [23]. Other published and anecdotal reports indicate the presence of myocarditis, cardiac arrest, and acute heart failure in SARS-CoV-2- infected patients. It is not clear whether these cardiac conditions are provoked by SARS-CoV-2 or are complications typical of any other pathology with higher cardio-metabolic demand, and thus unrelated to the viral infection. Epidemiological studies conducted during the flu epidemic in USA in 1990

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show that influenza and its related complications, such as secondary pneumonia, may cause myocardial infarction due to inflammation-induced destabilisation of coronary artery plaques [10]. This results from multiple mechanisms, such as tachycardia, hypoxia, increased wall stress, and thrombophilia or release of inflammatory cytokines [11]. So, a possible causal link cannot be excluded.

A similar link with myocardial infarction and acute heart failure was shown for the recent epidemics of SARS-CoV and MERS-nCoV [53]. In the absence of a specific treatment or a vaccine, which, according to experts, will not be ready before a year from now, there are only three possible remedies: (1) attempts to contain the spread of the infection with drastic and likely unpopular measures, such as quarantine or restriction of free movement in a specific area with the aim of getting the epidemic exhaust itself "naturally". This, hopefully, should be facilitated by the coming of the summer in the Northern hemisphere; (2) supportive treatment of respiratory and cardiologic complications of the infection, including admission to intensive care units (ICUS) and use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO); (3) proposal of novel approaches, based on evidence from a variety of fields of expertise, which could help in finding a possible therapy. With our short report, we would like to contribute with our experience on Notch signalling to the third option.

Cardiovascular drugs in the context of COVID-19

CoVs are enveloped single-stranded positive-sense RNA viruses with genomes ranging between 26.2 and 31.7 kb RNA. The genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein, all required to produce the viral particle [46]. Sequencing analyses on RNA of SARS-CoV-2 variants isolated from COVID-19 patients show 96% homology with a bat virus [54] suggesting that, as for the other coronaviruses, SARS-CoV-2 jumped from bats to humans, probably through an intermediate host, not yet identified, after the occurrence of a mutation that allowed the infection of human cells [3]. The S (spike) glycoprotein mediates the SARS-CoV-2 entry into cells following the binding to the angiotensin converting enzyme 2 (ACE2) [22]. ACE2 is highly expressed on cell surface of many tissues and organs including the lungs and the myocardium [53]. Of relevance, ACE2 is mainly located in the inner track of the respiratory system, thus explaining why SARS-CoV-2, differently from the flu virus which binds to the upper airways track, might cause serious respiratory insufficiency. This also explains why COVID-19 is not just a common influenza, like somebody believed [33]. Differently from ACE1, which catalyses the formation of Angiotensin (Ang) II, the active component of renin–angiotensin system involved in blood pressure regulation and cardiorenal function, ACE2 cleaves Ang II in Ang (1–7). Thus, ACE2 antagonises ACE1 activity. Ang II receptor blockers (ARBs), which are widely used to treat hypertension and heart failure, increase the levels of Ang II [44] and, indirectly, could activate ACE2 [1]. It has been proposed that patients receiving ARBs have higher susceptibility to COVID-19 [15] and, as a consequence, hypertensive or patients with heart failure should switch from ARBs to other drugs. This way of thinking, however, is not supported by any evidence [16]. Actually, there are caveats here: (1) ACE2 expression is reduced in hypertension models; (2) there is no evidence of increased ACE2 expression with ARBs in the lung; (3) hypertension and its treatment with ARBs did not affect previous coronavirus infections [16].

Based on the evidence discussed above, ACE2 could be targeted to prevent SARS-CoV-2 from entering the cells. To this aim, Lei et al. generated a recombinant protein by connecting the extracellular domain of human ACE2 to the Fc region of the human immunoglobulin IgG1 which neutralised SARS-CoV and SARS-CoV-2 in vitro [27]. Another approach to prevent viral infection could be the downregulation of ACE2 on cell membrane. Of relevance, ADAM17 (A Disintegrin And Metalloproteases 17), a metalloprotease significantly expressed also in the lungs and heart, is involved in the shedding of surface proteins, including ACE2 [26]. Ablation of ADAM17 expression reduces ACE2 shedding, whereas overexpression of ADAM17 significantly increases its shedding [26]. Furthermore, membrane translocation of ADAM17 leads to a reduction in myocardial ACE2 protein levels and activity which is associated with an increase in plasma ACE2 activity [32]. Based on these data, it is tempting to speculate that increasing ADAM17 levels and/or activity to enhance shedding and increase soluble/plasma ACE2 levels could represent a way of blocking SARS-CoV-2 entry into cells (Fig. 1a). Of relevance, treatment with the chemotherapeutic agent 5-fluorouracil strongly activates ADAM17 in an animal model of colorectal cancer [25]. Furthermore, in non-small cell lung cancer cell lines, estradiol increases the expression levels and activity of ADAM17 [41]. This last finding would suggest higher shedding of ACE2 in women and could, at least partially, explain the reduced incidence of COVID-19 in women compared to men [19].

Other than ACE2, the protease furin is also required to promote entrance of the virus into the cell [50]. Furin, a member of the subtilisin-like proprotein convertase family that processes protein of the secretory pathway, is a type 1 membrane-bound protease that is expressed in multiple organs, including the lungs. SARS-CoV-2, differently from SARS-CoV, presents a furin cleavage site between

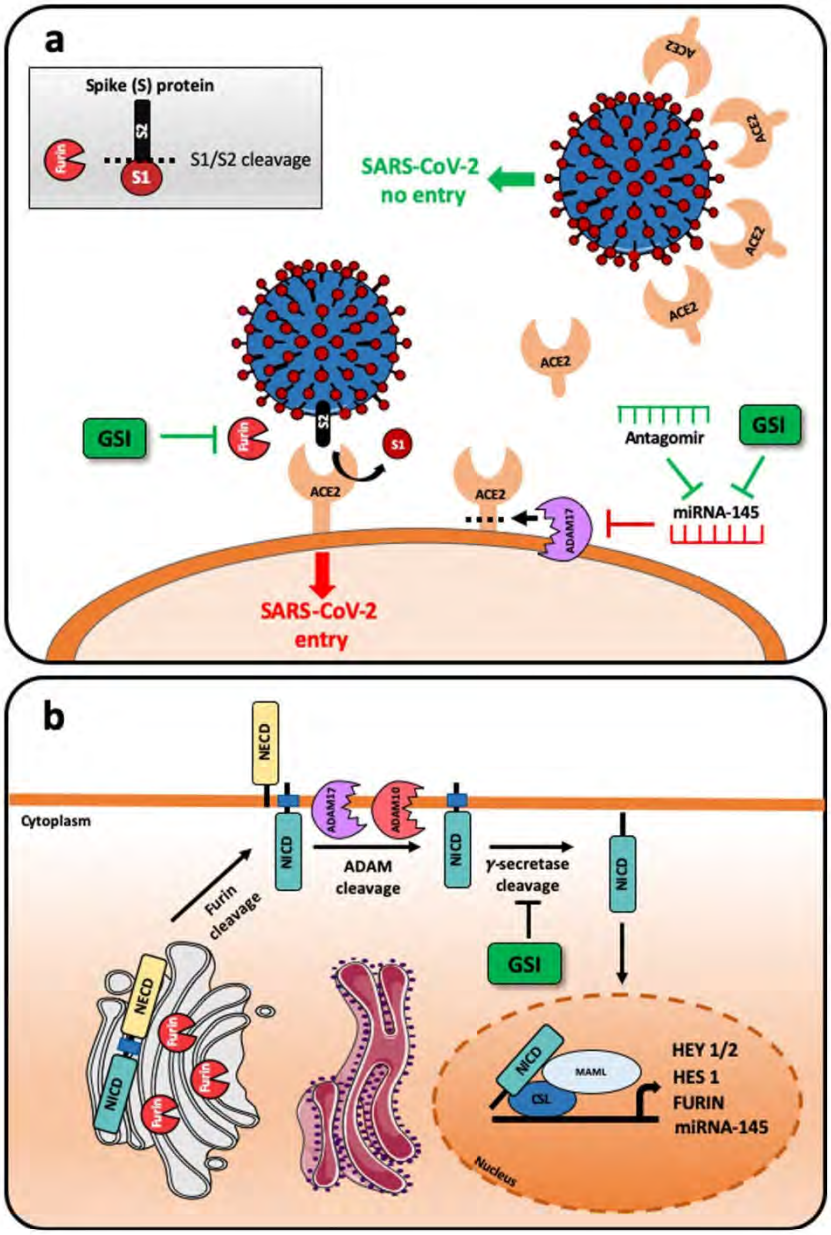

Fig. 1 **a** Severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2) entry into the cells is mediated by the binding of the viral spike (S) glycoprotein to the angiotensin converting enzyme 2 (ACE2) on the cells, followed by the proteolytic cut at the S_1/S_2 site of the S glycoprotein by the host protease furin. ACE2 levels on the plasma membrane are regulated by ADAM17, which promotes the shedding of the protein. The Notch signalling is a positive regulator of furin and a negative regulator of ADAM17 (through the transcription of miRNA-145), and thus γ-secretase inhibitor (GSI), which prevents Notch activation, may represent a strategy to interfere with the virus entry into the cells by reducing furin and increase ADAM17 shedding. An antagomir to miRNA-145 could represent an alternative approach for upregulation of ADAM17. **b** Notch precursor is cleaved by furin in the Golgi apparatus leading to a heterodimer on the plasma membrane consisting of Notch extracellular domain (NECD) and Notch transmembrane (TM), which contains the Notch intracellular domain (NICD). After the binding with the ligand, Notch is cleaved by ADAM (A Disintegrin And Metalloprotease) 10 or 17, and, after, by the γ-secretase complex. The resultant NICD translocates into the nucleus, where it interacts with the transcription factor CSL (CBF-1/RBP-Jk/Suppressor of hairless/Lag-1) and the transcriptional co-activator MAML (mastermind-like) to regulate the transcription of Notch target genes, such as HEY1 and 2, HES1, FURIN, and miRNA-145

the S1/S2 subunits of the S glycoprotein. Following the binding of the S glycoprotein to ACE2, furin-mediated proteolytic cut of the S protein is necessary for viral entry into the cell [50]. Inhibiting the expression of furin could then be a possible approach to prevent SARS-CoV-2 infection (Fig. 1a, b). Of relevance in this context, nanomolar concentrations of a peptide designed from the furin cleavage sequence of the avian influenza A H5N1 virus provide protection against infection by several furin-dependent pathogens [47].

Furin and ADAM17 are both intertwined with Notch, an evolutionarily conserved system of communication between adjacent cells, and thus targeting Notch could represent an alternative approach to inhibit furin and upregulate ADAM17 (Fig. 1b). Of interest, a recent study has investigated the physical association between SARS-CoV-2 and

human proteins, identifying 66 potential cellular proteins that could be targeted to prevent viral infection [13]. With this approach, it is impossible to identify host proteins crucial for viral infection, which do not interact directly with viral proteins, as is the case for furin and ADAM17. Thus, hypothesis-driven studies based on the knowledge of the molecular details of virus–cell interaction are still crucial for the identification of therapeutic targets to treat COVID-19.

Targeting Notch to prevent SARS-CoV-2 infection

The Notch signalling pathway plays a major role in controlling cell fate during the development and in postnatal life [2]. Growing evidence shows that the Notch signalling is involved in maintaining the homeostasis of the cardiovascular system and could represent a novel target to reduce atherosclerosis progression [18, 42] and remodelling following a myocardial infarction [17, 20, 34]. In humans, there are four receptors (Notch1–4) activated by binding with ligands (Jagged1,2 and Delta-like ligands (Dll)1,3,4) on the surface of adjacent cells [2]. Notch precursor is first cleaved by furin in the Golgi apparatus and then is found as a heterodimer on the cell membrane. Following ligand binding, Notch is first cleaved at the cell membrane by ADAM10 or ADAM17 thus enabling the final cleavage by the γ-secretase releasing the active Notch intracellular domain which migrates to the nucleus and regulates the transcription of target genes (Fig. 1b).

Furin is transcriptionally induced by Notch1 [38]. Inhibition of Notch signalling could, then, be useful to reduce furin levels and interfere with viral entry into the cell. Since Notch dysregulation is a feature of the majority of cancers, Notch inhibitors that target the γ-secretase are available and are being tested, with manageable gastrointestinal toxicity, in several clinical trials in cancer patients. Favorable response has been so far obtained in a limited number of patients indicating that it will be crucial to develop new strategies to identify "responders" to Notch inhibition-based cancer therapies [2].

Notch1-dependent enhancement of furin activity activates ADAM10 but not ADAM17 [38], suggesting that Notch1 does not control ADAM17. Nevertheless, a study on abdominal aorta showed that ADAM17 expression is downregulated by the γ-secretase inhibitor (GSI) DAPT [*N*-(*N*-[3,5-difluorophenacetyl]-L-alanyl)-*S*-phenylglycine *t*-butyl ester] [8]. Since GSIs with different specificities toward each isoform of Notch exist [2], more of these compounds could be tested to investigate their effects on ADAM17 and, possibly, on ACE2 shedding. Of interest, miRNA-145, which downregulates ADAM17 [14], is a target of Jagged1/Notch1 signalling in vascular smooth muscle cells [4]. It would be of interest to investigate whether antagomir to miRNA-145 would increase ADAM17 activity (Fig. 1a).

Notch and the "cytokine storm"

Among the proposed mechanisms of myocardial and lung injury caused by SARS-CoV-2, there is a "cytokine storm" triggered by an imbalanced response by type 1 and type 2 T helper (Th) cells [53]. The Notch pathway plays a major role during the differentiation and the activity of innate and adaptive immune cells [30, 49]. Dll4/Notch signalling is an important inducer of M1 macrophage polarisation and experiments in vitro and in vivo have shown that inhibition of the Notch by GSI or by anti-Dll4 antibodies leads to a dampening of the inflammation [49]. In macrophages, Notch1 directly binds to interleukin (IL)-6 promoter in response to interferon (IFN)-γ and positively regulates IL-6 production [52]. It is important to underline that IL-6, in turn, increases the expression of the Notch ligand Dll1, thus amplifying the Notch signalling and establishing a positive feedback loop that promotes the further production of IL-6 [21]. In Th cells, Notch signalling triggered by Dll1,4 ligands promotes the production of inflammatory Th1/Th17 cytokines, whereas Jagged1 suppresses IL-6-induced Th17 activation [49] (Fig. 2). A multicentre randomised controlled trial to test a monoclonal antibody against the IL-6 receptor (tocilizumab, Roche) in patients with COVID-19 pneumonia and elevated IL-6 has been conducted in China with promising results (ChiCTR2000029765). Based on these results, a phase II clinical trial to test the efficacy of tocilizumab in 330 Italian patients with COVID-19 pneumonia has been approved by the Italian Medicines Agency (https://www.agenziafarmaco.gov.it/en) and a phase III clinical trial enrolling 330 patients globally has been announced in the US (https://www.roche.com/media/releases/med-cor-2020-03-19.htm). In addition, other strategies have been attempted to reduce the cytokine storm. CytoSorb is an extracorporeal cytokine adsorber and, according to the manufacturers, over 65 patients with severe COVID-19 have been treated with CytoSorb in China, Italy and Germany (https://cytosorb-therapy.com/en/covid-19). However, data on the effectiveness of this approach are not yet available.

IL-6 is a predictor of mortality in COVID-19 patients [43]. However, in severely affected patients, IL-6 is moderately increased (25.2 pg/mL) [36] compared to typical levels in cytokine release syndromes (more than 1600 pg/mL in sepsis) [29]. This may explain why no serious vasoplegic shocks were observed. Nevertheless, the cytokine storm in COVID19 patients is characterised not only by hyperinnate immune response but also by activation of Th cell-mediated immunity. In this scenario, the idea of combining Notch

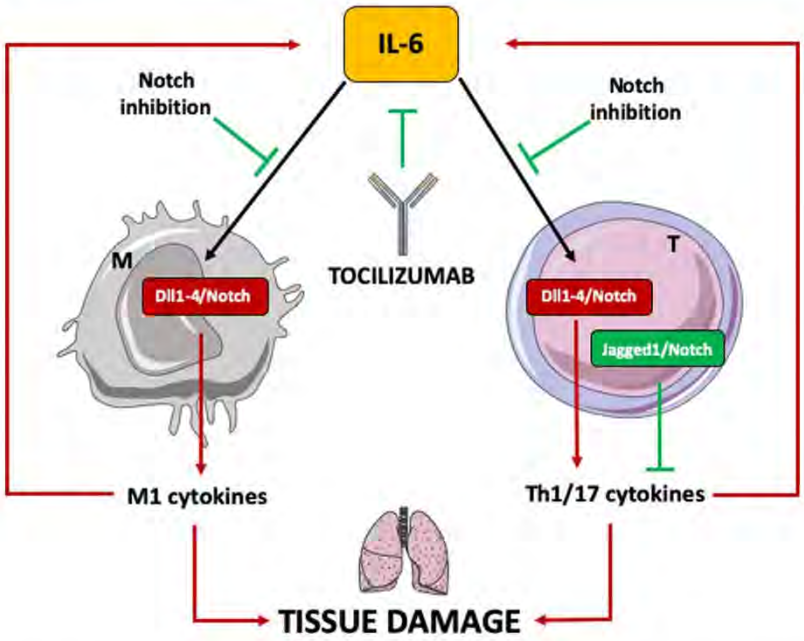

Fig. 2 Notch and IL-6 cooperate to activate the immune system and perpetuate the cytokine storm. In macrophages, Dll4/Notch signalling promotes the production of inflammatory cytokines, IL-6 among those. IL-6, in turn, increases the expression of the Notch ligands (Dll1,4), thus amplifying the Notch signalling and establishing a feedback loop that promotes the further production of IL-6. In T cells, Notch signalling triggered by Dll1/Dll4 ligands promote inflammatory Th1/Th17 cytokines; on the contrary, Jagged1 ligands dampen IL-6-induced Th17 activation. Tocilizumab is expected to block cytokine storm and prevent tissue damage. Notch inhibition by blocking Dll1,4 ligands may help to interrupt the positive feedback loop that fuels the cytokine storm. *M* Macrophages, *T* T cells

inhibitors with anti-IL-6 to dampen the cytokine storm is captivating (Fig. 2).

However, it must be also considered that Notch inhibition could interfere with the immune response during viral infection. Ito et al. [24] found that in mice infected with influenza A virus (H1N1), macrophages increase Notch ligand Dll1 expression. In these mice, inhibition of the Notch pathway using an anti-Dll1 antibody, or GSI by intranasal administration, resulted in increased mortality, defective viral clearance, and decreased IFN-γ production in lungs [24]. Notch signalling also modulates the immune response following respiratory syncytial virus (RSV) infection [28]. Of note, it has been reported that RSV infection causes an increase of Jagged1 in bronchial epithelial cells and, when co-cultured with CD4 + T cells, promotes Th2 differentiation. Conversely, the reduction of Jagged1 expression with siRNA abrogates this effect and promotes an increase in Th1 differentiation. On this basis, it has been suggested that Jagged1-mediated Th2 differentiation may cause RSV-induced airway hyperresponsiveness [37]. On the basis of these studies, it could be hypothesised that it may be preferable targeting specific components of the Notch signalling, such as Dll4 or Jagged1, rather than inhibiting Notch with a GSI. Of relevance, soluble Jagged1 has been shown to efficiently inhibit neointima formation after balloon injury by decreasing smooth muscle cell proliferation and migration through inhibition of Notch signalling [5].

Preclinical studies have shown that Notch inhibition can be useful not only for treatment of atherosclerosis but also for other inflammation-based conditions such as graft-versus-host disease [39], chronic obstructive pulmonary disease (COPD) [12] and arthritis [31]. It is important to point out that before Notch inhibition becomes a reality in the clinical managements of these patients, we should address issues that could arise upon chronic exposure to Notch inhibitors, likely required for many of these pathologies, such as (1) toxicity related to the multiple cellular targets of GSIs, due to the promiscuous activity of the γ-secretase, (2) alteration of the immune system activities and of the stem cell compartment, in which Notch plays a pivotal role, and (3) the potential oncogenicity of the treatment, given the tumour suppressor role of Notch in tissues like the skin, as observed in Alzheimer's patient treated with GSIs to inhibit the formation of amyloid A4 peptide [2, 35]. A possible approach to avoid systemic toxicity could be delivery of GSIs and Jagged1/Dll4 inhibitors directly to the lungs by the use of nanoparticles [45].

Based on these data, we should conclude that, even if it holds great promise, Notch inhibition to block the cytokine storm in COVID-19 patients is still not feasible and targeting the IL-6 receptor or depleting the cytokines by other means represent the only approaches available at this time.

Conclusions

The relationship between Notch and viruses is well documented. To replicate, some viruses, such as Human Papilloma Virus and Simian Virus 40, highjack the cell machinery, including the Notch signalling, and by doing so they can cause cancer [9]. Therefore, it has been proposed that the dysregulation of Notch signalling could provide diagnostic and therapeutic tools for virus-associated cancers [9]. By uncovering new aspects of this relationship, we might be able to target Notch also to fight heart and lung disease caused directly by SARS-CoV-2 infection and by the cytokine storm in response to the virus.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Eine großartige Erkenntnis, das die Inflammation durch Covir-19
eine thrombotisch-embolische Aktivität entfaltet – wie bei jeder Entzündung – Wo bleibt der Basis-Gerinnungs-Schutz? Kein ‚Hausverstand'.

ZAHLREICHE THROMBOSEN IN DER MIRKOZIRKULATION
COVID-19: WECHSELWIRKUNG VON BLUTPLÄTTCHEN UND GRANULOZYTEN

Offenbar hat eine pathophysiologische Schnittstelle zwischen Veränderungen in den Lungengefäßen und thrombotischen Komplikationen Einfluss auf den Verlauf einer COVID-19-Erkrankung. Das hat ein Forscher|innen-Team um Dr. Leo Johannes Nicolai von der Medizinischen Klinik und Poliklinik I (Kardiologie) am LMU-Klinikum München herausgefunden und kürzlich in Circulation publiziert.*
Die Lungengefäße von schwer an COVID-19 erkrankten Patient|inn|en wiesen zahlreiche Thrombosen in der Mikrozirkulation auf. Auch im Herzen und in der Niere konnten thrombotische Gefäßverschlüsse nachgeweisen werden. Die Thromben bestanden überwiegend aus Blutplättchen und aktivierten neutrophilen Granulozyten. Die nachgewiesenen immunothrombotischen Verschlüsse entstanden durch entzündliche Prozesse, die eine Aktivierung von Blutgerinnung und Blutplättchen auslösten. Dieser Vorgang soll eigentlich die Ausbreitung von Viren und Bakterien im Körper verhindern. Diese Gefäßverschlüsse beeinträchtigen aber auch die Blutversorgung des Gewebes, was zum Lungenversagen beiträgt und eine systemische Thromboseneigung fördert.
Die aktuelle Arbeit zeigt anhand multidimensionaler Analysen, dass im Blut von beatmungspflichtigen COVID-19-Patient|inn|en mit Lungenversagen aktivierte neutrophile Granulozyten und Blutplättchen zu finden sind. Die Interaktion dieser beiden Zelltypen führt zu einer wechselseitigen Aktivierung, die letztlich zu Gefäßverschlüssen in der Lunge führt. Ein wesentlicher Bestandteil dieser Verschlussbildung sind neutrophil extracellular traps (NETs), netzartige Strukturen bestehend aus DNA und Granulaproteinen der neutrophilen Granulozyten, die die Blutgerinnsel stabilisieren.

Nicolai L et al., Circulation 2020; online am 28.Juli 2020

Seroprevalence of Antibodies to SARS-CoV-2 in 120 Sites in the United States, March 23-May 12.2020
Fiona P. Havers et al., JAMA Intern Med., published online July 21, 2020
Question What proportion of persons in 10 US sites had detectable antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from March 23 to May 12, 2020?
Findings In this cross-sectional study of 16 025 residual clinical specimens, estimates of the proportion of persons with detectable SARS-CoV-2 antibodies ranged from 1.0% in the San Francisco Bay area (collected April 23-27) to 6.9%of persons in New York City (collected March 23-April 1). Six to 24 times more infections were estimated per site with seroprevalence than with coronavirus disease 2019 (COVID-19) case report data.
Meaning For most sites, it is likely that greater than 10 times more SARS-CoV-2 infections occurred than the number of reported COVID-19 cases; most persons in each site, however, likely had no detectable SARS-CoV-2 antibodies.

Antibodies, Immunity, and COVID-19
Brad Spellberg, Travis B. Nielsen, Arturo Casadevall. JAMA Intern Med. Published onle Nov 24, 2020

Widespread availability of commercial assays that detect anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies has enabled researchers to examine naturally acquired immunity to coronavirus disease 2019 (COVID-19) at the population level. Several studies have found that the SARS-CoV-2 seroprevalence (the percentage of the population with serum containing antibodies that recognize the virus) has remained below 20% even in the most adversely affected areas globally, such as Spain and Italy. In this issue of *JAMA Internal Medicine*, Bajema et al contribute new information on the shifting nature of SARS-CoV-2 seroprevalence in the US. The study uses national data to expand on an earlier US Centers for Disease Control and Prevention study of seroprevalence of antibodies to SARS-CoV-2 in 10 US sites. Using serum samples from commercial clinical laboratories, the investigators found the highest level of seroprevalence in New York, which surged from 6.9% in March to a peak of approximately 25% before mid-August 2020. For all but a few states, seroprevalence remained below 10% throughout the study period; New York was the only state where seroprevalence increased above 20%. In several states, seroprevalence stayed below 1%. Seroprevalence tended to wane over time, although in a few states, such as Georgia and Minnesota, rates increased over the study period. Thus, the primary takeaway from this study is that despite the pandemic raging across the US, most people do not have evidence of prior COVID-19 infection by antibodies to SARS-CoV-2.
A major strength of the study is its reliance on residual serum that had been sent to national commercial laboratories for routine clinical testing, rather than from patients suspected of having COVID-19. This approach enabled a less biased population sampling than in other studies. The samples were not enriched for people suspected of having infection, and thus the study provides a more accurate read of seroprevalence across disparate populations. However, a limitation of this approach is that the people most likely to have positive results for antibodies (those with clinical concern for prior infection) were excluded, which could result in an underestimate of true population-based seroprevalence. Another strength of the study is the testing of more than 130 000 samples from all 50 US states plus Washington, DC and Puerto Rico. By evaluating seroprevalence over time in each geographical area, the investigators imparted a spatiotemporal dynamic to the results.
The unifying hope for ending the global COVID-19 pandemic is the development of adequate population-level herd immunity to halt the continuing cycles of infection and disease. Although no data exist to define the exact threshold necessary to achieve herd immunity against COVID-19, modeling and extrapolation from similar diseases suggest that more than 60%, and perhaps up to 80%, of the population may need immunity for the viral replication rate to drop below 1, enabling a modest level of disease control. Such immunity may be achieved via recovery of many individuals from widespread infection, or preferably via the availability of safe and effective vaccines.
Unfortunately, history has shown that although herd immunity resulting from infection can curb pandemics, it does not eradicate diseases. The historical precedent that most closely approximates, and was substantially worse than, the current COVID-19 pandemic is the 1918 H1N1 influenza pandemic. After more than 2 years, 500 million infections, and 50 million deaths worldwide, sufficient levels of population-based herd immunity finally halted the continued spread of the virus, and society began to recover. Nevertheless, variants of that influenza virus are still present, such that resurgence of this H1N1 subtype remains a persistent concern. Similarly, measles, mumps, rubella, polio, and smallpox are respiratory tract viruses that once killed or maimed millions of people annually across the globe, despite inducing long-term protective immunity against reinfection following natural infection. In the prevaccine era, immunity following natural infection allowed people to coexist with these viruses, but never eradicated them. On their advent, vaccines reduced the disease burden of these viruses by more than 99%. Indeed, smallpox remains the only disease in human history to have been eradicated, an achievement of vaccination, not natural immunity.
And yet, until safe and effective vaccines are available, natural immunity and public health measures are the primary approaches to managing pandemics. Unfortunately, it is not yet known if detection of anti–SARS-CoV-2 antibodies by commercial clinical laboratory assays is associated with protective immunity. It is possible that protection requires achieving a specific quantity of a specific subtype of antibody. It is also possible that to achieve protection, antibodies must bind to specific epitopes on the virus, which may differ from the epitopes that are targeted in the commercial assays. Thus, we simply do not know if the seroprevalence of antibodies to SARS-CoV-2 that are detected by commercial assays will ultimately translate into protective herd immunity as the virus continues to spread.
Conversely, it is possible that people exposed to SARS-CoV-2 are protected against future infection regardless of whether they have measurable antibody titers or not. The role of T cells in protective immunity against COVID-19, and the association between immunity based on antibodies and memory T cells, remains undefined. Indeed, there are reasons to be optimistic that prior exposure to the virus does lead to protective immunity. Nearly a year into the COVID-19 pandemic, there have been more than 30 million confirmed

infections, but extremely few documented cases of reinfection with SARS-CoV-2 throughout the world. If natural infection did not lead to a high degree of protection, many more reinfections would be expected. Furthermore, analysis of convalescent plasma reveals that most individuals with symptomatic COVID-19 mount neutralizing antibody responses to SARS-CoV-2. Based on immunological experience with other viruses, the presence of neutralizing antibodies is likely associated with protection. Thus, until more data become available, it is reasonable to assume that natural infection with SARS-CoV-2 may lead to protective immunity and prior infection may be closely associated with protection. Furthermore, protection from natural infection suggests that vaccines should induce protective immunity.
The decline over time of the seroprevalence of antibodies to SARS-CoV-2 in the study by Bajema et al is neither unexpected nor alarming. For all infectious diseases, the waning of antibody titers is normal and does not necessarily indicate the loss of protective long-term immunity. Immunoglobulin G titers rise during the weeks following infection as active plasma cells secrete antibody into systemic circulation. Those titers then wane as the plasma cells actively secreting the antibodies senesce, whereas resting memory B and T lymphocytes continue to circulate for years to decades. These memory lymphocytes can mediate long-term immunity to infection even in the face of waning antibody titers. Thus, at present, no conclusions can be drawn from seroprevalence studies about the duration of immunity to SARS-CoV-2 infection. Experience with other respiratory tract viruses suggests that immunity to specific viral serotypes lasts for many years. This was the case with the H1N1 virus that caused the 1918 influenza pandemic, in which adolescent survivors experienced protection from reinfection into the tenth decade of their lives.
In summary, a robust and well-designed seroprevalence study using residual serum samples from across the US has found that herd immunity to SARS-Cov-2 is nowhere in sight, even as the COVID-19 pandemic has raged on for a year. The good news is that the limited number of reinfections of SARS-CoV-2 to date, and the experience with natural infections with other viruses, suggests that protective immunity to COVID-19 should result, a harbinger for the success of vaccines. The bad news is that, like the 1918 influenza pandemic, achieving herd immunity through natural infections will take years of painful sacrifice that are tallied in numerous deaths, severe long-term health sequelae, and widespread economic disruption and hardship. Let us hope that safe and effective vaccines help avoid the consequences of naturally developing herd immunity to COVID-19, as they have reliably done for so many other respiratory viruses.

SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates.
Gregory A. Poland, Inna G. Ovsyannikova, Richard B. Kennedy. The Lancect, published Oct 13, 2020. Volume 396, Issue 10262, P 1595-1606, 2020.

Understanding immune responses to severe acute respiratory syndrome coronavirus 2 is crucial to understanding disease pathogenesis and the usefulness of bridge therapies, such as hyperimmune globulin and convalescent human plasma, and to developing vaccines, antivirals, and monoclonal antibodies. A mere 11 months ago, the canvas we call COVID-19 was blank. Scientists around the world have worked collaboratively to fill in this blank canvas. In this Review, we discuss what is currently known about human humoral and cellular immune responses to severe acute respiratory syndrome coronavirus 2 and relate this knowledge to the COVID-19 vaccines currently in phase 3 clinical trials.
Much remains to be learned regarding coronavirus immunity in general and SARS-CoV-2 immunity in particular, including the protective immunity induced by vaccines and the maintenance of immunity against this virus. Furthermore, multiple vaccine types will probably be needed across different populations (eg, immune-immature infants, children, pregnant women, immunocompromised individuals, and immunosenescent individuals aged ≥65 years). In addition to the adaptive immune response, there are some data suggesting that trained innate immunity might also have a role in protection against COVID-19.
Multiple clinical trials are examining whether unrelated vaccines, such as the measles, mumps, and rubella vaccine and the Bacillus Calmette–Guérin vaccine, can elicit trained innate immunity and confer protection against COVID-19. It is crucial that research focuses on understanding the genetic drivers of infection and vaccine-induced humoral and cellular immunity to SARS-CoV-2, defining detailed targets of humoral and cellular immune responses at the epitope level, characterising the B-cell receptor and T-cell receptor repertoire elicited by infection or vaccination, and establishing the long-term durability, and maintenance, of protective immunity after infection or vaccination. A safe regulatory pathway leading to licensing must also be defined for use of these vaccines in children, pregnant women, immunocompromised people, and nursing home residents. Some have called for further shortening of the vaccine development process through the use of controlled human challenge models. As of Oct 5, 2020, no such studies have occurred, but the UK is considering initiating such trials in early 2021.

Ivermectin: a systematic review from antiviral effects to COVID-19 complementry regimen

Faterneh Heidery, Reza Gharebaghi. The Journal fo Antibiotics, Japan Antibiotics Research Association 2020. Published online 12 June 2020.

Abstract: Ivermectin proposes many potentials effects to treat a range of diseases, with its antimicrobial, antiviral, and anti-cancer propertiesas a wonder drug. It is highly effective against many microorganisms including some viruses. In this comprehensive systematicreview, antiviral effects of ivermectin are summarized includingin vitro and in vivo studies over the past 50 years. Several studiesreported antiviral effects of ivermectin on RNA viruses such as Zika, dengue, yellow fever, West Nile, Hendra, Newcastle,Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, Porcine Reproductive and RespiratorySyndrome, Human immunodeficiency virus type 1, and severe acute respiratory syndrome coronavirus 2. Furthermore, there aresome studies showing antiviral effects of ivermectin against DNA viruses such as Equine herpes type 1, BK polyomavirus,pseudorabies, porcine circovirus 2, and bovine herpesvirus 1. Ivermectin plays a role in several biological mechanisms, thereforeit could serve as a potential candidate in the treatment of a wide range of viruses including COVID-19 as well as other types ofpositive-sense single-stranded RNA viruses. In vivo studies of animal models revealed a broad range of antiviral effects ofivermectin, however, clinical trials are necessary to appraise the potential efficacy of ivermectin in clinical setting.

The Broad Spectrum Host-Directed Agent Ivermectin as an Antivral for SARS-CoV-2?
David A. Jans, Kylie M. Wagstaff.
Journal Pre-proof – BBRC Biochemical and Biophysical Research Communications 2020.

Abstract: FDA approved for parasitic indications, the small molecule ivermectin has been the focus of growing attention in the last 8 years due to its potential as an antiviral. We first identified ivermectin in a high throughput compound library screen as an agent potently able to inhibit recognition of the nuclear localizing Human Immunodeficiency Virus-1 (HIV-1) integrase protein by the host importin (IMP) α/β1 heterodimer, and recently demonstrated its ability to bind directly to IMPα to cause conformational changes that prevent its function in nuclear import of key viral as well as host proteins. Cell culture experiments have shown robust antiviral action towards a whole range of viruses, including HIV-1, dengue, Zika and West Nile Virus, Venezuelan equine encephalitis virus, Chikungunya, pseudorabies virus, adenovirus, and SARS-CoV-2 (COVID-19). Close to 70 clinical trials are currently in progress worldwide for SARS-CoV-2. Although few of these studies have been completed, the results that are available, as well as those from observational/retrospective studies, indicate clinical benefit. Here we discuss the case for ivermectin as a host-directed broad-spectrum antiviral agent, including for SARS-CoV-2.

S2k-Leitlinie – Empfehlungen zur stationären Therapie von Patienten mit COVID-19
Publiziert bei AWMF online – Register-Nr. 113/001 – Stand 23.11.2020
Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN); Berlin
Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI), Berlin
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), Berlin

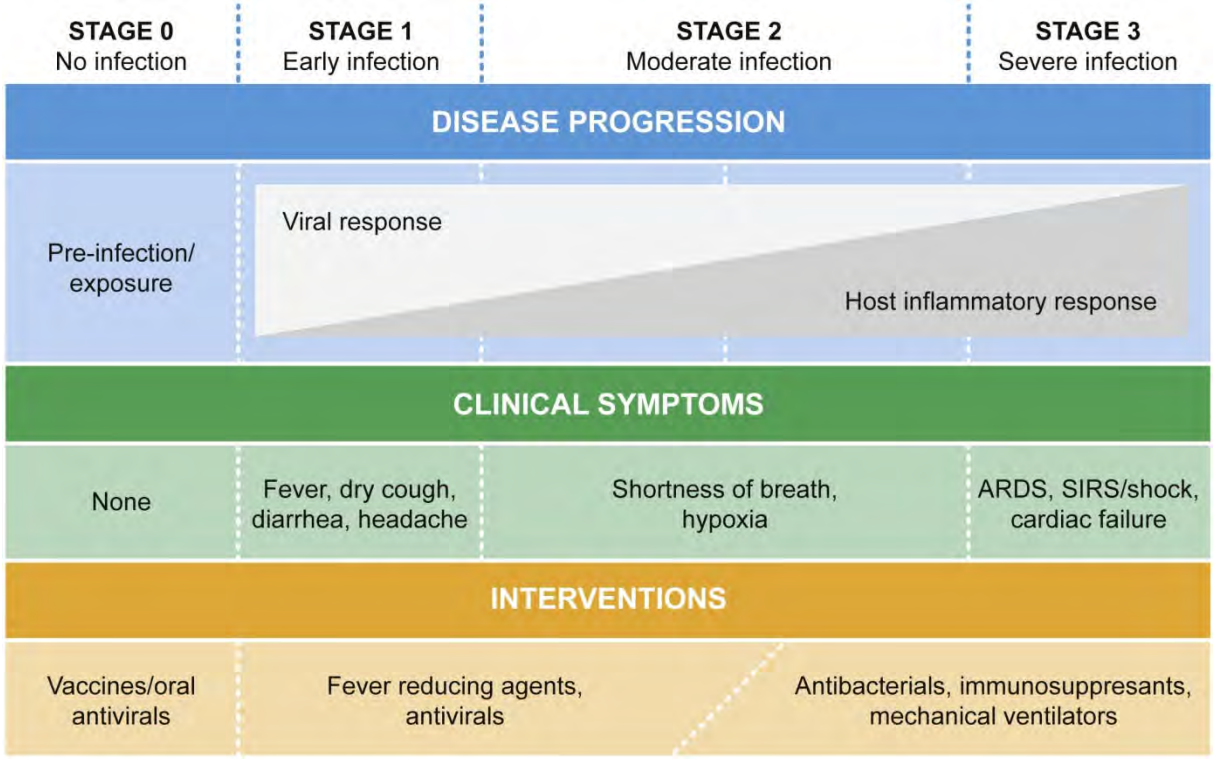
Bemerkung: kein Hinweis auf eine ‚Basis-Therapie' in der Frühphase der COVID-19 Erkrankung zur *Verhinderung der Aufnahme* auf eine Intensiv-Station.
Möglichkeiten zur frühzeitigen Therapie der Thrombose-Neigung und der inflammatorischen Autoaggression werden nicht (ausreichend) wahrgenommen – was bleibt ist eine Cortison-Medikation im Endstadium der Erkrankungsphase mit fraglich klinisch-relevantem Wert.
Mögliche Maßnahmen gegen den *Interleukin-Sturm* als organ-schädigendes Agens werden auf den Einsatz im Rahmen von ‚Studien' verwiesen (u.a. **Baricitinib**, selektiver u. reversibler Inhibitor von Januskinase JAK 1 und 2, dosisabhängige Hemmung der durch IL-6 induzierten STAT3-Phosphorylierung, Aktivierung von JAKS Signaltransduktoren und Aktivatoren der Transkription STATs).

Update SARS-CoV-2 Behandlungsempfehlungen für die Intensivmedizin: November 2020
ÖGARI, FASIM,ÖGIAIN
Aussage: Bei leichteren Verlaufsformen hilft die NIPPV die Intubation zu vermeiden. Bei Patientinnen und Patienten mit schwerer Hypoxämie und/oder klinisch fortschreitendem respiratorischem Versagen ist Intubation und mechanische Beatmung mit adäquaten PEEP-Werten die Therapie der Wahl, um die Lungenfunktion zu stabilisieren. Bei instabilen Patienten ist ein erweitertes hämodynamisches Monitoring in Betracht zu ziehen. Auf eine suffiziente Thromboseprophylaxe ist zu achten. Es gibt derzeit keine gesicherte, spezifische Therapie gegen SARS-CoV-2. Die aktuelle Evidenz zeigt eine Mortalitätsreduktion unter der

Gabe von Dexamethason. Die Anwendung anderer Substanzen wird derzeit nur im Rahmen von Studien empfohlen.
Bemerkung: ‚weiche' Therapie-Ansätze für das Endstadium einer Erkrankung.

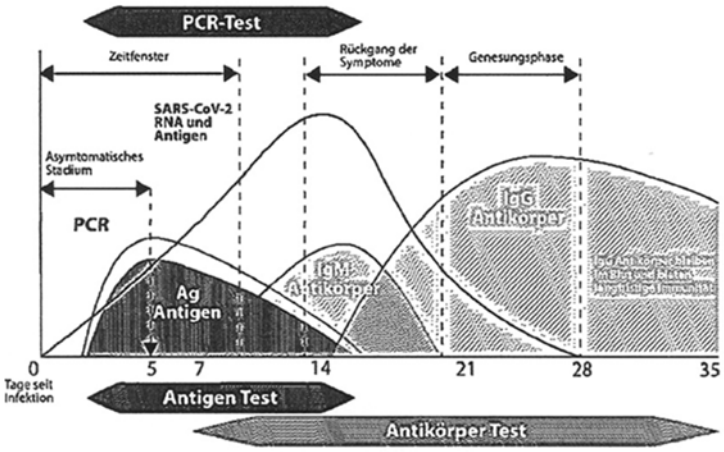
Accelerated Preclinical Paths to Support Rapid Development of COVID-19 Therapeutics.
Jay A. Grobler, Annaliesa S. Anderson, Porbhavathi Fernandes et al. Cell Host & Microbe, Perspective – Vol 28, Issue 5, P 638-645, Nov. 11. 2020. Published Oct 01, 2020.
When SARS-CoV-2 emerged at the end of 2019, no approved therapeutics or vaccines were available. An urgent need for countermeasures during this crisis challenges the current paradigm of traditional drug discovery and development, which usually takes years from start to finish. Approaches that accelerate this process need to be considered. Here we propose the minimum data package required to move a compound into clinical development safely. We further define the additional data that should be collected in parallel without impacting the rapid path to clinical development. Accelerated paths for antivirals, immunomodulators, anticoagulants, and other agents have been developed and can serve as "roadmaps" to support prioritization of compounds for clinical testing. These accelerated paths are fueled by a skewed risk-benefit ratio and are necessary to advance therapeutic agents into human trials rapidly and safely for COVID-19. Such paths are adaptable to other potential future pandemics.
The emergence of the COVID-19 global pandemic caused by SARS-CoV-2 is a crisis in which response requires immediate action, including adaptation of the drug discovery and development process to speed quality agents into clinical trials. These new processes require gating criteria to include only those sets of data absolutely required to ensure translational activity with acceptable pharmacokinetics and safety via the intended route of administration. Additional, non-gating data such as target identification, mechanism of action, and combination evaluation for all agents, as well as resistance profiling and expanded antiviral profiling for antiviral agents, will also be important to obtain. These assays should be done in parallel to the gating criteria and in a less urgent manner. Assessment of resistance potential for antivirals, while not gating and variable in risk from agent to agent, should be determined rapidly as these agents move through clinical development. This will preclude prioritizing an agent with high resistance potential over others with less resistance potential. To provide the best therapeutic options, multiple validated mechanisms should be pursued. The blueprints for defined therapeutic agent assessment presented here outline the critical data needed to most rapidly and efficiently evaluate and prioritize agents for clinical development for COVID-19. Hopefully, as therapeutic and prophylactic compounds and vaccines are approved for COVID-19, there will be a continuing effort for pandemic preparedness, which will discover and develop broadly active, potent therapeutics for many families of viruses with pandemic potential. Should such efforts not provide approved agents for a future pandemic, the principles described here could be adapted to generate blueprints for crisis mode drug discovery to address that pandemic.
To determine the best agents to prioritize for clinical trials, data must be of high quality and generated in standardized assays, or at minimum with robust and universally adopted controls that allow accurate comparison of potency. Dose-response assessment of all agents should be determined, and the datasets and analyses presented for prioritization rather than simply using a derived EC_{50} or EC_{90} number. The best practice is to include all known robust positive controls for the assay with each run such that relative potency can be compared from assay to assay to compensate for changes in protocol, cell adaptations, and other confounding variables from run to run and laboratory to laboratory. For antivirals against SARS-CoV-2, at a minimum, inclusion of remdesivir is recommended for *in vitro* assays. For best comparison, key assays should follow standardized protocols published and accepted by the global community. Additionally, for select profiles such as immunomodulators and in all cases requested by regulators, *in vivo* efficacy data in an appropriate model (see accompanying article by Hewitt et al., 2020) is essential. Indeed, though potentially unnecessary to start clinical assessment, such data is a selection criteria for consideration by networks such as the ACTIV clinical trials prioritization group. All data generated to support clinical development of agents should be made publicly available during pandemic crises to facilitate optimal learning and advancement in the shortest time frame.
Not addressed here, but critical to rapid response in a crisis mode, is availability of clinical drug supply. Most likely, the first agents to move to the clinical prioritization during a pandemic crisis will be molecules with sufficient potency, PK, and safety to provide therapeutic options until more potent compounds can be identified. There should also be sufficient amount of clinical drug supply on hand to support clinical trials. If not, accelerated paths to produce this clinical-grade material are mandatory. Additionally, commercial-scale manufacturing of any agent entering clinical trials must be established in parallel to the execution of the clinical trials to ensure adequate supplies are available to treat patients upon product approval, even though these efforts require a significant at-risk, front-loaded investment in material that may not be used for COVID-19 unless the product is approved.
The COVID-19 pandemic is a public health crisis due to the lack of vaccines and therapeutics developed ahead of time for preparedness. The problem has been compounded by the need to define, coordinate, and

execute an accelerated response in the face of a rapidly spreading and deadly human pathogen. Use of the blueprints presented here can lead to optimal compound prioritization of potential therapeutics to address all known stages of COVID-19 as well as any other disease aspects that remain to be defined.



Correspondence: Kara.carter@evotec.com

Verlaufskontrolle nach Covid-19-Infektion **–Ag-Ak-Titer**



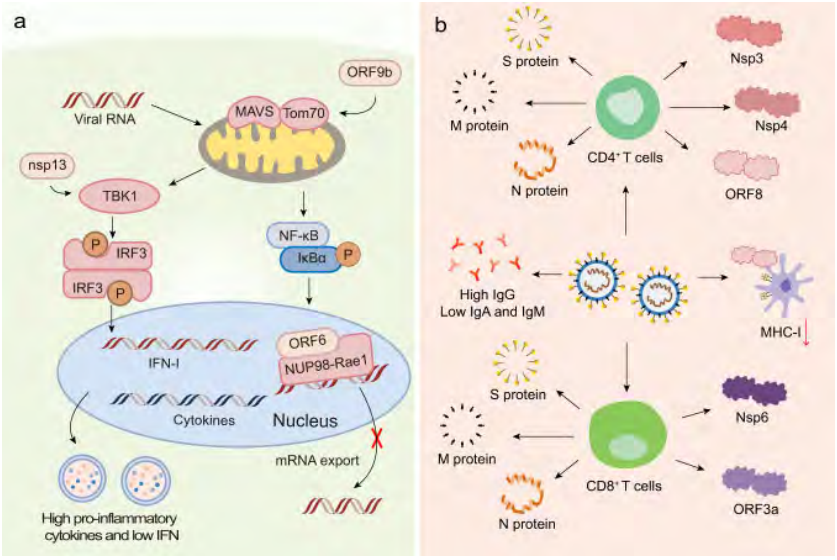
Immunological considerations for COVID-19 vaccine strategies.
Mangalakumari Jeyanathan, S. Afkhami, F. Smaill, M.S. Miller, B.D. Lichty and Zhou Xing.
Nat. Rev. Immunol. 2020 Sept 4:1-18, Epub ahead of print

Abstract | The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) is the most formidable challenge to humanity in a century. It is widely believed that prepandemic normalcy will never return until a safe and effective vaccine strategy becomes available and a global vaccination programme is implemented successfully. Here, we discuss the immunological principles that need to be taken into consideration in the development of COVID-19 vaccine strategies. On the basis of these principles, we examine the current COVID-19 vaccine candidates, their strengths and potential shortfalls, and make inferences about their chances of success. Finally, we discuss

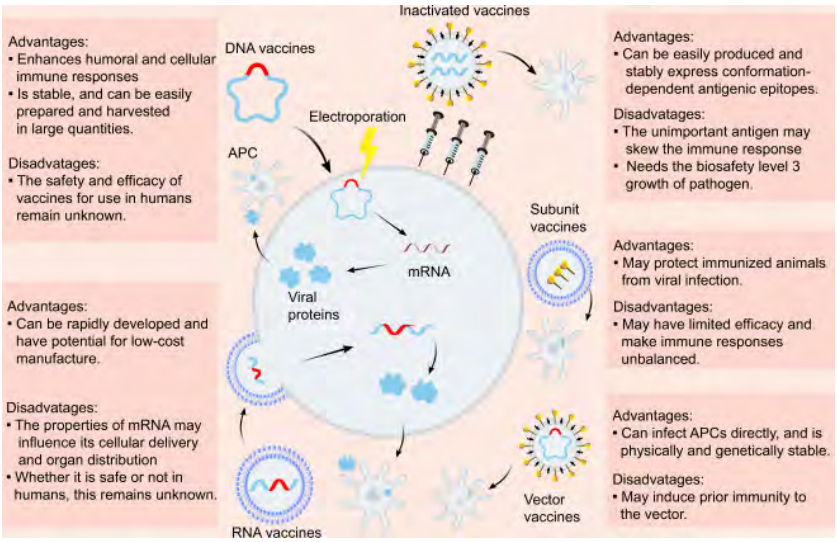
the scientific and practical challenges that will be faced in the process of developing a successful vaccine and the ways in which COVID-19 vaccine strategies may evolve over the next few years.

A systematic review of SARS-CoV-2 vaccine candidates.
Yetian Dong, Tong Dai, Yujun Wie, Lang Zhang, Min Zheng, Fangfang Zhou
Signal Transduct Target Ther. 2020, Oct 13; 5(1):237.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging virus that is highly pathogenic and has caused the recent worldwide pandemic officially named coronavirus disease (COVID-19). Currently, considerable efforts have been put into developing effective and safe drugs and vaccines against SARS-CoV-2. Vaccines, such as inactivated vaccines, nucleic acid-based vaccines, and vector vaccines, have already entered clinical trials. In this review, we provide an overview of the experimental and clinical data obtained from recent SARS-CoV-2 vaccines trials, and highlight certain potential safety issues that require consideration when developing vaccines. Furthermore, we summarize several strategies utilized in the development of vaccines against other infectious viruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), with the aim of aiding in the design of effective therapeutic approaches against SARS-CoV-2.



The immune responses induced by SARS-CoV-2. **a** Innate immune response. SARS-CoV-2 infection induces imbalanced host immune responses, such as low IFN-I and -III levels but high pro-inflammatory cytokines. Nsp13 of SARS-CoV-2 targets the IFN pathway by associating with TBK1. The ORF6 protein interacts with the mRNA export factor NUP98-Rae1. The ORF9b indirectly interacts with MAVS via its interaction with Tom70. **b** Adaptive immune response. $CD4^+$ T-cell responses are primarily directed against the S, M, and N proteins and partially against nsp3, nsp4, and ORF8. $CD8^+$ T cells recognize SARS-CoV-2 M, N, S proteins, nsp6, and ORF3a. ORF8 is able to downregulate MHC-I expression on diverse cell types. SARS-CoV-2 primarily induces S protein- and RBD-specific IgG, while IgM and IgA responses are lower



Overview of the diverse types of vaccines, and their potential advantages and disadvantages

Conclusions and perspectives
The widespread threat of SARS-CoV-2 to humans has spawned challenges to develop safe and effective **antiviral drugs** and **vaccines** for preventive use. Currently, several clinical trials have shown that ritonavir, lopinavir, chloroquine, and hydroxychloroquine had little benefit for COVID-19 treatment. A randomized, controlled and open-label trial revealed that ritonavir and lopinavir did not clearly shorten the time to clinical improvement compared to the standard care.138 Both chloroquine and hydroxychloroquine had the potential to affect the corrected QT (QTc) interval, and chloroquine is not recommended for severe patients.139–141 Several antibodies have been identified to target different
domains of SARS-CoV-2 and are effective in neutralizing SARSCoV-2. These antibodies may have the potential to treat SARSCoV-2-infected patients, and future work to define these antibody epitopes will further aid vaccine development. The experimental and clinical results of some vaccine andidates, such as BBIBPCorV and PiCoVacc, were reported, with most vaccines showing neutralizing capacity. For vaccine development, it is critical to generate protective T- and B-cell immune responses. The S protein has been shown to be the most potent antigen for SARS-CoV and MERS-CoV vaccines, and we hypothesize this may be similar for SARS-CoV-2 vaccines. However, the immunopathology induced by SARS-CoV or MERS-CoV vaccines was observed in animal models, which might be attributed to ADE, an aberrant Th2 response partially due to the N protein, as well as other unknown reasons. The mechanisms underlying this immunopathology deserve further investigation, which may provide instructive guidance for the future development of SARS-CoV-2 vaccines. Apart from
immunopathology, other important questions remain to be addressed, such as how to protect the population vulnerable to lethal human CoVs, such as the elderly, and how best to provide protection against variant and heterologous CoV strains. Recently, human ACE2 transgenic mice were eveloped that could be infected by SARS-CoV-2 and generated typical pathology that were similar to those of COVID-19 patients.142,143 Rhesus macaques infected by SARS-CoV-2 also exhibited humoral and
cellular immune responses and were protected from rechallenge. 144 In essence, it is equally important to identify the ideal animal model for evaluating potential SARS-CoV-2 vaccines. Herein, we reviewed current vaccine strategies of several pathogenic viruses with the aim to improve vaccine efficacy and safety against SARS-CoV-2. Antigen design plays a significant role in maximizing the immunogenicity. It is necessary to include the important epitopes while excluding the unimportant ones. Moreover, the structure design of the immunogen requires additional research. Employing a suitable delivery system is also critical for vaccine efficacy. Determining which method works best depends on many factors, including the types of vaccines and vaccination routes. Furthermore, adjuvants should be added to the various types of vaccines to enhance immunogenicity; therefore, the
selection of appropriate adjuvants is crucial for developing SARSCoV-2 vaccines. Until now, only several studies had reported the immune responses induced by SARS-CoV-2 vaccine candidates.
Further trials must test the safety and efficacy of vaccines and search for effective approaches to optimize the vaccines. In conclusion, we hope the insights provided above will aid in the development of SARS-CoV-2 vaccines.

WHO statement
Several different types of potential vaccines for COVID-19 are in development, including:
Inactivated or weakened virus vaccines, which use a form of the virus that has been inactivated or weakened so it doesn't cause disease, but still generates an immune response.
Protein-based vaccines, which use harmless fragments of proteins or protein shells that mimic the COVID-19 virus to safely generate an immune response.
Viral vector vaccines, which use a virus that has been genetically engineered so that it can't cause disease, but produces coronavirus proteins to safely generate an immune response.
RNA and DNA vaccines, a cutting-edge approach that uses genetically engineered RNA or DNA to generate a protein that itself safely prompts an immune response.

Covid vaccine update: when will others be ready? – James Gallabher – BBC News
Moderna vaccine
mRNA vaccine, tiny fragment of the virus's genetic code are used, can protect 94.5% of people, given in two doses, four weeks apart, stays stable at -20C for up to six months

AstraZeneca Vaccine – Oxford University
Protection 70 – 90% (perfection the dose), given in two doses; made form a weakened version of a common cold virus from chimpanzees, modified to not grow in humans.

Spike protein on the surface of the coronavirus are put into a harmless virus, the vaccine enters cells, which start to produce the spike protein, the body's immune system reacts, producing antibodies and activating T-cells to destroy cells with the spike protein. If the patient later catches covid-19 virus, antibodies and T-cells are triggered to fight the virus.

Pfizer-BioNtech Vaccine
95% effective, given in two doses, three weeks apart. V. stored at a temp of around -70C.
mRNA vaccine, the first to be approved for use in humans

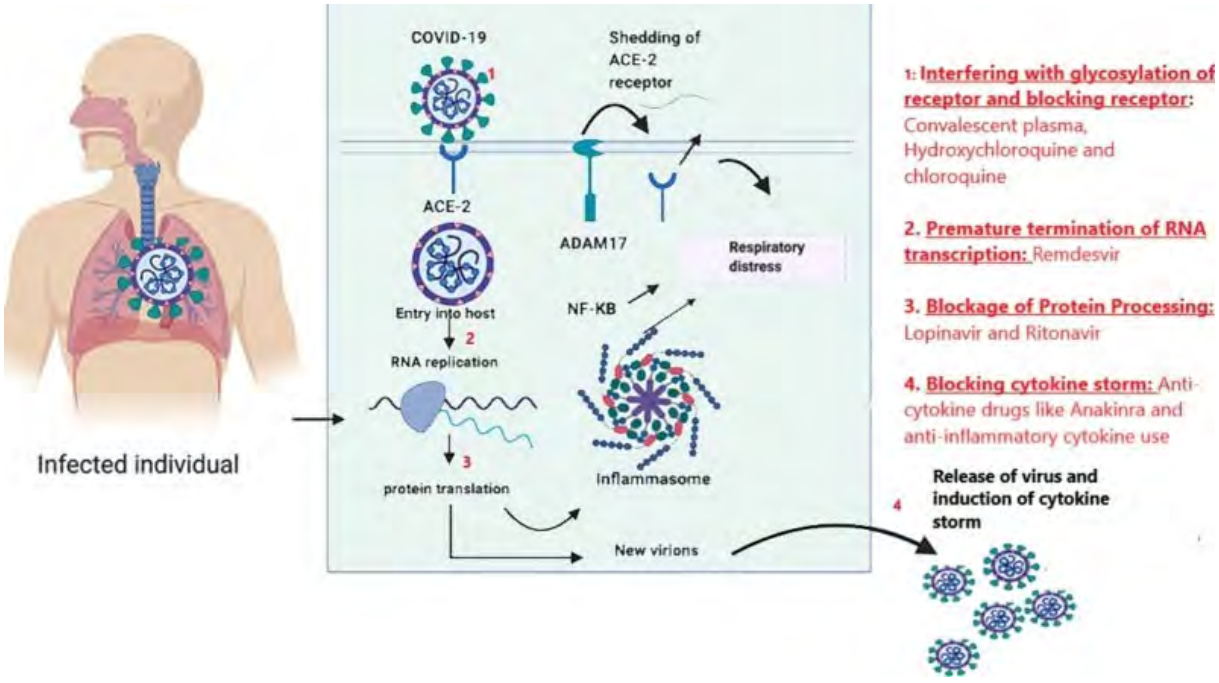
Russian Sputnik V Vaccine
works like the Oxford-AstraZeneca one, suggest it is 92% efficient

Probleme in Studien-Daten – cit. Peter Doshi, thebmjopinion, Jan/21
Wirkung – Nebenwirkung der Vaccination bei Personen mit history of SARS-CoV-2 infection or previous diagnosis – ‚post-Covid' patients.
Pfizer and Moderna's data sharing statement: data of the trials available upon request, and subject to review – after study completion (..2022).
Not full marketing approva

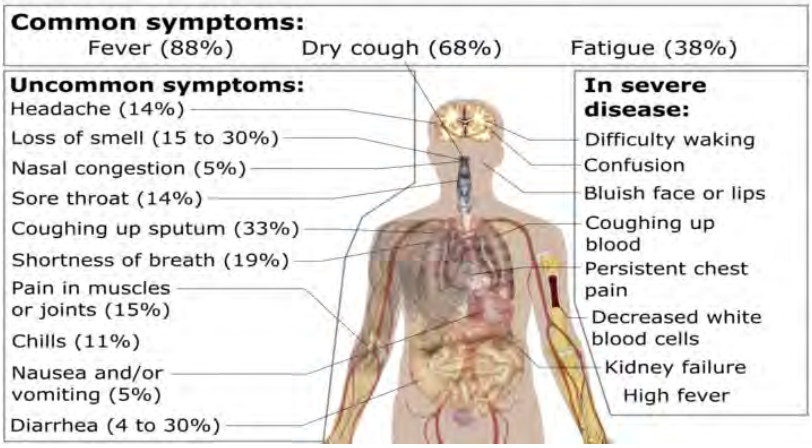
- cit. Helen Branswell, @HelenBranswell, Dec/2020

The vaccine's efficacy appeared to be slightly lower in people 65 and older, but during a presentation to the Food and Drug Administration's advisory committee the company explained that the numbers could have been influenced by the fact there were few cases in that age group in the trial. The vaccine appeared to be equally effective across different ethnic and racial groups.
Both vaccines seemed to reduce the risk of severe Covid disease. It's not yet known if either prevents asymptomatic infection with the SARS-CoV-2 virus. Nor is it known if vaccinated people can transmit the virus if they do become infected but don't show symptoms.
Both the *Moderna* and the *Pfizer/BioNTech vaccines* require two shots: a priming dose, followed by a booster shot. The interval between Moderna doses is 28 days; for the Pfizer vaccine, it's 21 days.
Each dose of Pfizer's contains 30 micrograms of vaccine. Moderna went with a much larger dose of vaccine, 100 micrograms. It means it is using a little more than three times as much vaccine per person as Pfizer is. And yet, they aren't getting better results.

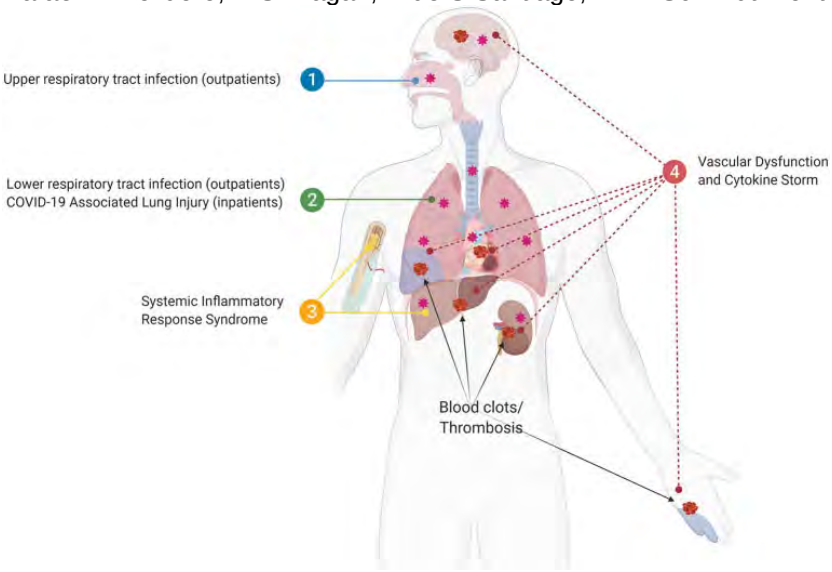
Emerging pharmacotherapies for COVID-19
Rachana Salvi, Panini Patankar, Biomed. Pharmacother. 2020, 128:1 10267

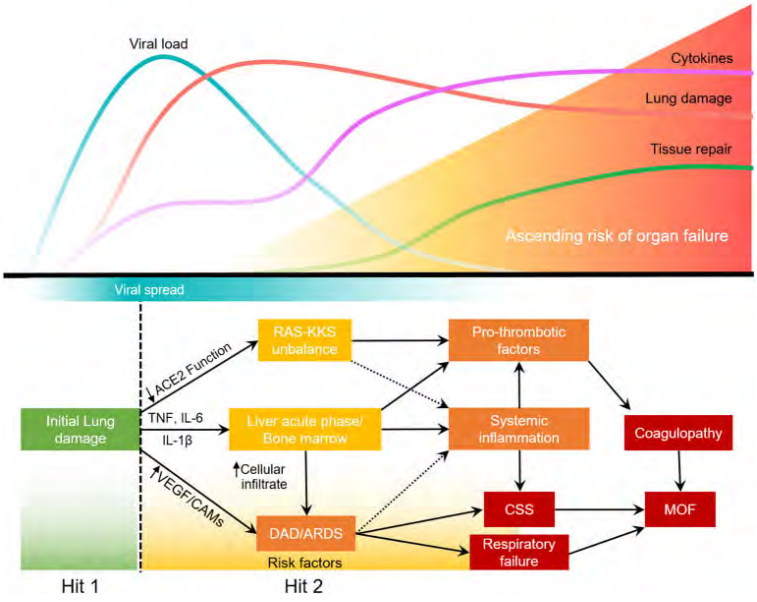


3. **Clinical Features:**



Overview: systemic inflammatory response derived from lung injury caused by SARS-CoV-1 infection explains severe aoutcomes in Covide-19.
Rafael B. Polidoro, R.S. Hagan, R de S Santiago, N.W. Schmidt. Font Immunol. 2020,11:1626.





Abstract
Most SARS-CoV2 infections will not develop into severe COVID-19. However, in some patients, lung infection leads to the activation of alveolar macrophages and lung epithelial cells that will release proinflammatory cytokines. IL-6, TNF, and IL-1β increase expression of cell adhesion molecules (CAMs) and VEGF, thereby increasing permeability of the lung endothelium and reducing barrier protection, allowing viral dissemination and infiltration of neutrophils and inflammatory monocytes. In the blood, these cytokines will stimulate the bone marrow to produce and release immature granulocytes, that return to the lung and further increase inflammation, leading to acute respiratory distress syndrome (ARDS). This lung-systemic loop leads to cytokine storm syndrome (CSS). Concurrently, the acute phase response increases the production of platelets, fibrinogen and other pro-thrombotic factors. Systemic decrease in ACE2 function impacts the Renin-Angiotensin-Kallikrein-Kinin systems (RAS-KKS) increasing clotting. The combination of acute lung injury with RAS-KKS unbalance is herein called COVID-19 Associated Lung Injury (CALI). This conservative two-hit model of systemic inflammation due to the lung injury allows new intervention windows and is more consistent with the current knowledge.
Keywords: SARS-CoV2, COVID-19, severe COVID-19, bisphosphonates, inflammatory monocytes, ARDS, renin-angiotensin system, kallikrein-kinin system

Could nasal nitric oxide help to mitigate the severity of COVID-19?
Jan Martel, Yun-Frei Ko, John D. Young, David M. Ojcius. Microbes and Infection 22 (20): 168-171.
Abstract
The nasal cavity and turbinates play important physiological functions by filtering, warming and humidifying inhaled air. Paranasal sinuses continually produce nitric oxide (NO), a reactive oxygen species that diffuses to the bronchi and lungs to produce bronchodilatory and vasodilatory effects. Studies indicate that NO may also help to reduce respiratory tract infection by inactivating viruses and inhibiting their replication in epithelial cells. In view of the pandemic caused by the novel coronavirus (SARS-CoV-2), clinical trials have been designed to examine the effects of inhaled nitric oxide in COVID-19 subjects. We discuss here additional lifestyle factors such as mouth breathing which may affect the antiviral response against SARS-CoV-2 by bypassing the filtering effect of the nose and by decreasing NO levels in the airways. Simple devices that promote nasal breathing during sleep may help prevent the common cold, suggesting potential benefits against coronavirus infection. In the absence of effective treatments against COVID-19, the alternative strategies proposed here should be considered and studied in more detail.

Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency
Shawn J. Green, Letter to the Editor, Microbes and Infection 22 (20), 149-150.
…Restoring nitric oxide through dietary inorganic nitrate may be aconsideration for prevention and early treatment which would oper-ate at two-levels: reverse platelet-endothelial dysfunction and asso-ciated thrombosis as well as lower viral burden.

Harnessing nitric oxide for preventing, limting and treating the severe pulmonary conssequences of COVID-19.
Nagasai C. Adusumilli, D. Zhang, J.M. Freidman, A.J. Freidman. Nitric Oxide 2020 Oct 1;103:4-8.
The ongoing outbreak of COVID-19 has quickly become a daunting challenge to global health. In the absence of targeted therapy and a reported 5.5% case fatality rate in the United States, treatments preventing rapid cardiopulmonary failure are urgently needed. Clinical features, pathology and homology to better understood pathogens suggest that uncontrolled inflammation and a cytokine storm likely drive COVID-19's unrelenting disease process. Interventions that are protective against acute lung injury and ARDS can play a critical role for patients and health systems during this pandemic. Nitric oxide is an antimicrobial and anti-inflammatory molecule with key roles in pulmonary vascular function in the context of viral infections and other pulmonary disease states. This article reviews the rationale for exogenous nitric oxide use for the pathogenesis of COVID-19 and highlights its potential for contributing to better clinical outcomes and alleviating the rapidly rising strain on healthcare capacity.

An Update on Current Therapeutic Drugs Treating Copvid-19.
Renyi Wu, Lujing Wang, Hsiao-Chen Dina Kuo et al., Curr Phrmacol Rep. 2020, May 11;1-15
Abstract:
The current pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented unprecedented challenges to the healthcare systems in almost every country around the world. Currently, there are no proven effective vaccines or therapeutic agents against the virus. Current clinical management includes infection prevention and control measures and supportive care including supplemental oxygen and mechanical ventilatory support. Evolving research and clinical data regarding the virologic SARS-CoV-2 suggest a potential list of repurposed drugs with

appropriate pharmacological effects and therapeutic efficacies in treating COVID-19 patients. In this review, we will update and summarize the most common and plausible drugs for the treatment of COVID-19 patients. These drugs and therapeutic agents include antiviral agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir), and supporting agents (Ascorbic acid, Azithromycin, Corticosteroids, Nitric oxide, IL-6 antagonists), among others. We hope that this review will provide useful and most updated therapeutic drugs to prevent, control, and treat COVID-19 patients until the approval of vaccines and specific drugs targeting SARS-CoV-2.
Keywords: Anakinra; Azithromycin; COVID-19; Chloroquine; Convalescent plasma; Epoprostenol; Favipiravir; Hydroxychloroquine; Lopinavir; Methylprednisolone; Nitric oxide; Oseltamivir; Remdesivir; SAR-CoV-2; Sarilumab; Sirolimus; Tocilizumab; Traditional Chinese Medicine; Umifenovir; Vitamin C.

The effect of nitric-oxide-related supplements on human performance
Raúl Bescós, Antoni Sureda, Josep A Tur, Antino Pons.
Review Sports Med 2012 Feb 1;42(2):99-117.

Abstract
Nitric oxide (NO) has led a revolution in physiology and pharmacology research during the last two decades. This labile molecule plays an important role in many functions in the body regulating vasodilatation, blood flow, mitochondrial respiration and platelet function. Currently, it is known that NO synthesis occurs via at least two physiological pathways: NO synthase (NOS) dependent and NOS independent. In the former, L-arginine is the main precursor. It is widely recognized that this amino acid is oxidized to NO by the action of the NOS enzymes. Additionally, L-citrulline has been indicated to be a secondary NO donor in the NOS-dependent pathway, since it can be converted to L-arginine. Nitrate and nitrite are the main substrates to produce NO via the NOS-independent pathway. These anions can be reduced in vivo to NO and other bioactive nitrogen oxides. Other molecules, such as the dietary supplement glycine propionyl-L-carnitine (GPLC), have also been suggested to increase levels of NO, although the physiological mechanisms remain to be elucidated. The interest in all these molecules has increased in many fields of research. In relation with exercise physiology, it has been suggested that an increase in NO production may enhance oxygen and nutrient delivery to active muscles, thus improving tolerance to physical exercise and recovery mechanisms. Several studies using NO donors have assessed this hypothesis in a healthy, trained population. However, the conclusions from these studies showed several discrepancies. While some reported that dietary supplementation with NO donors induced benefits in exercise performance, others did not find any positive effect. In this regard, training status of the subjects seems to be an important factor linked to the ergogenic effect of NO supplementation. Studies involving untrained or moderately trained healthy subjects showed that NO donors could improve tolerance to aerobic and anaerobic exercise. However, when highly trained subjects were supplemented, no positive effect on performance was indicated. In addition, all this evidence is mainly based on a young male population. Further research in elderly and female subjects is needed to determine whether NO supplements can induce benefit in exercise capacity when the NO metabolism is impaired by age and/or estrogen status.

5 Ways to Increase Nitric Oxide Naturally
Healthline, Gavin Van De Walle, 2018

Nitric oxide is a molecule that's produced naturally by your body, and it's important for many aspects of your health. Its most important function is vasodilation, meaning it relaxes the inner muscles of the blood vessels, causing them to widen and increase circulation. Nitric oxide production is essential for overall health because it allows blood, nutrients and oxygen to travel to every part of your body effectively and efficiently. In fact, a limited capacity to produce nitric oxide is associated with heart disease, diabetes and erectile dysfunction. Fortunately, there are many ways to maintain optimal levels of nitric oxide in your body. Here are the top 5 ways to increase nitric oxide naturally.

1.Eat Vegetables High in Nitrates
Nitrate, a compound found in certain vegetables, is one of the many reasons vegetables are healthy for you. Vegetables high in nitrate include: Celery, Cress, Chervil, Lettuce, Beetroot, Spinach, Arugula. When these foods are consumed, nitrates are converted into nitric oxide, which confers a wide range of health benefits related to heart health and exercise performance. In fact, several analyses have shown that eating nitrate-rich vegetables can lower blood pressure as much as some blood pressure medications. Strong evidence favors nitrates, especially from beetroot, for improving exercise performance in athletes. Despite the effects that nitrates have on nitric oxide production in your body, some people avoid them for fear they are harmful and contribute to cancer. This is likely because sodium nitrates are commonly used as a preservative and color fixative in bacon, cold cuts and hot dogs. Eating these foods is linked to bowel cancer, and nitrates are thought to be the culprit .

Nitrates can form N-nitroso compounds, such as nitrosamine, which are capable of causing cancer. However, vegetables, which account for more than 80 percent of nitrate intake, contain antioxidants like vitamin C, which help prevent the formation of N-nitroso compounds. Therefore, nitrates from vegetables are harmless, whereas nitrates in processed meats can be troublesome to health, particularly when consumed in excess over long periods.
Vegetables are good sources of nitrates, which help form nitric oxide in your body. Consuming nitrate-rich vegetables improves heart health and exercise performance.

2. Increase Your Intake of Antioxidants
Nitric oxide is an unstable molecule that degrades quickly in the bloodstream, so it must be constantly replenished. One way to increase its stability and limit its breakdown is by consuming antioxidants.
Antioxidants are molecules that neutralize free radicals, which contribute to the short life of nitric oxide.
These antioxidants are found in all foods but primarily those of plant origin, such as fruits, vegetables, nuts, seeds and grains.
A few important antioxidants include:
Vitamin C: This antioxidant helps your body form connective tissues, including skin, bones, tendons and cartilage. It also produces brain chemicals that help nerve cells communicate.
Vitamin E: This antioxidant protects cells from the damaging effects of free radicals, which are thought to contribute to aging and disease. It also plays an important role in keeping the immune system strong.
Polyphenols: This category of antioxidants is associated with several health benefits, including a reduced risk of cancer and cardiovascular disease.
Glutathione: Coined "the mother of all antioxidants," glutathione is the master antioxidant and detoxifier of every cell in your body. Several studies have found that ingesting nitric oxide precursors, such as nitrate or citrulline, with antioxidants maintains greater levels of nitric oxide in your body by helping reduce its breakdown.
Vegetables that are high in nitrate are also inherently high in antioxidants, which is likely why vegetables are so effective at increasing and maintaining optimal levels of nitric oxide.
Antioxidants help decrease the breakdown and extend the life of nitric oxide in your body.

3. Use Nitric-Oxide-Boosting Supplements
Several dietary supplements are marketed as "nitric oxide boosters."
These supplements don't contain nitric oxide itself, but they include ingredients that help form nitric oxide in your body. Two of the most commonly used ingredients are L-arginine and L-citrulline.
L-Arginine
L-arginine is a conditionally essential amino acid, meaning it only has to be consumed in the diet under certain conditions, while healthy adults can make all they need. It directly produces nitric oxide through a process called the L-arginine-NO pathway. Several studies support the use of L-arginine for increasing blood flow, but only in certain populations. In those with high blood pressure, including pregnant women, L-arginine is effective at lowering blood pressure. However, evidence on the ability of L-arginine to improve blood flow or exercise performance in healthy individuals remains mixed. L-arginine is generally recognized as safe when taking 20 grams per day, but it may cause digestive symptoms at dosages as low as 10 grams.
L-Citrulline
L-citrulline is a dispensable amino acid, meaning your body can make all it needs. When L-arginine is converted to nitric oxide, L-citrulline is produced as a byproduct. L-citrulline can then be recycled back to L-arginine and used to increase your body's natural production of nitric oxide. In fact, L-citrulline increases levels of L-arginine in your body more than supplementing with L-arginine itself does. This is because a large percentage of L-arginine is broken down before reaching your bloodstream. Studies have found L-citrulline to increase blood flow, improve exercise performance and lower blood pressure. L-citrulline is considered relatively safe, and there is a low risk of side effects, even with high doses.
The amino acids L-arginine and L-citrulline are used to produce nitric oxide in your body. They are available as supplements and have beneficial effects on vascular health and blood flow.
4. Limit Your Use of Mouthwash
Mouthwash destroys bacteria in your mouth that can contribute to the growth of cavities and other dental diseases. Unfortunately, mouthwash kills all types of bacteria, including the beneficial ones that help produce nitric oxide. Special bacteria in the mouth convert nitrate to nitric oxide. In fact, humans cannot produce nitric oxide from nitrate without these bacteria. Research has shown that mouthwash kills the oral bacteria needed to produce nitric oxide for up to 12 hours. This leads to a decrease in nitric oxide production and, in some instances, an increase in blood pressure. The detrimental effects of mouthwash on nitric oxide production may even contribute to the development of diabetes, which is characterized by malfunctions in insulin production or action. This is because nitric oxide also regulates insulin, which helps cells utilize the energy obtained from food after it's digested. Without nitric oxide, insulin cannot work properly. One study found that people who used mouthwash at least twice daily were 65% more likely to develop diabetes than those who never used mouthwash.
Therefore, to maintain adequate nitric oxide production, it's best to use mouthwash sparingly.
Mouthwash kills many types of bacteria in the mouth, including the ones that help produce nitric oxide. This limits your body's ability to produce nitric oxide, which can lead to high blood pressure and diabetes.
5. Get Your Blood Flowing With Exercise
Exercise really does get your blood pumping, largely because it improves endothelial function.
Endothelium refers to the thin layer of cells that line the blood vessels. These cells produce nitric oxide, which keeps blood vessels healthy. Insufficient nitric oxide production results in endothelium dysfunction, which can contribute to atherosclerosis, high blood pressure and other risk factors for heart disease. Exercise keeps your endothelial cells and

blood vessels healthy by increasing your body's natural ability to produce nitric oxide. Several studies have shown that regular physical activity increases endothelial vasodilation in people who have high blood pressure and heart disease, as well as in healthy individuals. Studies have also shown that exercise increases antioxidant activity, which helps inhibit the breakdown of nitric oxide caused by free radicals. The benefits of exericse on endothelial health and nitric oxide production can be seen in as little as 10 weeks when exercising for 30 minutes at least three times a week. For optimal results, combine aerobic training, such as walking or jogging, with anaerobic training, such as resistance training. The types of exercise you choose should be things you enjoy and can do long term. Finally, speak with your doctor to determine any limitations you may have in regards to exercise.
Engaging in regular exercise can improve your endothelial function and thus your natural production of nitric oxide.
The Bottom Line
Nitric oxide is an essential molecule required for overall health. As a vasodilator, nitric oxide signals the blood vessels to relax, allowing them to expand. This effect allows blood, nutrients, and oxygen to flow freely to every part of your body. But when nitric oxide production is decreased, your health can become compromised. Therefore, it's important to achieve and maintain optimal levels of nitric oxide in your body. A diet high in nitrate-rich vegetables and antioxidants or the use of supplements, such as L-arginine or L-citrulline, are beneficial ways to boost your body's natural production of nitric oxide. Other proven strategies include limiting mouthwash and exercising regularly. For optimal nitric oxide production, increase your intake of nitrate-rich vegetables and exercise at least 30 minutes per day.

Bamlanivimab (s. Wikipedia)
Ein mononoklonaer Ak, bindet an Abschnitte des Spike-Proteins, verhindert Eindringen des Virus.
Fa Lilly. I.v. Anwendung. FDA Notfallzulassung.

Casirivimab/Imdevimab (s. Wkipedia)
Fa Regeneron. Monoklonaler Ak-Cocktail, i.v. Therapie. FDA Nov/20 EUA Emergency Use Authorization.

Favipiravir – Avigan (T-705)
Virostatikum, RNA-Polymerase-Inhibitor. Wirkt gegen Infuenza und weitere RNA-Viren, wird als Prodrug intrazellulär zur virustatischen Substanz. Einsatz bei Maul- u. Klauenseuche Virus, West-Nil-Virus, Ebola-Virus, Arena-Virus, Alpha-Virus, Bunya-Viren, Gelbfieber-Viren, Riftalfieber-Viren, Flavi-Viren.

Editor's Note, February 24, 2021, JAMA Intern Med., doi:10.1001/jamainternmed.2021.0374
How to Advise Persons Who Are Antibody Positive for SARS-CoV-2 About Future Infection Risk
Mitchell H. Katz, MD[1]
Original Investigation: Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection.
Raymond A. Harvey et al.

As a physician working in New York, New York, where coronavirus disease 2019 (COVID-19) hit hard in March and April of 2020, people often ask me how to interpret their severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody results. Many people have positive test results for the antibody, some of them received a diagnosis of COVID-19, some of them had symptoms that were consistent with COVID-19 but were never tested because of a limited availability of testing, and some were never symptomatic but learned that they were positive for the antibody on a subsequent laboratory test. If they are positive, they want to know whether they are protected from a future infection with the virus.

Underlying the question of whether the presence of antibodies provides protection against future infections are 3 questions: are antibodies protective, how good are the available tests for accurately detecting antibodies, and how long does protection last? To address the first question, we know that most patients who recover from COVID-19 have antibodies and that reinfection (as opposed to extended symptoms or ongoing viral shedding) is rare, at least at this date. However, even if antibodies are protective, there remains a question of how accurate commercial tests are for detecting antibodies.

The study in this issue of *JAMA Internal Medicine* by Harvey and colleagues[1] provides reassuring answers to the first and second questions. Using a national database with more than 3 million unique patients, the authors found that patients with a positive antibody test result were more likely than those with a negative test result to have a subsequent positive nucleic acid amplification test result for SARS-CoV-2 in the first 30 days from the test result (viral shedding), but that starting at beyond 30 days, the risk of a positive nucleic acid amplification test declined every 30 days, until the risk ratio for those with an initial positive test at 90 days or greater follow-up was only 0.10 compared with those with a negative test. Antibody tests, in this study, appeared accurate and the antibodies protective. Their findings are consistent with a study of health

care workers that found that the incidence of SARS-CoV-2 infection in 1265 workers with antispike antibodies was 0.13 per 10 000 days at risk compared with 1.09 for 11 364 workers who were seronegative for these antibodies.[2]

Unfortunately, neither study can answer how long antibody protection will last because of natural infection. For this reason, vaccination against SARS-CoV-2 is recommended regardless of antibody status. How long the antibody protection provided by vaccines will last is also unknown. To know how long protection will last with antibodies because of natural infection or vaccination is something only time will tell.

Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients with Coronavirus Diseaes 2019: The Ivermectin in COVID Nineteen Study.
Juliana Cepelowicz Rajter et al., CHEST Vol 159,1:85-92, 2021
Conclusion: Ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement. Randomized controlled trails are needed to confirm these findings.

Covid-19 Wirkstoffkandidat – News & Views, Dr Internist, 62,2,Feb. 2021
Opaganib – Sphingosinkinase-2-Inhibitor – verringert bei ADS-Syndrom die Thrombose-Neigung, Virusreplikation und die Hyperimmunantwort

Remdesivir (Veklury®, 3.7.20 – EMA-Zulassung)
Info:www.rki.dehttps://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Erfahrungen_Umgang_Erkrankten.pdf?__blob=publicationFile. T.Feldt, C. Karagiannidis et. al. DOI 10.25646/6939.6
Bedingte EU-Zulasung für Patienten, sauerstoffpflichtig mit NIV (ACTT-I-Studie) – nur **frühe Entscheidung zur Therapie ist sinnvoll und effektiv!**
ACTT-II Studie zur Kombination von Remdesivir mit JAK 1 u 2 Inhibitor Baricitnib.
In der Frühphase von COVID-19 ist die Viruslast am höchsten, korreliert mit dem ct-Wert (cycle threshold) in der RT-PCR. Ein ct-Wert<30 weist auf eine relevante Viruslast hin (je niedriger der ct-Wert, je höher die Virus-Konzentration)..
Remdesivir ist ein Nukleotid-Analogon der Firma Gilead, entwickelt primär für die Behandlung von Infektionen mit Ebola- und Nipahviren, ein RNA-abhängiger RNA-Polymerase (RdRp)-Inhibitor, der die Replikation von tierischen und humanen Coronaviren (inkl. MERS-CoV und SARS-CoV-1) in respiratorischen Epithelzellen innerhalb von 12 Stunden hemmen kann mit einer deutlichen Reduktion der Virusreplikation, Besserung von klinischen Symptomen und Reduktion der Rate an Lungengewebeschäden. In Bezug auf diese Effekte war Remdesivir anderen antiviralen Substanzen wie Ribavirin oder Lopinavir/Ritonavir überlegen.
Loading Dose von 200 mg i.v. am Tag 1, Erhaltungsdosis von 100 mg i.v. durch weitere 4 Tage.
Monitoring der Leber- u. Nieren-Daten.

Pathological features of COVID-19-associated lung injury:a preliminary proteomics report based on clinical samples
Ling Leng, Ruiyuan Cao, Jie Ma et al.
Signal Transduction and Targeted Therapy (2020) 5:240. www.nature.com/sigtrans
https://doi.org/10.1038/s41392-020-00355-9 - 15.10.20

The COVID-19 pandemic has emerged as a global health emergency due to its association with severe pneumonia andrelative high mortality. However, the molecular characteristics and pathologicalfeatures underlying COVID-19 pneumoniaremain largely unknown. To characterize molecular mechanisms underlying COVID-19 pathogenesis in the lung tissue usinga proteomic approach, fresh lung tissues were obtained from newly deceased patients with COVID-19 pneumonia. After virusinactivation, a quantitative proteomic approach combinedwith bioinformatics analysis was used to detect proteomicchanges in the SARS-CoV-2-infected lung tissues. We identified significant differentially expressed proteins involved in avariety of fundamental biological processes including cellular metabolism, blood coagulation, immune response,angiogenesis, and cell microenvironment regulation. Several inflammatory factors were upregulated, which was possiblycaused by the activation of NF-κB signaling. Extensive dysregulation of thelungproteomeinresponsetoSARS-CoV-2infection was discovered. Our results systematically outlined the molecular pathological features in terms of the lungresponse to SARS-CoV-2 infection, and provided the scientific basis for the therapeutic target that is urgently needed tocontrol the COVID-19 pandemic.
DISCUSSION
At present, researches on epidemiology and pathology provided descriptive information in terms of clinical pathology of COVID-19-associated pneumonia. However, the landscape of molecular pathogenesis remains

to be elucidated. As known, the pulmonary gas exchange depends on the structural basis of the lung, especially the structure of the connection between the air in the alveoli and the blood in the alveoli capillaries. Our results revealed three kinds of changes occurred in the sub-structure of SARS-CoV-2-infected lung tissue. (i) Changes of surfactant proteins. Surfactant proteins have been identified as critical components of alveolar surfactant, each contributing to lung homeostasis via their distinct protein structures and activities.45We found all four surfactant proteins severely downregulated in lungs with COVID-19, which could lead to respiratory distress. Therefore, correcting loss of surfactants in clinical treatment may alleviate the respiratory symptoms of patients. (ii) Changes of cell–matrix adhesion. ECM of BM not only help epithelial cells or endothelial cells to adhere to lung tissue scaffold, but also support the polarity and function of cells as an important microenvironment. Results showed that most of the ECM on BM was lost in lung tissue of COVID-19 patients, which could lead to epithelial cells abscission and dysfunction. (iii) Changes of the core ECM. The ECM is the complex of hundreds of proteins that constitutes the scaffold of all multicellular organisms and provides a bioactive structure that fundamentally controls cell behaviour through chemical and mechanical signals. Core ECM including collagens, ECM glycoproteins, and proteoglycans that account for most of the components of lung tissue were found lost in the lungs with COVID-19, leading to the fundamental damage of mechanical characteristics of COVID-19 lung. Another important finding was the coagulation disorders in theCOVID-19 lungs. Hypercoagulation can lead to microvascular thrombosis and sepsis, as well as oxygen deficiency and vascular remodelling, leading to the loss of respiratory function. Sepsis leads to production of a large number of inflammatory cytokines, which in turn activate the coagulation pathways. In addition, we found that many immune-related signalling pathways (Fc-epsilon, NF-κB/NFKB2, and C-type lectin receptor) could be activated in the lungs of COVID-19 patients. Notably, the non-canonical NF-κB/NFKB2 pathway was significantly activated, which led to production of chemokines and cytokines, as well as lymphoid organogenesis. Activation of the non-canonical NF-κB/NFKB2 pathway was never reported in the cytokine storms caused by other respiratory viruses such as influenza; thus, this finding provided a unique insight to the pathogenesis of SARS-CoV-2. These key pathways may pose potential targets for drug design. Taken together, the pathogenesis of SARS-CoV-2 were, for the first time, characterized at the molecular level in clinical sample tissues. Multiple molecular features, including expiratory dyspnoea, coagulation disorder, immune activation, and ECM imbalance, are revealed in the lung tissues of COVID-19 patients, which explained the major clinical manifestations of the severe COVID-19 cases in terms of proteins. These findings provided systematical scientific insights into pathogenic mechanisms of SARS-CoV-2 in physiological state, which are helpful for the understanding of COVID-19pneumonia

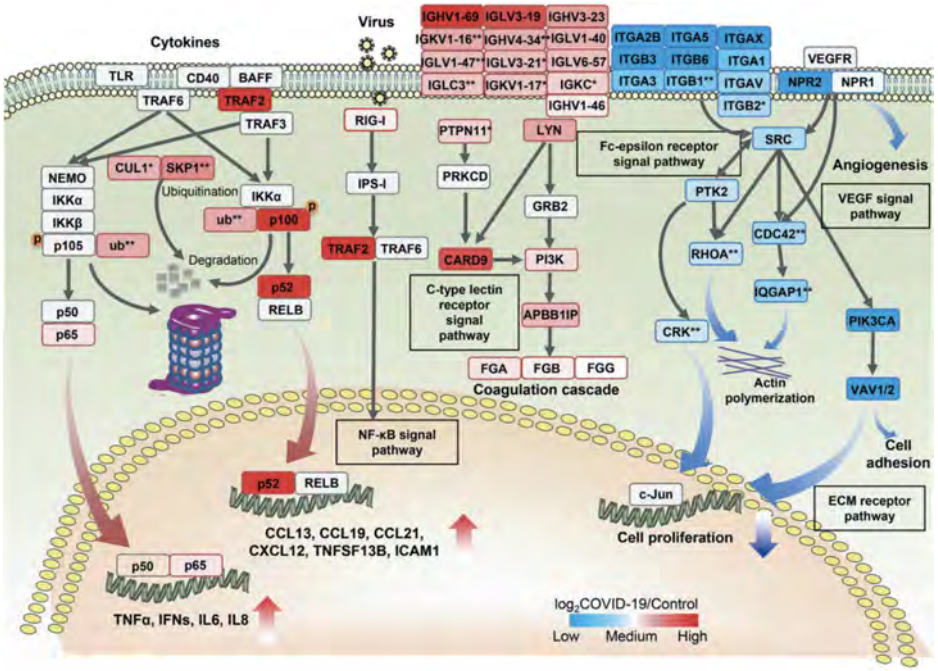


Fig. 2 Selected cellular pathways of upregulated and downregulated proteins in lungs of patients diagnosed with COVID-19. Colours of protein nodes indicate the measured $\log_2$ fold change of proteins expressed in COVID-19 and substrates of KEGG pathways. Red and blue boxes indicate proteins with increased and decreased abundance, respectively, in lung tissue from patients diagnosed with COVID-19 compared with control lung tissue

MedWiss.Online – 26.4.21
Studienübersicht zu Impfstoffen: CureVac, Novavax, Sputnik, BioNTech, Moderna, Astra-Zeneca
MedWiss – Die Impfungen schreiten voran und nehmen an Geschwindigkeit auf. Zu den in der EU zugelassenen Impfstoffen kommen bald womöglich weitere hinzu, zu denen bereits Studiendaten vorliegen. Wir listen hier eine Übersicht über die klinischen Studien der zugelassenen Vakzine (BioNTech/Pfizer, Moderna, AstraZeneca/Oxford und Johnson & Johnson) sowie der Impfstoffe, von denen wir eventuell in den nächsten Monaten mehr hören werden: Sputnik V (Russland, Adenovirus-Vektor), CureVac (Tübingen, mRNA) und Novavax (Protein-basiert).

Vier zugelassene Impfstoffe mit großer Studienteilnehmerzahl
Grundsätzlich stehen viele Daten zu allen zugelassenen Vakzinen bereit, die zeigen, dass sie hochwirksam vor schweren Erkrankungen mit COVID-19 sind. Aber welche Personengruppen werden getestet? Wie viel ist bereits zu den neueren Impfstoffen bekannt, in welchen Ländern werden diese getestet und wie viele Studien laufen aktuell? Zur Einschätzung der Forschung hilft unser Überblick über die klinischen Studien. Auch zu den neueren Vakzinen, die derzeit in Diskussion und teils im Zulassungsprozess sind, berichten wir über die vorliegenden Informationen. Gelistet werden hier alle Studien, in denen zumindest eine Rekrutierung von Teilnehmern begonnen hat.

Klinische Studien- und Teilnehmerzahl (Stand 23.04.2021)

BioNTech/Pfizer (Comirnaty) – clinicaltrials.gov unter "BNT162b"
Gelistete klinische Studien: 13 (Studiengruppen: Erwachsene, Schwangere, Jugendliche, Kinder, COVID-Genesene, Immungeschwächte) Teilnehmerzahl geplant: 61 148
Moderna – clinicaltrials.gov unter "mRNA-1273"
Gelistete klinische Studien: 9 (Studiengruppen: Erwachsene, Jugendliche, Kinder, bereits Geimpfte) Teilnehmerzahl geplant: 82 185
Oxford/Astra-Zeneca (Vaxzevria) – clinicaltrials.gov unter "AZD1222", "ChAdOx1 nCoV-19" und "ChAdOx1-S"
Gelistete klinische Studien: 11 (Studiengruppen: Erwachsene, HIV-Infizierte, Leberzirrhose, Jugendliche) Teilnehmerzahl geplant: 71 855
Johnson & Johnson – clinicaltrials.gov unter "Ad26.CoV2.S" und "JNJ-78436735"
Gelistete klinische Studien: 6 (Studiengruppen: medizinische Angestellte in Südafrika, Erwachsene, Jugendliche) Teilnehmerzahl geplant: 576 870

Zu den bereits zugelassenen Impfstoffen werden inzwischen zusätzlich zu weiter laufenden Studien zur Wirksamkeit und Verträglichkeit auch zunehmend spezielle Personengruppen in die Untersuchungen eingeschlossen. So ist die Impfung mit allen vier Impfstoffen inzwischen auch bei Jugendlichen in der Prüfung, die mRNA-Impfstoffe werden zudem auch bereits mit Kindern untersucht. BNT162b wird auch klinisch bei schwangeren Frauen, zuvor bereits infizierten Menschen und Patienten mit einer Immunschwäche untersucht. Mit mRNA-1273 werden Teilnehmer mit Zweitimpfung nach einer vorherigen Impfung mit einem anderen Vakzin untersucht. Auch HIV-Infizierte und Patienten mit Leberzirrhose stellen spezielle Patientengruppen dar, bei denen die Impfwirksamkeit, in diesem Fall mit AZD1222, gezielt klinisch untersucht wird.
Zu den beiden bereits in der EU zugelassenen mRNA-Impfstoffen stehen demnach bislang Daten von fast 130 000 Menschen zur Verfügung, die eine gute Einschätzung sowohl der Wirksamkeit als auch der Impfreaktion und möglicher Nebenwirkungen erlauben. Auch zu den beiden zugelassenen Vektor-Impfstoffen gibt es inzwischen jeweils über 70 000 Teilnehmer in klinischen Studien, von denen zunehmend auch Veröffentlichungen der Ergebnisse zu erwarten sind.

Drei Vakzine in Wartestellung: mRNA versus Adenovirus-Vektor versus Protein-Vakzin
Der mRNA-Impfstoff der Tübinger Firma CureVac wird aktuell bei der europäischen Arzneimittelbehörde EMA überprüft und könnte vielleicht noch im Mai oder Juni zugelassen werden. Die Studienübersicht zeigt fast 40 000 Teilnehmer, die allerdings im rollenden Verfahren nicht notwendigerweise bereits alle geimpft sind, sondern nach und nach die Daten liefern, die für eine Zulassung sprechen können. Auch der russische Impfstoff Sputnik wird viel diskutiert und als möglicher zukünftiger Kandidat für eine Zulassung gehandelt. Auch hier sollen bislang ca. 40 000 Teilnehmer in Studien eingeschlossen werden. Der dritte Kandidat ist der Protein-Impfstoffe der Firma Novavax, von dem bereits verschiedene vielversprechende Daten veröffentlicht wurden. Dieses Vakzin stellt in der EU den ersten Vertreter der Protein-basierten Impfstoffe gegen das neue Coronavirus dar. Zu allen drei Impfstoffen läuft aktuell ein rollendes Verfahren zur möglichen Zulassung in der EU.

Klinische Studien- und Teilnehmerzahl (Stand 23.04.2021)
CureVac – clinicaltrials.gov unter "CVnCoV": Gelistete klinische Studien: 4 (Südamerika/Europa), Teilnehmerzahl geplant: 39 974
Gamaleya Research Institute – clinicaltrials.gov unter "Sputnik" oder „Gam-COVID"
Gelistete klinische Studien: 9 (Indien/Russland), Teilnehmerzahl geplant: 41 754
Novavax – clinicaltrials.gov unter „NVX-CoV2373"
Gelistete klinische Studien: 4 (Großbritannien/Südafrika/USA/Australien/Südamerika), Teilnehmerzahl geplant: 50 819

Sämtliche hier aufgeführten Vakzine sowie die bislang in der EU noch nicht geprüften BBV152 (Covaxin, Indien), Sinopharm Vero Cell COVID-19 Vakzin (Sinopharm, China) und Sinovac COVID-19 Vaccine (CoronaVac, China) sollen zusätzlich in einer gemeinsamen Studie mit Blick auf kurzfristige Impfeffekte, Nebenwirkungen und die langfristige Sicherheit der Impfungen verglichen werden. Hintergrund ist das weltweit relevante Thema der Impfzweifel, dem mit einer unabhängigen, globalen Studie mit konkreten Daten begegnet werden soll.Die Teilnehmerzahl in den klinischen Studien ist mehr als beeindruckend, wenn man bedenkt, dass diese Prüfungen der Impfstoffe erst seit Monaten, statt wie sonst seit Jahren, durchgeführt werden. Solche großen Studien konzentriert weltweit zu stemmen, ist nur mit sehr großem organisatorischen Aufwand zu leisten. Auch hier, wie in allen anderen Bereichen der Gesellschaft, wurde und wird also immer noch Beachtliches geleistet.

Bemerkung: viel Text,keine Aussage

Medscape.com 29.4.21
Safty of AstraZeneca Covid-19 Vaccine: prothrombotic disorder and thrombocytopenia, mainly in younger individuals – *appears like* heparin-induced thrombocytopenia (**HIT**).
Cit. Prof. Andreas Greinacher, Greifswald: prothrombotic disorder caused by platelet-activating antibodies directed against PF4.

Discrimination of COVID-19 from inflammation –induced cytokine storm syndromes by disease-related blood biomakers
Christoph Kessel et al., accept. for publication doi: 10.1002/ART.41763
Serum biomarker profiles clearly separate Covid-19 from MAS (macrophage activation syndrome) or sHLH, (secondary hemophagocytic lymphohistiocytosis) which questions the significance of systemic hyperinflammation following SARS-CoV-2 infection as well the efficacy of drugs tarageting key molecules and pathways specifically associated with systemic cytokine storm conditions in the treatment of covid-19.
Found: **dramatic activation of the IL-18 interferon (INF)-γ axis,** increased serum levesl of IL1 redeptor antagonist (IL-1 Ra), intracellular adhesion molecule 1 (ICAM-1) and IL-8, strongly< reduced levels of soluble Fas ligand (sFasL).

Clinical strategies for the blockade of IL-18 in inflammatory bowe. Disease
Takanori Kanai, et al., DOI: 10.2174/1389450113149990006
Interleukin 18 (IL-18) is an IL-1 super family cytokine that is involved in infection, inflammation and autoimmune diseases. Mounting evidence suggests that IL-18 exert a dual role in inflammation and homeostasis. IL-18 can act as a promoter of T cell immunities, such as type 1 and 17 helper T cell responses, and thus enhances T cell-mediated inflammation, whereas IL-18 increases the barrier function and regeneration of epithelial cells and protects the host from inflammatory stimuli. Although the functional role of IL-18 in regulation of inflammation remains controversial, accumulating evidence indicates the contribution of IL-18 to the pathogenesis of inflammatory bowel diseases (IBD). For example, levels of serum and/or mucosal IL-18 and IL-18 binding protein are elevated in the patients with IBD. Furthermore, polymorphisms in IL-18 and IL-18-related molecules, such as the IL-18 receptor and/or an IL-18 activator NLRP3, genes are found in the patients with IBD. Thus, these preclinical data imply that IL-18 can be a novel therapeutic target for the treatment of IBD. In this review, we focus on IL-18 biology and physiological roles in animal models and human IBD, to provide an outline for development of IL-18 blockade strategies.

Sinusvenenthrombose nach Covid-19 Impfung
Bewertet als VITT Vakzin-induzierte, immun-vermittelte thrombotische Thrombopenie mit Hirnvenen-Thrombose. Nach Impfung mit Johnson-6Johnson-Wirkstoff und mit dem Astra-Zeneca-Vacczin.

Therapie: nicht-heparin-artige Antikoagulantien, wie Argaroban, Bivalirudin, Danaparoid, Fondaparinux oder ein direktes orales Antikoagulans (Marcoumar) – keine Heparin-Produkte- gleichartiges Krankheitsbild wie bei Heparin-induzierter Thrombopenie.
Bewertung von Basis-Labordaten mit Gerinnung (Fbg, D-Dimer), PF4-Ak; MRT –Gehirn mit Venogramm.

CHEST, Vol 159,3 (März 21):
A Clinical Blueprint for Post-Coronavirus Disease 2019 RECOVERY. Learning form the Past, Looking to the Future.
Sonali Narain et al., Covid-19 Research Consortium, p 949.

Impact of Corticosteroids in Coronavirus Disease 2019 Outcome: Systemic Review and Meta-analysis.
Edison J. Cano et al., p 1019.

System-Wide Strategies Were Associated With Improved Outcome in Critically Ill Patients With Coronavirus Disease 2019: Experience From a Large Health-Care Network.
Peng Zhang, et al., p 1072.

Hypercoagulability in ICU Patients With Coronavirus Disease 2019 With Respiratory Failure Results in Increased Prevalence of Venous Thromboembolic Disease.
Sarah A. Long et. Atl., p 1208

Störung der Mikrozirkulation bei COVID-19
A. Rovas, Ph Kümpers. Med. Klein Intensivmed Notfmed 2021,116:530-534.
Die Pathophysiologie des Covid-19 Infektes ist gekennzeichnet durch eine micro-vasculäre Schädigung der Endothelzellen durch Bindung an vasculär exprimierte ACE2-Rezeptoren. Die endotheliale Glykokalyx reguliert die Homöostase der Mikrozirkulation. Die Schädigung der Glykokalyx spielt eine zentrale Rolle bei der akuten und chronischen vasculären Entzündungs, wie bei bakterieller Sepsis als initialer Trigger der Organdysfunktion. Im Tiermodell kann durch Hemmung des enzymatischen Glykokalyxabbaus das Auftreten einer akuten Lungenschädigung vollständig verhindert werden.
Bewertung der microvasculären bzw. endothelialen Schädigung durch Bestimmung von Endothel- u. Glykokalyx-Markern im Plasma (Syndecan-1, Hyaluronsäure) und Visualisierung der sublinqualen Microgefäße mittels Intravital-Mikroskopie zum Erkennen der Eindringtiefe der Erythrocyten in die endotheliale Matrix. Somit erfolgt eine Analyse der Kapillardichte per Durchmesserklassen (4 – 25 µm Gefäß-DM).
Die Kapillarschädigung bei COVID-19 Patienten zeigt sich an der Abnahme der Kapillardichte und einer ausgeprägten Schädigung der endothelialen Glykokalyx. Prädiktiv für die Mortalität sind die Dicke der endothelialen Glykokalyx, der zirkulierende Spiegel von ADMTS13 (von-Willebrand-Faktor-spaltende Proteinase) und der vasculäre endotheliale Wachstumsfaktor A (VEGF-A), ergänzt durch ACE2 (angiotensinkonvertierendes Enzym 2) und D-Dimere. Prädiktiv für thrombo-embolische Ereignisse waren bei mittelschweren bis schweren ARDS Syndecan-1 u. D-Dimere-Spiegel.
Durch einen weiteren Mechanismus kann die Glykokalyx enzymatisch abgebaut werden: Bindung von zirkulierendem Angpt-2 (Angiopoietin-2) am endothelial exprimierten Tie2-Rezeptor aktiviert dieSekretion von Heparanase aus zellulären Speicherpools. Somit war ein erhöhter Angpt-2 Spiegel bei Covid-19 Patienten zu messen.

X/2021:
Welcher Impf-Titer (SARS-Covid-19 Ak Spike): >300 BAU/ml sollte sicher schützen nach meiner Meinung. Ab 0.8 BAU/ml positiv, ab 15 BAU/ml neutralisierende Ak.

Feng, S. et al. (2021): Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med 2021 Sep; DOI: 10.1038/s41591-021-01540-1.
Cit.: Dr. Christian Kretschmer, 06.10.2021
Die Forscher untersuchten die Antikörpertiter von Personen, die zweimal mit dem COVID-19-Impfstoff von AstraZeneca geimpft wurden. Genauer ermittelten sie die bindenden und neutralisierenden Antikörper 28 Tage nach der zweiten Dosis bei infizierten und nicht-infizierten Impfstoffempfängern. Zum Wirksamkeitsnachweis der Impfung wurden die Schwellenwerte für vier Immunmarker (Anti-Spike-IgG, IgG-Antikörper gegen die Rezeptor-Bindungsdomäne [RBD], Pseudovirus-Neutralisierung und Corona-Lebendvirus-Neutralisierung) ermittelt, die mit dem Schutz vor einer symptomatischen Infektion in Verbindung stehen.
Unter den 4.372 Teilnehmern in der Korrelatspopulation gab es insgesamt 174 Durchbruchsfälle einer

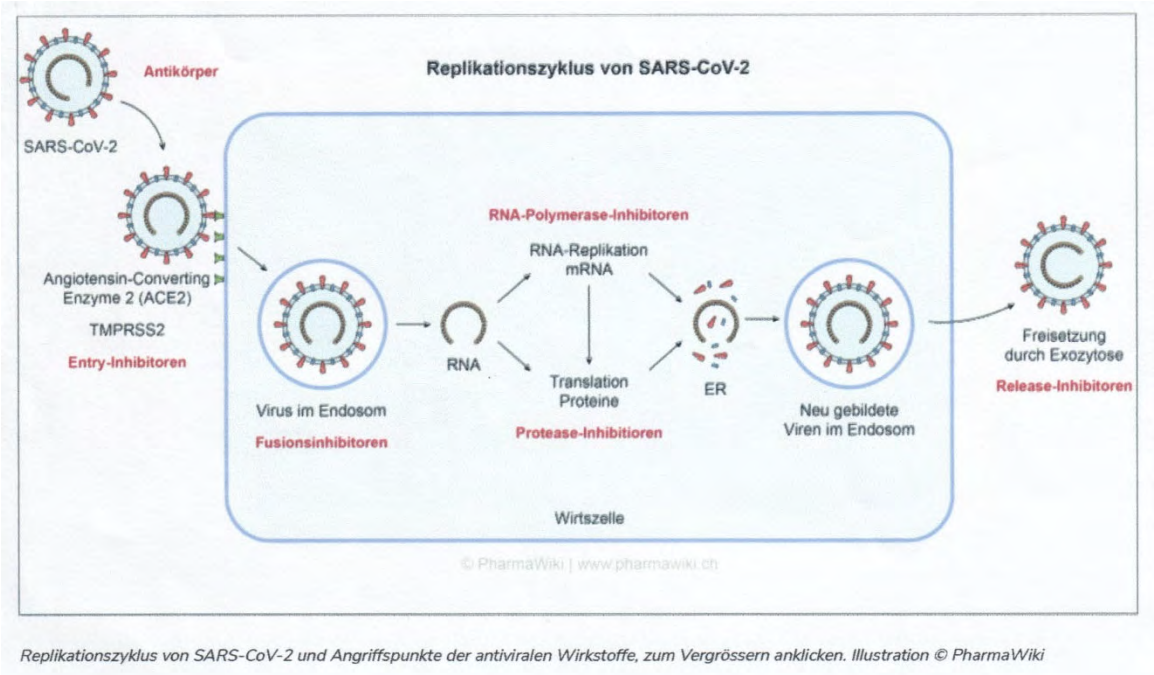
SARS-CoV-2-Infektion. Im Ergebnis waren höhere Werte aller Immunmarker mit einem geringeren Risiko für eine symptomatische COVID-19-Erkrankung assoziiert.
Eine 80-prozentige Schutzwirkung gegen eine symptomatische Infektion mit der Alpha-Variante von SARS-CoV-2 werde mit 264 bindenden Antikörpereinheiten (BAU)/ml von gegen das Spike-Protein von SARS-CoV-2 gerichteten IgG-Antikörpern und 506 BAU/ml für Anti-RBD-Antikörper erzielt, so die Studienautoren. Mit dem Auftreten von asymptomatischen Infektionen korrelierten die Immunmarker indes nicht (Signifikanzniveau 5%).
Die Ergebnisse der Studie zeigen, dass es für keinen der untersuchten Immunmarker einen definitiven Schwellenwert gibt, der auf eine sichere Immunität hindeutet. Eine verringerte Infektionswahrscheinlichkeit liegt im Durchschnitt aber bei einer höheren Immunreaktion vor. Die einzelnen Immunkorrelate könnten je nach Altersstruktur variieren. Dies war in der vorliegenden Studie aufgrund der geringen Anzahl älterer Erwachsener nicht überprüfbar.
Die ermittelten Antikörperspiegel bilden lediglich einen punktuellen Zustand ab, und zwar exakt 28 Tage nach der zweiten Impfstoffdosis. Dieser soll in den folgenden vier bis sechs Monaten die Wirksamkeit und Immunogenität gewährleisten. Für Angaben zur Dauerhaftigkeit der Antikörper und des Langzeitschutzes nach der Impfung werden weitere Untersuchungen benötigt.
Ein anderes Problem sind die großen Konfidenzintervalle bei sehr niedrigen oder sehr hohen Titern, etwa ein 95%-KI von 108–806 bei den Anti-Spike-IgG-Werten. Für eine genauere Schätzung sind weitere Studien mit größeren Populationen erforderlich.
Die Studie bezieht sich nur auf den Impfstoff von AstraZeneca und die zum Studienzeitpunkt vorherrschende Alpha-Variante. Die derzeit mehrheitlich kursierende Delta-Variante ist jedoch rund 50 Prozent ansteckender. Darüber hinaus verwenden andere Impfstoffhersteller andere Impfstofftechnologien. Das Verhältnis zwischen Antikörper- und T-Zell-Reaktionen kann je nach Art des verwendeten Impfstoffs unterschiedlich ausfallen. Die Ergebnisse können somit nicht auf alle zugelassenen COVID-19-Vakzine und nicht auf alle Virus-Varianten übertragen werden.

XI/21:
EMA - CHMP: vorgesehene Freigabe für neue anti-Covid-Medikamente, monoklonale Antikörper Ronapreve (Roche, Schweiz) u. **Regkirona** (Redanvimab – Celltrion, Südkorea). Einsetzbar im frühen Stadium der Infektion, antivirale monoklonale Ak. Bislang war nur Remdesivir (Veklury) in der EU zugelassen – aber für schwer Erkrankte (ungenügende Wirkung bei später Intervention – Bemerkung). Ronapreve besteht auf zwei Ak (Casirivimab u. Imdevimab)
Ronapreve and Regkirona are the first monoclonal antibody medicines to receive a positive opinion from the CHMP for COVID-19 and join the list of COVID-19 products that have received a positive opinion since Veklury (remdesivir) was recommended for authorisation in June 2020.
Monoclonal antibodies are proteins designed to attach to a specific target, in this case the spike protein of SARS-CoV-2, which the virus uses to enter human cells. In reaching its conclusion, the CHMP evaluated data from studies showing that treatment with Ronapreve or Regkirona significantly reduces hospitalisation and deaths in COVID-19 patients at risk of severe COVID-19. Another study showed that Ronapreve reduces the chance of having COVID-19 if a household member is infected with SARS-CoV-2, the virus that causes COVID-19. The Committee has giben advice to assist EU Member States in deciding on the early use of these medicines. This means the medicines were already available to some patients in the EU.
The safety profile of both medicines was favourable with a small number of infusion-related reactions, and the CHMP concluded that the medicines' benefits are greater than their risks for their approved uses.

Study data for Ronapreve
A main study involving patients with COVID-19 who did not require oxygen and were at increased risk of their illness becoming severe showed that treatment with Ronapreve at the approved dose led to fewer hospitalisations or deaths when compared with placebo (dummy treatment). Overall 0.9% of patients treated with Ronapreve (11 out of 1,192 patients) were hospitalised or died within 29 days of treatment compared with 3.4% of patients on placebo (40 out of 1,193 patients).
Another main study looked at the benefits of Ronapreve for prevention of COVID-19 in people who had close contact with an infected household member. Ronapreve was found to be effective at preventing people from getting infected and developing symptoms after contact: amongst people who tested negative for SARS-CoV-2 following contact, fewer people given Ronapreve developed symptoms within 29 days of their test results compared with people given placebo (1.5% (11 out of 753) for Ronapreve compared with 7.8% (59 out of 752 people) for placebo).
Ronapreve was also found to be effective at preventing symptoms in infected people. Amongst the people who tested positive for SARS-CoV-2 after contact, 29% of people (29 out of 100) who received Ronapreve developed symptoms compared with 42.3% of people (44 out of 104) who received a placebo.

Study data for Regkirona
A main study in patients with COVID-19 showed that Regkirona treatment led to fewer patients requiring hospitalisations or oxygen therapy or dying when compared with placebo. Among the patients at increased risk of their illness becoming severe, 3.1% of patients treated with Regkirona (14 out 446) were hospitalised, required supplemental oxygen or died within 28 days of treatment compared with 11.1% of patients on placebo (48 out of 434).

Molnupiravir
Molnupiravir ist ein antiviraler Wirkstoff aus der Gruppe der RNA-Polymerase-Inhibitoren für die medikamentöse Vorbeugung und Behandlung der Coronaviruskrankheit Covid-19. Die Effekte beruhe auf der Hemmung der RNA-abhängigen RNA-Polymerase des Virus. M. ist ein Prodrug, das zunächst im Plasma zu einem Metaboliten hydrolysiert und anschließend von Kinasen triphosphoryliert wird. Das Triphosphat ist der aktive Wirkstoff, welcher der RNA-Polymerase als falsches Substrat dient. M kann peroral verabreicht werden. Zulassung in England unter Lagevrio. Entwickelt an der Emory University, Atlanta Georgia. Dosiserung: 2x1 Kps durdch 5 Tage.



Replikationszyklus von SARS-CoV-2 und Angriffspunkte der antiviralen Wirkstoffe, zum Vergrössern anklicken. Illustration © PharmaWiki

II/2022
The US Food and Drug Administration (FDA) also recently granted the first emergency use authorisation for the monoclonal antibody combination **tixagevimab–cilgavimab** (AstraZeneca) as pre-exposure prophylaxis in vulnerable populations. Pfizer's oral antiviral drug **nirmatrelvir–ritonavir** was also recently FDA approved for treatment of mild-to-moderate COVID-19.

The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity

Marcin F Osuchowski, Martin S Winkler*, Tomasz Skirecki, Sara Cajander, Manu Shankar-Hari, Gunnar Lachmann, Guillaume Monneret, Fabienne Venet, Michael Bauer, Frank M Brunkhorst, Sebastian Weis, Alberto Garcia-Salido, Matthijs Kox, Jean-Marc Cavaillon, Florian Uhle, Markus A Weigand, Stefanie B Flohé, W Joost Wiersinga, Raquel Almansa, Amanda de la Fuente, Ignacio Martin-Loeches, Christian Meisel, Thibaud Spinetti, Joerg C Schefold, Catia Cilloniz, Antoni Torres, Evangelos J Giamarellos-Bourboulis, Ricard Ferrer, Massimo Girardis, Andrea Cossarizza, Mihai G Netea, Tom van der Poll, Jesús F Bermejo-Martín, Ignacio Rubio*

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The zoonotic SARS-CoV-2 virus that causes COVID-19 continues to spread worldwide, with devastating consequences. While the medical community has gained insight into the epidemiology of COVID-19, important questions remain about the clinical complexities and underlying mechanisms of disease phenotypes. Severe COVID-19 most commonly involves respiratory manifestations,

although other systems are also affected, and acute disease is often followed by protracted complications. Such complex manifestations suggest that SARS-CoV-2 dysregulates the host response, triggering wide-ranging immuno-inflammatory, thrombotic, and parenchymal derangements. We review the intricacies of COVID-19 pathophysioloZgy, its various phenotypes, and the anti-SARS-CoV-2 host response at the humoral and cellular levels. Some similarities exist between COVID-19 and respiratory failure of other origins, but evidence for many distinctive mechanistic features indicates that COVID-19 constitutes a new disease entity, with emerging data suggesting involvement of an endotheliopathy-centred pathophysiology. Further research, combining basic and clinical studies, is needed to advance understanding of pathophysiological mechanisms and to characterise immuno-inflammatory derangements across the range of phenotypes to enable optimum care for patients with COVID-19.

EU-zugelassene Impfstoffe gegen Covid-19 – Der Internist 11, 20201, 1192. Anahita Fathi et al.

BioNTech/Pfizer	mRNA	ab 12 Jahren	seit 12/20	2 Vacc in 2-3 Wochen	Wirkung bis zu 95%
Moderna	mRNA	ab 12 Jahren	seit 01/21	2 Vacc in 4-6 Wochen	bis zu 95%
AstraZenaca	Vector	ab 18 Jahren	seit 01/21	2 Vacc in 9-12 Wochen	bis zu 80%
Johnson&Johnson	Vektor	ab 18 Jahren	seit 03/21	1 Vacc	bis zu 70%

Nebenwirkungen: lokale Schmerzen, grippale Symptome
Bei adeno-viralen Vektor-Impfstoffen: Kapillarlecksyndrom, Thrombose-mit-Thrombocytopenie TTS
Bei mRNA-Impfstoffen Myokarditis u. Perikarditis
Kontraindikation: Allergie, anaphylaktischer Schock

Conclusion – mit updates – 15.3.20 – 20.10.22 (mixed GER/ENG)

Pdf-File durchsuchbar für Citationen

Minimale Basis-Durchseuchung (mit Antikörper) gegen gering-pathogene Corona-Viren auch in Europe
pathogene Coronaviren in China (Fledermäuse, Wildkatzen) - **SARS-CoV-2**,
in Arabien (Dromedare) - MERS-CoV
Quelle durch Fernreisen, Verlagerung der Produktionsstellen, Fernhandel – alles muss in China billig produziert werden – die Folgen

Basis-Schutz durch *Grippe-Impfung im Allgemeinen* zur rascheren Antikörper-Entwicklung
Ein *höherer Vitamin-D-Spiegel* sollte die Widerstandsfähigkeit gegen die virale Infektion erhöhen
Dzt. keine spezifische Prävention – *Vaccination* in Entwicklung (cave Spontan-Mutationen)
Serum-Therapie (Serum von Patienten mit überstandener Krankheit – China)

Erkenntnisse zur **Virus-Pathologie**: *Andock-Mechanismus* des Virus an der Wirtszelle, Mechanismus der *Vermehrung in der Wirtszelle*, Folgen der *Entzündungsreaktion* (Gewebeschaden, aktivierte Gerinnung u.a., Superinfektion durch Bakterien…)
Virus entry depends on ACE2 and TMPRSS2 and is blocked by a Clinically Proven Protease Inhibitor (HIV-Therapeutika)

Therapiekonzepte
Chloroquine; antiviral treatment of human pathogen coronavirus: Proteasen-Hemmer *Lopinavir/Ritonavir* als Kombinations-Präparate Kaletra Filmtbl 200/50 mg; *Ritonavir* Norvir Filmtbl 100 mg *als Monosubstanz (HIV-Medikation),* Nucleoside analogues, Neuraminidase inhibitors (*Tamiflu*), *Remdesivir (gegen Ebola)*, Peptide (EK1), Arbidol (Umifenovir, Rus.), RNA synthesis inhibitors (such as TDF, 3TC), anti-inflammatory drugs (such as hormones and other molecules), Chinese traditional medicine

Minderung der heftigen Infekt-Reaktion:
a) unspezifische Entzündungs-Hemmung via *Vit C* (Ce-Limo 1.0 g), Vit E; *Paracetamol (Mexalen),* Claversal (Mesalazin) 2-4 x 500 mg, aggressiv gegen IL1-, IL6-Produktion
b) Schutz gegen Thrombose u. Embolie – aktivierte Gerinnung (Thrombo-ASS, Lovenox…) – Endothel-Schaden (Thrombocyten, Fibrinogen, D-Dimer, Lysefähigkeit ect.).
c) Monitoring des Gasaustausches (SaO2), pO2 erhöhen (NIV), Anti-Ödem-Maßnahmen
Gefährdete Personen isolieren: Immunglobulin-Mangel (IgG, IgA, γ-Globulin), Schwäche der B/T-Zell-Lymphocyten, Chemo-Therapie; Patienten mit vorbestehenden Organ-Schäden von Lunge, Nieren und Herz – selektiver Virus-Befall als zusätzliche schädigende Noxe führt zum Organ-Versagen

Übertragungs-Risiko Einschränken
UV-Licht-Sperren, Kontaminations-Schutz (Hände-Desinfektion, *Gesicht* waschen, Mundspülung; Ausatmung, sonstige Ausscheidungen), Isolation
aber: eine kontrollierte Durchseuchung der Bevölkerung mit SARS-CoV-2 *wäre* günstig gegen die Pandemie, optimal jedoch Vaccination, Immunisierung.

Update: 22.3.20

Zur Infekt-Kontrolle und zur Minimierung des Organ-Schadens (Lunge - SARS severe acute respiratory syndrome) gilt es die Infekt/Entzündungs-Reaktion (**overexuberant inflammatory response**) abzudämpfen, den resultierenden Organ-Schaden – ist unabhängig von der Virus-Last (SARS-CoV-2).

a) Effekt auf clathrin-gesteuerte *Endocytosis* durch Inhibitoren der numb-associated kinase (NAK family, including AAK1 und GAK): ***Baricitinib***, Olumiant 4 mg Filmtbl.

b) Medikation mit *antiviraler und anti-inflammatorischer Wirkung*: selektive JAK-Inhibitoren, wie ***Baricitinib*** (Olumiant), Fedratinib u. Ruxolitinib (Jakavi) – bereits eingesetzt bei rheumatischer Arthritis und Myelofibrose.
Die heftige Entzündungsreaktion beruht auf einen *Cytokinin-Sturm* (IL-6 mit Interferon γ).
Die Wahl wäre neben unspezifischen Entzündungshemmern (cave NSAR, wie Diclofenac, Ibuprofen bei Hypertonie, Herzschaden u. Magen-Problemen) zusätzlich mit Baricitinib 10 mg/die, Tocilizumab iv. zu treffen (neben allgemeinen Maßnahmen gegen Inflammation, s. oben).

Als Therapie-Option gegen COVID-19 bietet sich somit die Kombination von Baricitinib (Olumiant) mit antiviralen Drugs an, wie Lopinavir, Ritonavir (Kaletra; Norvir) u. Remdesivir an.

Somit kann/wird die virale Infekt-Power, die virale Replikation und die fehlgeleitete Entzündungsreaktion via Interleukinen (IL-6) unter Kontrolle gebracht werden. Die Notwendigkeit zu maximaler Intensiv-Therapie (Respirator, ECMO) kann damit reduziert werden.

Ergänzung: 23.3.20
Therapie-Versuche starten im Ausland (EU)
in Austria antivirale Drugs (Kaletra, Norvir) NICHT verfügbar!
Olumiant ist lieferbar

Ergänzung: 27.3.20
*Inhibition der Adhäsion – Camostat NI-03 (Japan, Einsatz bei chron. Pankreatitis), siehe Andock-Mechanismus obenstehend – neue Option gegen COVID-19
*Krankheits-Immun-Modulation durch *Azithromycin* (Zithromax)
*früher Einsatz von Chloroquine (nicht verfügbar in AUT) gegen Virus-Aktivierung in die Zelle
*bei manifester Erkrankung (Verschlechterung) *Hemmung des IL-6 Sturmes*:
Baricitinib - *Olumiant (tbl),* Tocilizumab - *Roactemra* (i.v.) verfügbar

Ergänzung: 2.4.20
***Avigan Favipiravir** als Proteasen-Hemmer als möglicher Virus-Replikations-Hemmer (Jap) – entwickelt gegen Ebola. Siehe Wikipedia als News-Quelle.
Sonstige Proteasenhemmer gegen HIV-Infekt.

Viele Ankündigungen, Wunschvorstellungen zur Therapie.

Meinungen: 7.4.20
Vorrangiges Ziel: rasche *Identifikation und Isolation der Infizierten*, Verhinderung der Ansteckung, Kontamination (*Replikationsfaktor* R soll gegen 0 gehen, anfangs R >>1, dann <1, u.a. 0.5 – d.h. kein weiterer Infizierter – social distancing, isolation).
Problem: Erkennen der *Infizierten mit ‚stummen', subklinischem Verlauf*,
Identifikation der Kontakt-Personen zur Organisation einer effektiven Quarantäne und Verhinderung der Ausbreitung – ‚superspreader'.
Cave Latenz zwischen Infektion und Beginn manifester Anzeichen der Erkrankung
Bewertung verordneter Maßnahmen - AUT, EU-Staaten…

Bei ungenügender Eindämmung der Epidemie droht der Zusammenbruch der medizinischen Versorgung für spitals- und intensiv-pflichtigen Patienten.
Die ‚sorglose Duldung' einer *Durchseuchung* zum Erreichen einer ‚Herdenimmunität' muss als Fehlentscheidung mit katastrophalen Folgen angesehen werden.
Die Möglichkeit zur *Vaccination*, zur aktiven Immunisierung, wird in absehbarer Zeit nicht ausreichend zur Verfügung stehen (anfangs 2021?).

Für eine *pharmakologische Intervention* gibt es noch keine *statistisch gesicherte Medikation* zur Auswahl. Eine Prüfung von Substanzen gegen Placebo und doppel-blind wäre m.E. ethisch nicht zu rechtfertigen bei der Dringlichkeit zur Therapie-Findung.
Vernünftig ist der WHO-Ansatz ausgewählte Substanzen in der Beurteilung der Wirksamkeit gegenüber zu stellen (remdesivir, chloroquine/ hydroychloroquine, combination of two HIV drugs – lopinavir u. ritonavir and this combination with interferon-beta, favipiravir may be added to the trial). „The design ist not double-blind, we have to *balance scientific rigor against speed*".

Berichte: 12.4.20
Vorbeugung - Therapie – Risiko
Vaccination against viral and bacterial infectious diseases, vitamin D supplementation
Problem der stummen Infektion und folglich die Zahl der **anonymen Infekt-Träger und Virus-Ausscheider (spreader)**, cave persistierende Virus-Ausscheidung nach überstandener Infektion (Quarantäne nach überstandenem Infekt), **Monitoring der Kontakt-Personen (App).**
Virus-Kontakt und unausweichlicher Infekt? Ursache für stummen, milden und deletären Verlauf?

Pathophysiologie des Covir-Infektes:

Cytokine dysregulation (L1, L6 u.a.), T-cell repertoire reduction (CD3/CD8), Endothel-Schäden, male population, relatively reduced antiviral immunity, hyperinflammation,
immune dysregulation (IgA-deficit u.a.).
Blocking interleukin-1: anakinra (IL-1 receptor antagonist), rilonacept, canakinumab (neutralizing monoclonal anti-IL-1β)
Interleukin-6 inhibition: tocilizumab (improved endothelial function; promoter of TH17 cells, inhibitor of T-regulatory cells – humanized receptor antibody), infliximab (remicade®)

Intervention – manifester Infekt: gegen Inflammation (overshoot), allgemeine Medikation (s. oben – Vit C, Perfalgan-Mexalen, Claversal u.a.), spezifische Intervention gegen Cytokinin-Sturm (anti-IL1, -IL6 u.a.), Schutz gegen Superinfektion (viral, bacteriell), Gerinnungs-Thrombose-Schutz, Gewebe-Ödem (Aldosteron-Antagonist), subtile Beatmungstechnik - O2-high-flow-ventilation, NIV, ECMO; Schutz gegen pulmonary fibrosis (pirfenidone, nintedanib), Schutz der Myokardfunktion (Vastarel, Sartane als AT1-Rezeptor-Antagonistén)

Fatal risk: bacterial infection, mal nutrition, organ damage to lung heart, kidney and liver.
Disease progression marked by: fever, leucocytosis, acute phase proteins such as elevation of SAA (serum amyloid A), PCT (calcitonin) CRP (Entzündungsmarker) and Ferritin, Troponin (heart muscles damage), D-Dimer (embolic-thrombotic activity), LDH, Lactatacidose, Lymphopenie.

Kommentar: 21.4.20
Die Lunge ist das hauptsächlich durch den Covir-19 Infekt betroffene Organ mit einer teils überschießenden Entzündungs-Reaktion und nachfolgendem Organ-Schaden. Es folgt die Notwendigkeit den Gasaustausch durch Beatmung mit höherem O2-Atmungsgemisch und Beatmungsdruck zu sichern. Anhaltende Gewebeveränderungen können noch Wochen nach der Akutphase durch bildgebende Verfahren (wie bei jeder Pneumonie) beobachtet werden mit Zeichen der Inflammation und einer aktivierten Blutgerinnung. Funktionelle Störungen betreffen eine Strömungsbehinderung in den kleineren Atemwegen, Steifigkeit des Lungengewebes, ein Mismatch zwischen Belüftung und Durchblutung mit Behinderung des Gasaustausches (CO2, O2) und Beeinträchtigung des Lungenkreislaufes mit erhöhten Druckwerten. Als Folge einer chronischen Entzündung können sich Gewebeveränderungen im Sinne einer Lungenfibrose entwickeln.

Durch eine subtile Funktionsdiagnostik nach dem Infekt sollten anhaltende Störungen erkannt und beeinflussbar werden, um die kardio-pulmonale Belastbarkeit wiederherzustellen (s. Herz-Lungen-Labor Prof. Reiterer).

Der komplexe Reaktionsmechanismus der Epithel-Zelle im Bronchialbaum kann aus der Graphik abgelesen werden (Or Kalchiem-Dekel, Xianglan Yao and Stewart J. Levine. CHEST 2020; 157(1):26-33), wobei sich diese Arbeit auf die Pathobiologie bei type 2-low neutrophilic asthma bezieht (selected pathways mediating airway inflammation) – National Institute of Health, Bethesda, MD.

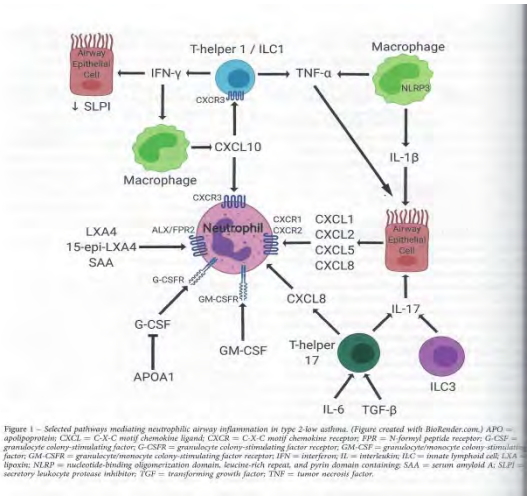


Figure 1 – Selected pathways mediating neutrophilic airway inflammation in type 2-low asthma. (Figure created with BioRender.com.) APO = apolipoprotein; CXCL = C-X-C motif chemokine ligand; CXCR = C-X-C motif chemokine receptor; FPR = N-formyl peptide receptor; G-CSF = granulocyte colony-stimulating factor; G-CSFR = granulocyte colony-stimulating factor receptor; GM-CSF = granulocyte/monocyte colony-stimulating factor; GM-CSFR = granulocyte/monocyte colony-stimulating factor receptor; IFN = interferon; IL = interleukin; ILC = innate lymphoid cell; LXA = lipoxin; NLRP = nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain containing; SAA = serum amyloid A; SLPI = secretory leukocyte protease inhibitor; TGF = transforming growth factor; TNF = tumor necrosis factor.

Update mit Obduktionsbefunden, Cytokine Storm Syndrome, wie III/20 von mir diskutiert (s. oben).

Im Verlauf entwickeln sich Treatment guidelines (u.a. NIH) mit Bezug auf erste Studien-Daten – aber keine klare Stellungnahme und Empfehlung zum Einsatz diverser Substanzen.

Update: **21.5.20**
Ausbreitung der Endemie gehemmt durch Isolation der Betroffenen und potentieller Kontakt-Personen (ziviles shut down) – Vorbeugung durch Abstand halten und Mundschutz. Weiterhin mutmaßlich aktive Spreader, durch milde Symptomatik nicht erkennbar, Infekt-Cluster somit konsequent isolieren (Quarantäne) – Problematischer Widerstand gegen eine lückenlose Kontakt-Erfassung der Virus-Träger/Infizierten (**Trace-**

App). Entlassung aus Behandlung/Quarantäne nur mit negativem Virus-Nachweis, zusätzlich sind Daten zur Antikörperbildung in der Bevölkerung von Interesse.

Erfassung potentieller Infekt-Träger bei Grenzüberschreitung, *Infekt-Risiko* durch Personen in der symptomlosen Phase bei bereits einsetzender Virus-Ausscheidung. Eine umsichtige Kontrolle und Selbstbewertung im beruflichen/privaten Umfeld auf *Infekt-Zeichen* sollte nicht nachlassen. Endogenes *Virus-Reservoir* bei Mensch und Tieren in Europa?

Guidelines u.a. vom NIH https://www.covid19treatmentguidelines.nih.gov lassen keine Empfehlungen zur medikamentösen Therapie erkennen, weder im Sinne einer Prävention, zum Schutz nach Kontakt mit Erkrankten noch zum Einsatz bei schwerwiegenden Krankheitsverlauf.

Ich halte an **meinem Basis-Konzept**, cit anfangs März. d.J., als medizinisch-wissenschaftlich fundierte **Empfehlung** fest, auch wenn Placebo-kontrollierte Studien-Daten bislang fehlen:
Basis-Schutz durch höheren Vitamin-D-Spiegel;
allgemeiner Schutz gegen Inflammation, Thrombose-Embolie-Schutz,
Infekt-Modulation (Azithromycin), Proteasen-Hemmer (u.a. *Lopinavir/Ritonavir; auch Tamiflu bei viralem Mehrfach-Infekt),*
bei heftiger Fieber-Reaktion: Schutz gegen Interleukin-Sturm (anti-IL1/6) u.a. Baricitinib - *Olumiant (tbl),* Tocilizumab - *Roactemra* (i.v.); JAK-Inhibitoren, wie *Baricitinib (Olumiant).*
Vorbeugung gegen Organ-Schäden (Lunge, Gefäße, Herz, Nieren).
Verzögerter Therapie-Einsatz bei schwerwiegendem Verlauf kommt dann zu spät.

Remdesivir (nucleotide prodrug of an adenosine analog) hat in einer placebo-kontrollierten Studie eine raschere Erholung vom Infekt ergeben (11 gegen 15 Tage), Mortalität etwas geringer (8.0 gegen 11.6%) – N = 1063 participants.

Chloroquine oder Hydroxchloroquine: unter hoher Dosis (600 mg 2x/die, 10 Tage) Nebenwirkung mit Arrhythmien (teils in Kombination mit Azithromycin) – prolonged QT interval. Sichere Dosierung wäre 450 mg/die durch 4 Tage. Wirkung auf Virus-Bindung an Zell-Rezeptoren und auf intrazellulären Transport (Freisetzung vom Virus-Genom), immunmodulierende Effekte (früher Einsatz bei SLE, RA).
Studien-Ergebnisse: *kein Unterschied* zu SOC (standard of care)

Lopinavir/Ritonavir und andere HIV-Proteasen-Inhibitoren:
Lopinavir ist ein potenter Hemmer von CYP3A – cave Toxizität eingesetzter Medikamente.
Nur in hohen Dosen kann L/R als Inhibitor von SARS-CoV 3Clpro (chymotrypsoin-line protease zur Spaltung der Virus-Polyproteine für die Bildung einer Helicase/RNA-Polymerase) wirken.
Geringere Mortalitätsrate (19.2 gegen 25.0%, N=199 pat.), *shorter ICU-stay* (6 vs 11 days) zu später Einsatz in Studien!
L/R und Arbidol: Zeit für virus-positiven pharyngeal swab nicht verbessert (N=86 pat).
L/R gegen Chloroquine: keine ausreichenden Daten.

Immune-based therapy under evaluation for treatment of covid-19 in the context of a clinical trial:
Covid-19 convalescent plasma, Sars-CoV-2 immune globulins
Severe systemic inflammatory responses occur in patients with SARS-CoV-2 infection; cytokine release syndrome (CRS). Cytokine profiles of serum from some patients with moderate to severe COVID-19 overlap with those seen in macrophage activation syndrome (MAS) und secondary hemophagocytic lymphohistiocytosis (sHLH), CAR-T cell mediated cytokine release syndrome;

IL-1 Inhibitors, e.g. anakinra (Kineret)– no data
IL-6 Inhibitors, e.g. sarilumab, siltuximab, tocilizumab (Roactemra) – insufficient data
Interferons: lack of efficacy (SARS, MERS)
Janus kinase Inhibitors, e.g. baricitinib (broad immunosuppressive effect – Olumiant 4 mg) – less data
Link zur kompletten Berichts-Analyse, **Link** zur Conclusion - siehe Homepage
https://www.nih.gov/health-information/coronavirus - COVID-19, **NIH** National Institutes of Health

Update: 6.6.20
Computersimulation zum **Erkennen von Wirkstoffen gegen SARS-Cov-2**. Cit.: C't magazin für computer technik 13/2020, 136, ct.de/y3xp, WHO-Bulletin, 21.3.20
Team Prof. Dr. Thomas Efferth, Univ. Mainz: *molekulare Docking-Versuche in Computersimulationen.*

42000 Substanzen wurden getestet – die *räumliche Struktur von Wirkstoffen* wird eingesetzt zur Analyse der möglichen *molekularen Docking-Möglichkeit mit elektrostatischer Wechselwirkung* gegen Proteine im Corona-Virus, wie das *Spike-Protein an der Virus-Oberfläche, ein Nucleocapsid-Protein* (Schutz-Kapsel für das Virus-Erbgut) und ein *Replications-Protein* (2'-o-Ribose-Methyltransferase) – Ergebnisse nach ca 30 Milliarden Einzelberechnungen. Programme, wie AutoDock VINA u. AutoDock 4.2 suchen auf der Basis der *Molekularstruktur* nach *Andockstellen für Wirkstoffmoleküle am Virus* mit Bewertung der *Bindungskraft*. Mittels künstlicher Intelligenz zum Aufbau von neuronalen Netzen bewerteten zusätzliche Untersuchungen Eigenschaften von möglichen Medikamenten, wie Wasserlöslichkeit, Molekülgröße und die Existenz bestimmter funktionaler Bausteine.
Um das Andocken des Virus an menschliche Zellen zu unterbinden sind *Wirkstoffe gegen das Spike-Protein* durch die Computer-Simulation gefunden worden: bereits zugelassene *Hepatitis-C-Medikamente, wie Simeprevir, Paritaprevir* (in **Viekirax** mit Ombitasvir u. Ritonavir – s. oben), *Grazopervir* (in Zepatier mit Elbasvir) und *Velpatasvir* (in **Epclusa** mit Sofosbuvir) - *Behandlungs-Kosten für ca 6 Tage in der Inkubations-Phase bei € 2500* - und ein Naturstoff aus Lonicera japonica.
Bei bereits verfügbaren Medikamenten aus der Wirkstoffgruppe gegen Hepatitis-C werden entsprechende klinische Studien rascher eine Freigabe für den Einsatz bei Erkrankten erwarten lassen.

Review article – clinical microbiology and infection CMI, 26 (2020), 988-998.
Review of trials currently testing treatment and prevention of COVID-19. P.C. Fragkou et al.
Background: As COVID-19 cases continue to rise globally, evidence from large randomized controlled trials is still lacking. Currently, numerous trials testing potential treatment and preventative options are being undertaken all over the world.
Objectives: We summarized all registered clinical trials examining treatment and prevention options for COVID-19. Additionally, we evaluated the quality of the retrieved studies.
Data sources: Clinicaltrials.gov, the Chinese Clinical Trial Registry and the European Union Clinical Trials Register were systematically searched.
Study eligibility criteria: Registered clinical trials examining treatment and/or prevention options for COVID-19 were included. No language, country or study design restrictions were applied. We excluded withdrawn or cancelled studies and trials not reporting therapeutic or preventative strategies for COVID-19. Participants and interventions: No restrictions in terms of participants' age and medical background or type of intervention were enforced.
Methods: The registries were searched using the term 'coronavirus' or 'COVID-19' from their inception until 26 March 2020. Additional manual search of the registries was also performed. Eligible studies were summarized and tabulated. Interventional trials were methodologically analysed, excluding expanded access studies and trials testing traditional Chinese medicine.
Results: In total, 309 trials evaluating therapeutic management options, 23 studies assessing preventive strategies and three studies examining both were retrieved. Finally, 214 studies were methodologically reviewed. Interventional treatment studies were mostly randomized (n ¼ 150/198, 76%) and open label (n ¼ 73/198, 37%) with a median number of planned inclusions of 90 (interquartile range 40e200). Major categories of interventions that are currently being investigated are discussed.
Conclusions: Numerous clinical trials have been registered since the onset of the COVID-19 pandemic. Summarized data on these trials will assist physicians and researchers to promote patient care and guide future research efforts for COVID-19 pandemic containment. P.C. Fragkou, Clin Microbiol Infect 2020;26:988

Review article - nature nanotechnology, vol 15, August 2020, 630-645.
Immune-mediated approaches against Covid-19, H.F. Florindo et al.
The coronavirus disease-19 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The long incubation period of this new virus, which is mostly asymptomatic yet contagious, is a key reason for its rapid spread across the world. Currently, there is no worldwide-approved treatment for COVID-19. Therefore, the clinical and scientific communities have joint efforts to reduce the severe impact of the outbreak. Research on previous emerging infectious diseases have created valuable knowledge that is being exploited for drug repurposing and accelerated vaccine development. Nevertheless, it is important to generate knowledge on SARS-CoV-2 mechanisms of infection and its impact on host immunity, to guide the design of COVID-19 specific therapeutics and vaccines suitable for mass immunization. Nanoscale delivery systems are expected to play a paramount role in the success of these prophylactic and therapeutic approaches. This Review provides an overview of SARS-CoV-2 pathogenesis and examines immune-mediated approaches currently explored for COVID-19 treatments, with an emphasis on nanotechnological tools.

Update seit Nov/20
Cortison-Therapie ist keine Option gegen die Hyperinflammation, gegen den Interleukin-Sturm (IL1/IL6) mit Hyperpyrexie und Organschädigung: Auswahl von Kinase Inhibitors – Type Bruton's tyrosine kinase BTK, *JAK inhibitors* bei ersten Anzeichen der Hyperpyrexie mit Desaturation. Patienten sollten dadurch vor der desaströsen Organschädigung mit Notwendigkeit zur Intensiv-Therapie mit unsicherem Ausgang bewahrt werden.

Wo bleibt die Aufklärung der Bevölkerung für eine Basis-Medikation bei Infekt-Nachweis mit einsetzenden Beschwerden?

Antibodies, Immunity, future infection risk and COVID-19: s. oben/update

SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates.
Gregory A Poland, I. G. Ovsyannikova, R.B. Kennedy. The Lancet, Vol 396,P1595-1606, Nov 2020.
Understanding immune responses to severe acute respiratory syndrome coronavirus 2 is crucial to understanding disease pathogenesis and the usefulness of bridge therapies, such as hyperimmune globulin and convalescent human plasma, and to developing vaccines, antivirals, and monoclonal antibodies'. A mere 11 months ago, the canvas we call COVID-19 was blank. Scientists around the world have worked collaboratively to fill in the blank canvas. In this Review, we discuss what is currently known about human humoral and cellular immune responses to severe acute respiratory syndrome coronavirus 2 and relate this knowledge to the covid-19 vaccines currently in phase 3 clinical trials.

Entwicklung von Impf-Stoffen – Auswahl von viralen Struktur-Proteinen zur Generierung einer Antikörper-Bildung, von neutralisierenden Antikörpern: s.oben/update
spike glycoprotein, membrane protein, envelope protein, nucleocapsid protein

Ivermectin – an antiparasitic drug
Behindert die Replikation von RNA und DAN Viren, einschließlich HIV-1, dengue virus, equine encephalitis virus und Zika virus: s.oben/update

Interdisziplinäre COVID-Board bei SARS-CoV-2 getriggerter hyperferritinämischer Inflammation
P. La Rosée, H.C. Bremer et al.
Medizinische Klinik – Intensivmedizin und Notfallmedizin, 2021, 116:138-145
Bemerkung: zögerliche Entscheidungsfindung zur gezielten Dämpfung der Hyperinflammation – allerdings erst im fortgeschrittenem Stadium der Erkrankung, da ‚fehlende Standartherapie' bei lebensbedrohlicher COVID-19 Erkrankung….
Studien-Zeitraum II-VI/20, N=196 Patienten.
Med.: Vit C 12.0 g, ASS 500 mg, D-Dimer stratifizierte Antikoagulation, Hydroxchloroquin (600 mg bid Tag 1, 200 mg bid Tag 2-5), Prednisolon (2 mg/kg Tag 1-3).
Immunmodulation durch selektiv Zytokin-gerichtete Substanzen (Tocilizumab, Anakinra) oder Kinaseinhibitoren des Zytokin-Signalweges JAK/STAT (Ruxolitinib, Baricitinib) zur Dämpfung der Inflammation.
COVID-Inflammations-Score CIS – Punkte: bei >10 Punkten Immunmodulation mit Ruxolitinib.
Radiologisch bds. *Lungeninfiltrate* 3, *CRP* >20*ULN (upper limit of normal) 2, *Ferritin* >2*ULN 2, *TG* >1.5*ULN 1, *IL-6* >3*ULN 1, *Fibrinogen* >ULN 1, *Leucocyten* >ULN 1, *Lymphopenie* 2, *Fieber >38°* 2, *Gerinnungsaktivierung* 1.
Sonstige Routine-Parameter: IL6, sIL2R, Procalcitonin, LDH, Fibringoen, D-Dimer, CRP, Leuco-Diff.

Der kritisch kranke Patient nach CART-T-Zell-Therapie
Relevante Nebenwirkungen, deren Management und Herausforderungen an die Intensivmedizin
J. Gacia Borrega, K. Heindel et al., Med Klin Intensivmed Notfmed 2021, 116:121-128
Bemerkung: die Nebenwirkungen durch die Behandlung mit chimeric-antigen-receptor (CAR)-T-Zellen gleichen sehr dem *schädigendem Spektrum des Covid-19 Infektes*:
CRS *cytokine release syndrome*
Fieber als Leitsyndrom, schwieriger Unterschied zu Sepsis und septischen Schock, therapierefraktäre Hypotonie, disseminierte intravasale Koagulopathie, Organversagen
Überaktivierung des Immunsystems, Zytokininsturm – Interleukin IL-6, Interferon-γ (INF-γ).
Sepsis-Therapie, Breitbandantibiotikum, Fokussuche. IL-6-Rezeptor-Antagonist Tocilizumab, hochdosierte Steroide empfohlen (mein Bedenken!), Immunsuppression mit Anakinra (IL-1-Rezeptor-Antagonist), Siltuximab (IL-6-Antagonist). *Frühzeitiger* und kurzer Einsatz vom IL-6-Rezeptor Antagonist als Option erkannt. Katecholamintherapie, Vasopressor.
ICANS *immune effector cell-associated neurotoxicity syndrome*
Kopfschmerzen, Vigilanzminderung, kognitive Defizite, epileptische Anfälle, Hirnödem.
Testung nach Themen, wie Orientierung, Objekte benennen, Aufforderungen befolgen, Schriftbild, Konzentration (Zahlenmanipulation) – encephalopathy score.
Systemische Inflammation IL-1 eher im Vordergrund, Permeabilitätsstörung der Blut-Hirn-Schranke, Migration von CAR-T-Zellen und Zytokinen in das zentrale Nervensystem.

Ausschluß von Hirnblutung, Hirninfarkt und raumforderndem Hirnödem (MRT), Epilepsie (EEG), Hirndruckzeichen, Liquorpunktion (Enzephalitis, Meningitis).
Steroide, IL-1.Rezeptor-Antagonist Anakinra, Tocilizumab.

Die hämophagozytische Lymphohistiozytose bei kritisch kranken Patienten HLH
D.A. Eichenauer, G.Lachmann, P. La Rosèe.
Med Klin Intensivmed Notfmed 2021, 116:129-134
Bemerkung: HLH-ähnliche Symptomatik bei kritisch an COVID-19 Erkrankten.
Pirmäre Form, genetisch bedingt, sekundäre Form bei Infektionen, Malignomen und Autoimmunerkrankungen als Trigger – HLH bei Infektionen und Malignomen und MAS-HLH (Makrophagen-Aktivierungssyndrom) bei rheumatologischer Erkrankung: Hyperinflammation, Zytokininstrum, Hyperferritinämie. Phagozytose hämato-poetischer Zellen durch Makrophagen, Proliferation des zytotoxischen T-Zell-Kompartiments, Multiorganversagen.
Erscheinungsbilder: hohes Fieber, Spleno-Hepatomegalie, Bi-Panzytopenie. CRP- u. Fibrinogen-Anstieg anfangs, Leberschaden, Gerinnungsstörung. Ferritinämie, Hypofibrinogenämie, IL-2-Rezeptor Anstieg, erhöhte Natural-Killer (NK)-Zell-Aktivität, Nachweis der Hämophagozytose im Knochenmark, Lnn u. Liquor.
Auslöser: Infektion (59%), Malignome (28%), Autoimmunerkrankung (12%).
Versorgung mit Beatmung, Vasopressoren, Nierenersatz-Therapie, immunsuppressive Therapie gegen die Hyperinflammation. Therapie spezifischer Auslöser (Virus-, Pilzinfektion), bei Malignomem (Kortikoide und Etoposid, bei MAS-HLH (rheumatisch-autoimmunologische Grundkrankheit) Auswahl von Kortikoiden und Zyktokinin-Blockern (IL-1 Rezeptor-Antagonist Anakinra, IL-6-Antikörper Tocilizumab), Januskinase (JAK)-2-Inhibitor Ruxolitinib. Beachtung der hepatobiliären Funktionsstörung und einer disseminierten intravasalen Gerinnung.

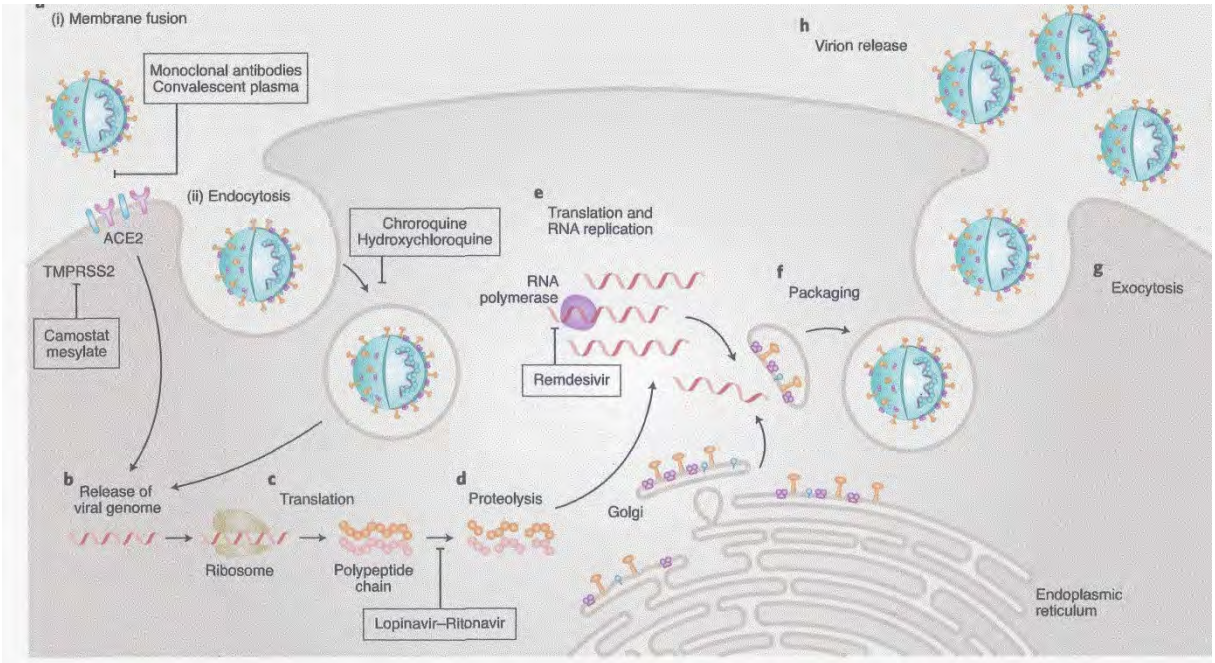


Fig. 3 | SARS-CoV-2 entry and mechanism of infection. a–d, SARS-CoV-2 is internalized by the cell via (i) membrane fusion or (ii) endocytosis. The SARS-CoV-2 spike binds to the angiotensin-converting enzyme 2 (ACE2) via its receptor-binding domain (RBD) and further releases its RNA (**b**), which will be translated into viral proteins (**c**,**d**). **e–h**, These proteins will form a replication complex to create additional RNA (**e**) that will further assemble with the viral proteins into a new virus (**f**), which will be released (**g**,**h**). The transmembrane protease serine 2 (TMPRSS2) is a protease shown to affect virus entry, even though its knockout does not inhibit cell infection by SARS-CoV-2. TMPRSS2, transmembrane protease serine 2; ACE2, angiotensin-converting enzyme 2.

CONCLUSION **II/21**

allgemeine Maßnahmen gegen Infekte – Basiswissen in der Bevölkerung,
gelebter Infekt-Schutz weiterhin (*Selbst-Isolation* bei Infekt-Verdacht); Basis-**Hygiene** – Atmung (Maske), Nasenatmung, Haut-Schleimhaut-Kontakt (**Desinfektion** – Hand, Rachen)
Vitamin C, *Vitamin D*, Vitamin B-Komplex, Zink Supplementation, NO-Donatoren
Personen-Kontakt, **Abstand**-Kontrolle, **Luft**-Filterung (Hepa-Kohle-Staub-Filter mit **UV-Lichtquelle**)

Post-Exposure Prophylaxis: Chloroquine (?), HIV-Medikation, wie *Lopinavir/Ritonavir* (**Kaletra** 200/50), *Ritonavir* (**Norvir**, Ritonavir 100 mg), Nitazoxanide (clincal trial, thiazolide – broad-spectrum antiparasitic, antiviral) und *Ivermectin*/**Scabioral** 4 mg. *Hepatitis-C-Medikamente, wie Paritaprevir* (in **Viekirax** mit Ombitasvir u. Ritonavir) und *Velpatasvir* (in **Epclusa** mit Sofosbuvir)

Risiko-Patient (Organ-Schäden) ist besonders schützenswert, beachte **Reaktionstyp:**
a) thrombotisch-embolisch (ASS, Heparin), b) hyperreaktive Inflammation mit *Interleukin-Sturm*, Hyperpyrexie (Fieber)*****, terminale Gewebe-Schädigung (Lunge, Darm, Herz, Gehirn u.a.)

Rasche Modulation der **Inflammation** durch Pharmaka (Parcetamol, Mesalazin als Basis; Immunomodulators – Interferon-β, Kinase Inhibitors – Type Bruton's tyrosine kinase BTK, *******JAK inhibitors* – Baricitinib/ **Olumiant** 4 mg). Erkennen der Superinfektion, Schutz gegen Organschäden, gegen Organ-Versagen

spezifische anti-virale Therapie vor dem Endstadium, rascher Therapie-Beginn!
Andockmechanismus (Virus-Oberfläche und Wirts-Zell-Oberflächen-Rezeptoren mit Eintritts-Mechanismen): **Bamlanivimab Ak** i.v. gegen receptor binding domain of spike protein.
In der Wirtszelle Isolation des Virus-Genom, Blockade der Virusreplikation: *Medikation gegen **HIV u. Hepatitis C**; auch **Azithromycin**/Zithromax, **Ivermectin**/Scabioral;* Umifenovir (Arbidol, Ru) combined with protease inhibitors; Cobicistat (in Genvoya), Darunavir (HIV); **Remdesivir** (RNA-Poymerase blockiert; Ebola; Covid-19 – EU-Zulassung), **Favipiravir** (T-705, Avigan; Japan); Oseltamivir (Tamiflu; Neuraminidase-Hemmer), Baloxavirmarboxil (Enonuklease-Hemmung – Untereinheit der RNA-Polymerase), Azvudine (Ro-0622, reverse transcriptase inhibitor – Hepatitis C). Serum-Therapie.
Nachsorge nach Infektion (kardio-pulmonale Funktion, Nervenschäden), noch spreader?, Antikörper-Titer nach Infektion. Primäre **Prävention** durch **Vaccination** – Auswahl der **Impfstoffe**.

Praktische Umsetzung - von der Theorie zur praktikablen Therapie gegen Covid19

Geringe Prävalenz der Infizierten in der Bevölkerung – Erscheinungsbilder:
Symptomlos nahezu sind 60-70% der Infizierten (Spreader!)
Symptomatisch mit leichtgradigen Erscheinungen nur 20-30% der Infizierten,
Fieber als Hauptmarker (Temp. ≤38°), trockener Husten, Müdigkeit
Erhebliche Symptomatik, stationäre Aufnahme notwendig bei 1-2% der Infizierten wegen Hyperpyrexie (Temp. ≥38°), Atemnot mit SaO2-Abfall, Risiko zur deletären Entwicklung mit Notwendigkeit zur Intensivpflege, davon letaler Ausgang bei 30% der Intensiv-Patienten – *keine entsprechenden Therapie-Ansätze*, dubiöse ‚Leitlinien' hemmen den off-Label Einsatz von wirksamen Pharmaka (da keine 'doppel-verblindete' Studienergebnisse) – die Notlage verlangt intellektuell untermauerte Entscheidungen, die medizinische Versorgung bricht ein

Allgemeine Maßnahmen gegen Covid-19-Infekt
Prophylaxe: Vit C, Vit D, Zk; Grippe-Impfung; Nasenatmung, NO-Spiegel anheben
Basis-Hygiene mit Abstand-Kontrolle, Maske gegen Keim-Ausbreitung via Atmung/Husten, Haut-Schleimhaut-Desinfektion, Selbst-Isolation bei Infekt-Verdacht, rascher Infekt-Nachweis
Luftfilterung mit UV-Lichtquelle (Ordination, Büro, Klassenzimmer) – UV vor 50 Jahren ein Standard

Infekt: rasche/sofortige Diagnose – Gen-Test mit Wiederholung, falls negativ; PCR-Test (Ergebnis nach Tagen bislang! – unzumutbar zum Erkennen einer Infekt-Quelle) - **Isolation**

Verhinderung der Organ-Schäden – Basis-Therapie sofort für jeden Infizierten, Basis-Wissen in der Bevölkerung fehlt, auch für die medizinische Versorgung, kuriose Darstellungen in Leitlinien der deutsch. Ges. für Intensivmedizin, Aussage der österr. Ges. f. Pneumologie

Schutz sofort gegen die Organschädigung durch den Virus Covid-19 als Therapie-Basis:
Ziel ist die Verhinderung der stationären Aufnahme, der intensiv-medizinischen Betreuung

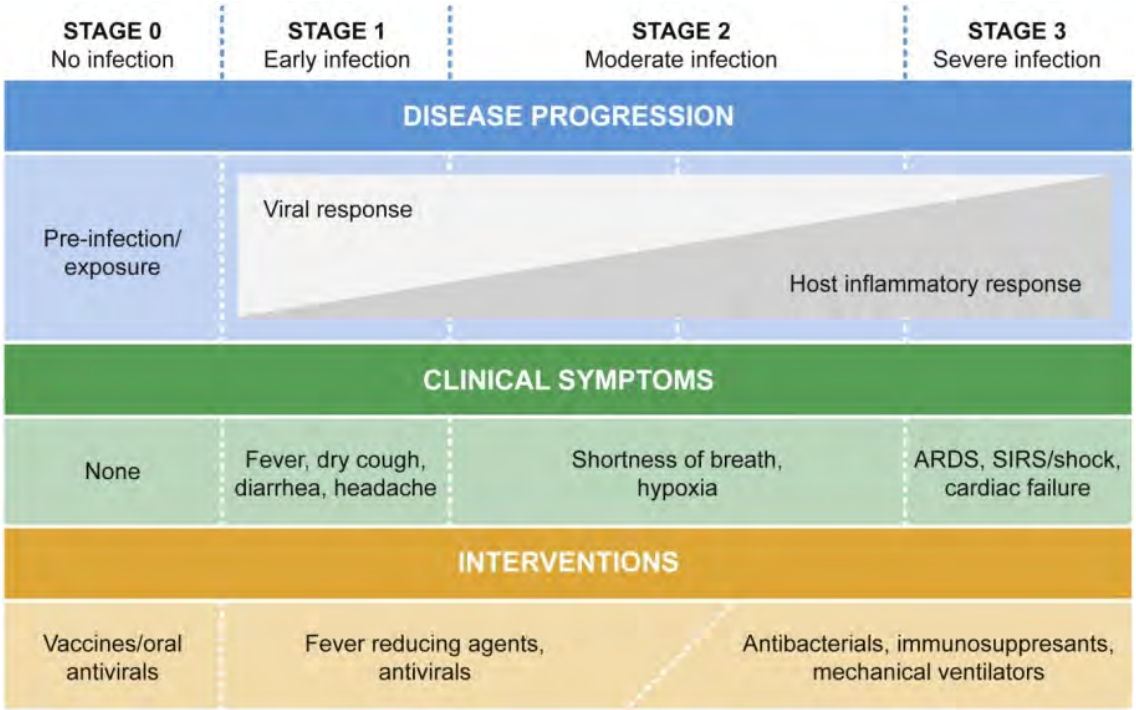
1. **Hemmung der viralen einzigartigen Entzündungsreaktion (Inflammation):** frühzeitiger Start mit einfachen Entzündungshemmern, wie Mexalen, Paracetamol, Novalgin (höher dosiert), Claversal Mesalazin; ev. NSAR wie Ibuprofen (cave Hypertonie, Magenulcus, Herzschaden), NO-Spiegel
2. **Verhinderung der thrombotisch-embolische Organ-Schädigung:** Aspirin (250 – 500 mg), Anti-Thrombose-Injektion (Heparin), NOAKs (teuer), Antikoagulation (Marcoumar)

beim Übergang in eine erhebliche Symptomatik – rasch Therapie ausdehnen:

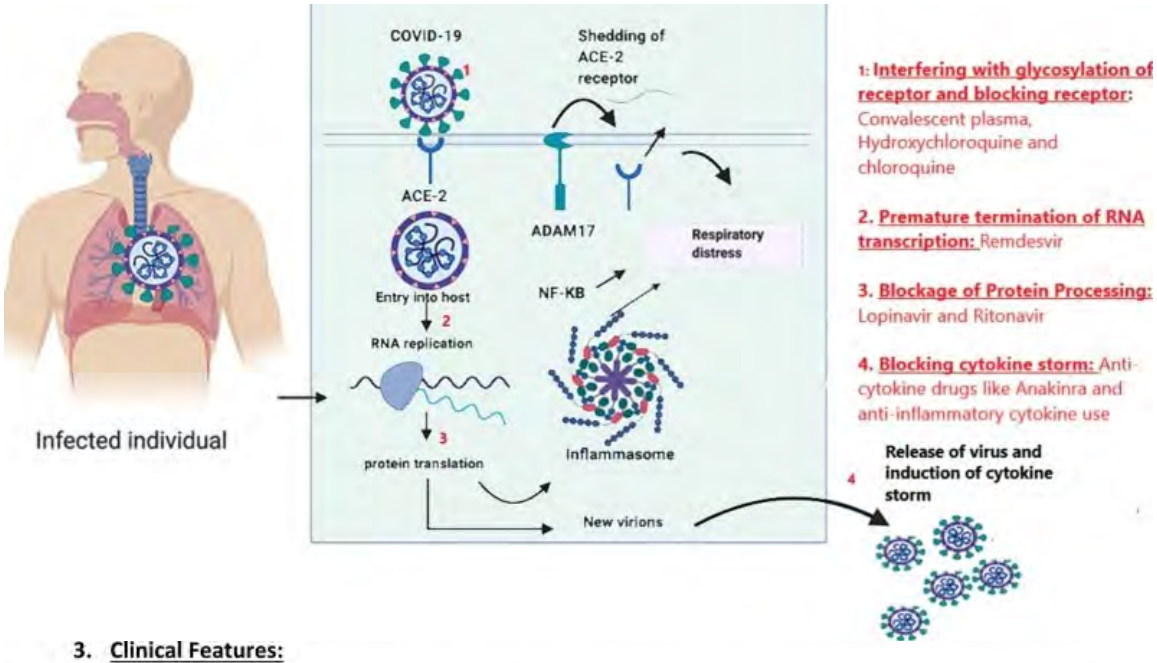
3. **gegen den Interleukin-Sturm (IL1, IL6) mit massiver Organ-Schädigung (primär ist die Lunge betroffen) mit Hyperpyrexie (Fieber >38%), Hypoxie – SaO2-Abfall:** bei ersten Anzeichen JAK Inhibitor verordnen, wie Baricitinib Olumiant (528.5 €)
   Die präventive Cortison-Medikation (Leitlinie) ist m.E. unzureichend begründet!

Direkte Intervention gegen den Virus Covid-19 beim Infizierten (auch bei Kontakt mit Infizierten, post-exposure)**: zugleich mit Schutz-Maßnahmen gegen die Organschäden (Inflammation, Gerinnungsaktivierung)**
Blockade des Andockmechanismus: Ak gegen Spike-Protein, **Bamlanivimab** i.v. (USA), **Casirivimab/Imdevimab (REGN-CoV2)** monoklolnaer Ak-Cocktail i.v. (FDA-Zulassung)
Unterbrechung der Virus-Replication: als Hauptangriffspunkt neben Mund-Rachen-Desinfektion; anfangs: p.o. **Ivermectin** Scabioral tbl (66 €), **Azithromycin** Zithromax tbl (11.3 €), auch **Oseltamivir** Tamiflu (Virustatica – 33.9 €), **Favipiravir- Avigan** tbl (USA), NO-Donatoren; i.v. **Remdesivir** (Veklury)
HIV-Medikation: Norvir (45.6 €), Darunavir (241.9 €), Kaletra (678.7 €)
Hepatitis C Medikation: *Viekirax (12582.1 €) , Epclusa (11573.9 €)*
Preisangaben AVP pro Packungsgröße

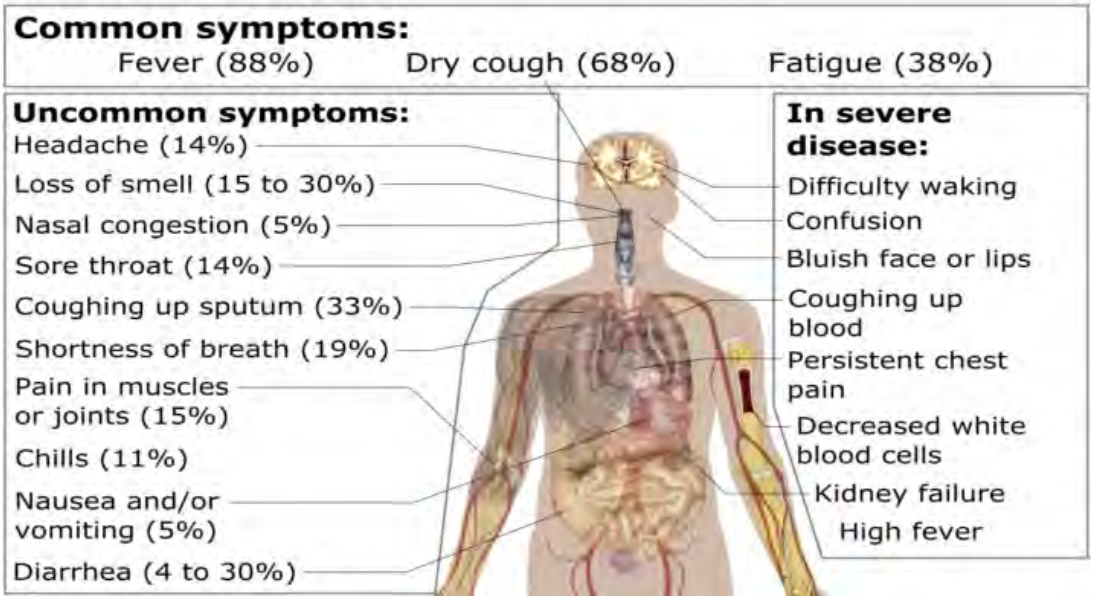
Entlassung des Infizierten aus der Quarantäne nur nach einem negativen Gen-Test-Befund, cave Virus-Ausscheidung durch Exkremente
Verlaufskontrolle mit Antikörper-Test, Nachsorge wegen Organ-Schäden (Lunge, Herz, Nerven, Psyche u.a.) – Bewertung des Gastransfers (Diffusion; SaO2), der systolisch-diastolische Herzmechanik….



Emerging pharmacotherapies for COVID-19
Rachana Salvi, Panini Patankar, Biomed. Pharmacother. 2020, 128:1 10267



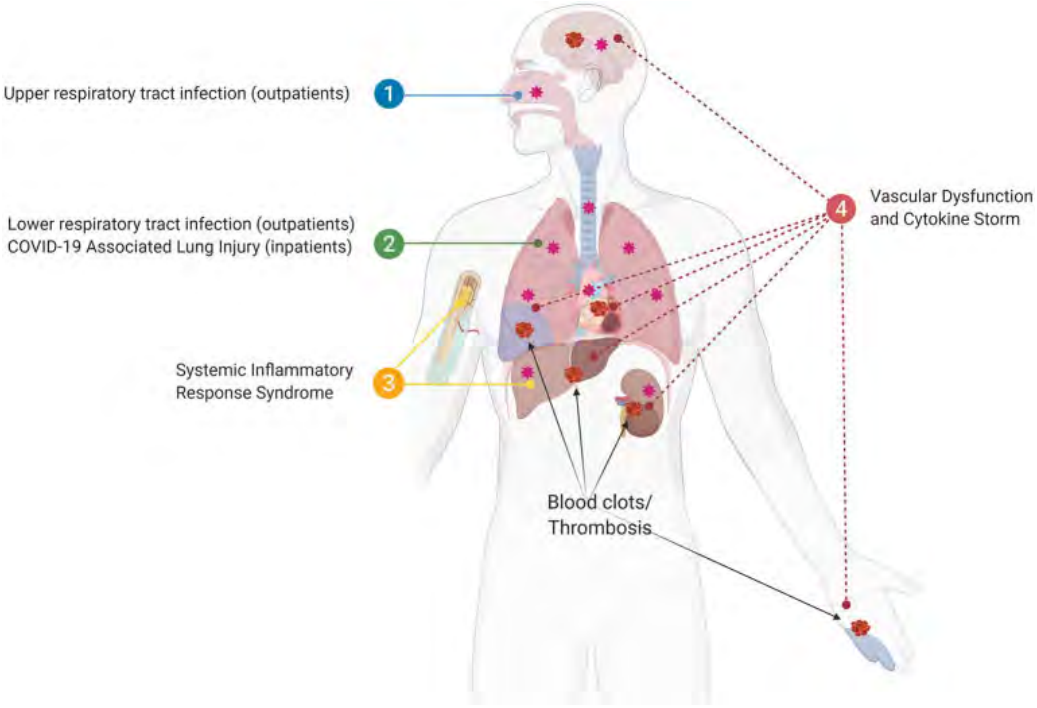
3. **Clinical Features:**

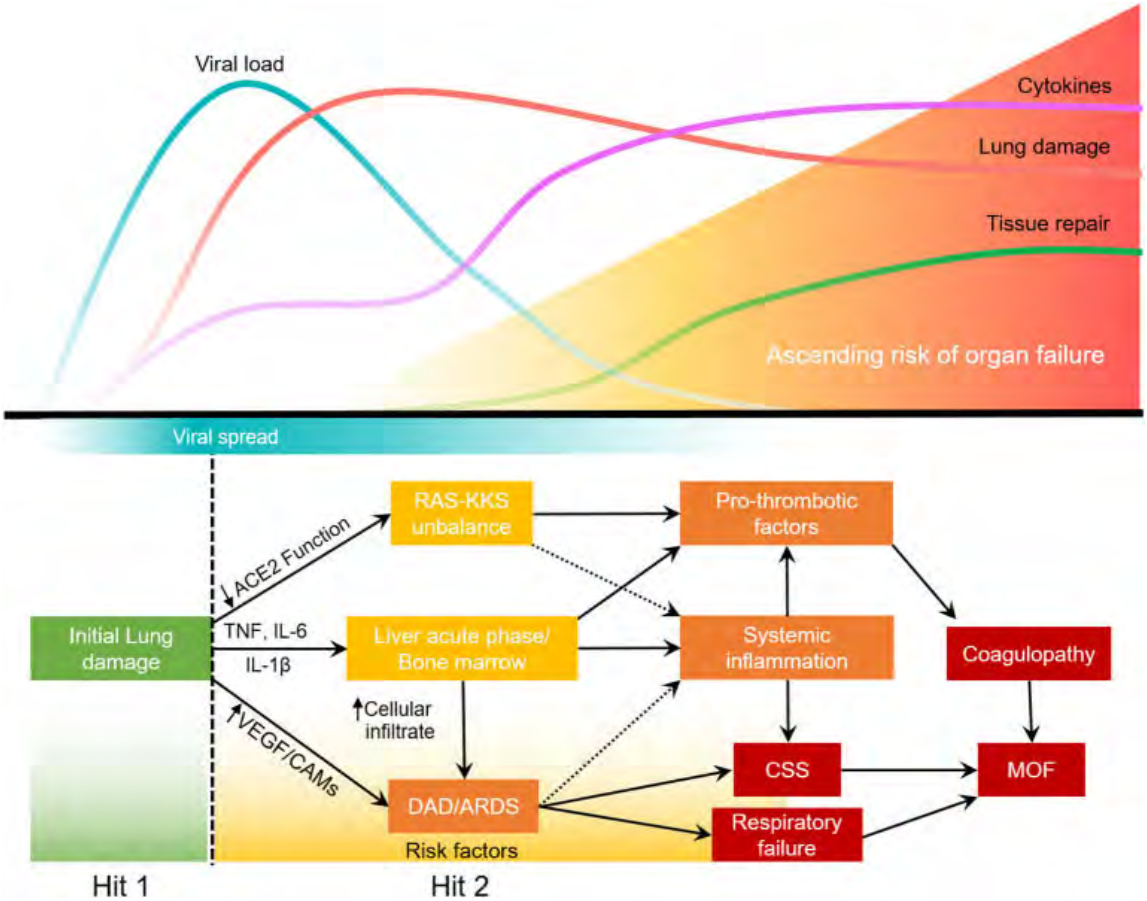


Overview: systemic inflammatory response derived from lung injury caused by SARS-CoV-1 infection explains severe outcomes in Covide-19.
Rafael B. Polidoro, R.S. Hagan, R de S Santiago, N.W. Schmidt. Font Immunol. 2020,11:1626.

Abstract
Most SARS-CoV2 infections will not develop into severe COVID-19. However, in some patients, lung infection leads to the activation of alveolar macrophages and lung epithelial cells that will release proinflammatory cytokines. IL-6, TNF, and IL-1β increase expression of cell adhesion molecules (CAMs) and VEGF, thereby increasing permeability of the lung endothelium and reducing barrier protection, allowing viral dissemination and infiltration of neutrophils and inflammatory monocytes. In the blood, these cytokines will stimulate the bone marrow to produce and release immature granulocytes, that return to the lung and further increase inflammation, leading to acute respiratory distress syndrome (ARDS). This lung-systemic loop leads to cytokine storm syndrome (CSS). Concurrently, the acute phase response increases the production of platelets, fibrinogen and other pro-thrombotic factors. Systemic decrease in ACE2 function impacts the Renin-Angiotensin-Kallikrein-Kinin systems (RAS-KKS) increasing clotting. The combination of acute lung injury with RAS-KKS unbalance is herein called COVID-19 Associated Lung Injury (CALI). This conservative two-hit model of systemic inflammation due to the lung injury allows new intervention windows and is more

consistent with the current knowledge.
Keywords: SARS-CoV2, COVID-19, severe COVID-19, bisphosphonates, inflammatory monocytes, ARDS, renin-angiotensin system, kallikrein-kinin system





Discrimination of COVID-19 from inflammation –induced cytokine storm syndromes by disease-related blood biomarkers
Christoph Kessel et al., accept. for publication doi: 10.1002/ART.41763

Found: **dramatic activation of the IL-18 interferon (INF)-γ axis,** increased serum levels of IL1 receptor antagonist (IL-1 Ra), intracellular adhesion molecule 1 (ICAM-1) and IL-8, strongly reduced levels of soluble Fas ligand (sFasL).

Marker für Störung der Mikrozirkulation bei Covid-19
Schädigung der endothelialen Glykokalyx, prädiktiv für out-come, thrombotisch-embolische Ereignisse. Abnahme der Kapillardichte (Intravital-Mikroskopie), Spiegel von ADMTS13 (von-Willebrand-Faktor-spaltende Proteinase), VEFG-A, ACE2, D-Dimere, Syndecan-1, Angpt-2.

X/2021:
Welcher Impf-Titer (SARS-Covid-19 Ak Spike): **>300-500 BAU/ml** sollte sicher schützen nach meiner Meinung. Sonst Re-Vacciantion anstreben.
Ab 0.8 BAU/ml positiv, ab 15 BAU/ml neutralisierende Ak.
Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection.
Feng, S. et al. Nat Med 2021 Sept. DOI: 10.1038/s41591-021-01540-1.

XI/21:
EMA - CHMP: vorgesehene Freigabe für neue anti-Covid-Medikamente, monoklonale Antikörper **Ronapreve** (Roche, Schweiz) u. **Regkirona** (Redanvimab – Celltrion, Südkorea). Einsetzbar im frühen Stadium der Infektion, antivirale monoklonale Ak. Bislang war nur Remdesivir (Veklury) in der EU zugelassen – aber für schwer Erkrankte (ungenügende Wirkung bei später Intervention – Bemerkung).
Ronapreve besteht auf zwei Ak (Casirivimab u. Imdevimab)

Study data for Ronapreve
A main study involving patients with COVID-19 who did not require oxygen and were at increased risk of their illness becoming severe showed that treatment with Ronapreve at the approved dose led to fewer hospitalisations or deaths when compared with placebo (dummy treatment). Overall 0.9% of patients treated with Ronapreve (11 out of 1,192 patients) were hospitalised or died within 29 days of treatment compared with 3.4% of patients on placebo (40 out of 1,193 patients).
Another main study looked at the benefits of Ronapreve for prevention of COVID-19 in people who had close contact with an infected household member. Ronapreve was found to be effective at preventing people from getting infected and developing symptoms after contact: amongst people who tested negative for SARS-CoV-2 following contact, fewer people given Ronapreve developed symptoms within 29 days of their test results compared with people given placebo (1.5% (11 out of 753) for Ronapreve compared with 7.8% (59 out of 752 people) for placebo).
Ronapreve was also found to be effective at preventing symptoms in infected people. Amongst the people who tested positive for SARS-CoV-2 after contact, 29% of people (29 out of 100) who received Ronapreve developed symptoms compared with 42.3% of people (44 out of 104) who received a placebo.

Study data for Regkirona
A main study in patients with COVID-19 showed that Regkirona treatment led to fewer patients requiring hospitalisations or oxygen therapy or dying when compared with placebo. Among the patients at increased risk of their illness becoming severe, 3.1% of patients treated with Regkirona (14 out 446) were hospitalised, required supplemental oxygen or died within 28 days of treatment compared with 11.1% of patients on placebo (48 out of 434).

Molnupiravir
Molnupiravir ist ein antiviraler Wirkstoff aus der Gruppe der RNA-Polymerase-Inhibitoren für die medikamentöse Vorbeugung und Behandlung der Coronaviruskrankheit Covid-19. Die Effekte beruhe auf der Hemmung der RNA-abhängigen RNA-Polymerase des Virus. Applikation p.o.

IV/22:
Covid-19 – Therapie auf der Intensivstation.
MedKlinIntensivmedNotfamed 2022, 117, 177-186.

Remdesivir: Fa Gilead Sciences
Time to clincal recovery von 15 auf 10 Tage verkürzt, kein Effekt auf die Sterblichkeit. Ab 7. Krankheitstag ist kein Effekt zu erwarten
Rekombinantes humanes lösliches angiotensinkonvertierendes Enzym 2:
In Phase III – Auswertung offen. HsACE2 wirkt direkt antiviral i.v. verabreicht, reduziert die Dysregulation der Antiotensin-Achsen-Antwort in verschiedenen Organen.

Rekonvaszentenplasma
Kein positiver Effekt auf das Überleben
Monoklonale Antikörper gegen SARS-CoV2-Epitope:
Prophylaktisch und bei sehr frühzeitiger Anwendung können schwere Verläufe verhindert werden.
Bei zwei gemeinsam verabreichten monoklonalen Antikörpern gegen Epitope auf der receptor binding domain – 28-Tage Mortalität reduziert (Recovery-Studie).
Regdanvimab, Casirivimab-Imdevimab Cocktail, Sotrovimab

Jegliche antivirale Therapie kommt auf der ICU oft zu spät – Aufnahme in der 2. Woche nach Symptomenbeginn. Beim Auftreten der Virus-Varianten α und δ zuletzt verkürzte Zeitspanne zwischen dem Auftreten der Symptome und der Aufnahme auf der ICU.

Therapie der Ko- u. Superinfektion:
Rechtzeitiger Beginn einer *antiinfektiven Therapie* ist für die Prognose essentiell.
Ventilator-assoziierte Pneumonien, Blutstrom-Infektion durch Verweilkatheter, Candidämien, pulmonale Aspergillosen.
Immunmodellierung:
Systemische Glucocorticoid-Gabe (Neben-Nieren-Schaden durch den Covid-19-Infekt – micro-vasculäre thrombotische Schädigung). Ohne O2-Bedarf war die Gabe von Dexamethason (6 mg/die) potenziellt kontraproduktiv. Effekte bei invasiv beatmeten Patienten, bei Erkrankten mit O2-Sufflation war der Einfluß von Cortison weniger ausgeprägt. Früher Therapie-Beginn, später Therapiebeginn mit Cortison brachte kein Benefit – Hydrocortison, Cortison, Dexamethason.
Interleukin-6-Antagonisten:
Tocilizumab – signifikant verbessertes 90-Tage Überleben (Recovery-Plattform). Durch die Blockade kein Feed-back zur Infekt-Kontrolle via IL-6 u. CRP – Detektion von Superinfektionen erschwert.
Januskinasen-Inhibitoren:
Tofacitinib (2 x 10 mg durch 14 Tage), teils in Kombination mit Steroiden (Brasilien) vorteilhaft im Verlgeich zur Placebo-Gruppe (!). Baricitinib führte in Kombination mit Remdesivir zu einer rascheren klinischen Erholung – Pat. unter O2-Hochfluß oder nicht-invasiver Atemhilfe.
Antikoagulation:
Schwerer COVID-19-Verlauf führt durch die ausgeprägte Inflammation zur Gerinnungsaktivierung und Heaprin-Resistenz – ‚COVID-19-assoziierte Koaguloapthie'. Venöse Thromboembolien, Mikrothrombosen. Hochdosis-Prophylaxe mit 0.5 mg/kg low-molecular-weight heparin 2x/die.
Beatmung:
Nicht-invasive Beatmung, Lagerungstherapie (Bauchlage, steile Seitenlagerung). Nasale High-flow-Therapie zur präziser titrierten Oxygenierung, intermittierende Maskenbeatmung (CPAP, BIPAP).
Invasive Beatmung, extrakorporale Membranoxygenierung, Nierenersatz-Therapie.

Long-Covid-Symptome – VI/22
Ref/ *Journal of Clinical & Translational Endocrinology*, 2022; DOI: 10.1016/j.jcte.2021.100284) u. eigene Erfahrung. *cw/aerzteblatt.de*
Manche Patienten, die sich von einer COVID-19-Infektion erholen, haben langfristige Beeinträchtigungen wie Fatigue, Kurzatmigkeit, Geschmacks- und Geruchsveränderungen sowie Gelenkschmerzen, die eine individuell zugeschnittene Rehabilitation erfordern.
Fatigue zählt zu den häufigsten Beschwerden bei Long-COVID-Patienten und ist eine heterogene Erkrankung mit einer multifaktoriellen Ätiologie, die unter anderem immunologische, virologische, psychologische und endokrine Veränderungen umfasst.
Die Long-COVID-bedingte Fatigue wird einerseits durch Schädigung mehrerer Organsysteme (z.B. Herz-, Lungen- oder Nierenfunktion) begünstigt. Zum anderen können COVID-19-induzierte endokrine Dysfunktionen, die zu Hypokortisolismus, Hypothyreose oder einer Dysregulation der Hypothalamus-Hypophysen-Nebennierenrinden-Achse (HPA-Achse) führen, weitere mögliche Erklärungen für Fatigue sein, heben die Studienautoren hervor.
ACE2-Rezeptoren (Angiotensin, Converting Enzyme 2) stellen Eintrittspforten für SARS-CoV-2-Viren in menschliche Körperzellen dar, die von endokrinen Organen wie Hypothalamus, Hypophyse, Nebenniere, Schilddrüse, Hoden und Langerhans-Inseln exprimiert werden. Somit sind endokrine Organe bei akuter COVID-19-Infektion und bei Genesungsprozessen ebenfalls betroffen.
Gewebeuntersuchungen (postmortal) zeigten, dass SARS-CoV-RNA zum Beispiel in der Hypophyse, Nebenschilddrüse, Bauchspeicheldrüse und Nebenniere nachweisbar war. Weitere Gewebeanalysen entdeckten apoptotische parafollikuläre und follikuläre Zellen, was die niedrigen Serum Thyroxin- und Triiodthyroninspiegel und Osteonekrosen des Hüftkopfes bei Patienten mit SARS-CoV-2 erklären könnte, so

die Wissenschaftler. Autopsien des Hypothalamus von verstorbenen Patienten lieferten zudem Hinweise auf virale-RNA, Ödeme und neuronale Degeneration.
Studien zur Beteiligung der HPA-Achse nach COVID-19-Infektion sind nach wie vor begrenzt. Eine Studie zur Bewertung des Nebennierenrindenfunktion bei akuten COVID-19-Infektionen bei 28 hospitalisierten Patienten ergab, dass 32 % der Patienten subnormale Kortikosteroidspiegel aufwiesen und Patienten mit schwereren Erkrankungen sowohl subnormale Kortikosteroid- als auch ACTH-Spiegel (Adrenocortikotropes Hormon) aufwiesen, was auf einen direkten Zusammenhang zwischen dem Schweregrad der COVID-19-Infektion und einer beeinträchtigten Kortikosteroidsynthese hindeutet.
Die Studienautoren schlussfolgern, dass Rehabilitations-Maßnahmen auch ein endokrinologisches Assessment beinhalten sollten, zum Beispiel zur Bewertung der HPA-Achse bei Long-COVID-Symptomen wie Fatigue.

Eigene Programme: seit I/21
Herzecho in 3D – erweiterte Analyse zur systolisch-diastolischen Mechanik (bi-ventrikulär), Pulsregulation, Arrhythmie-Neigung. Erweitert mit Basis-Ergometrie mit Lactat-Profil, allenfalls Ergospirometrie als Zweit-Test.; Belastungshämodynamik.
Erweiterte Atemphysiologie mit Bewertung der Atemarbeit, Atemmuskelkraft und Diffusion mit Schlaf-Schnarch-Polygraphie
Blutchemie mit erweiterter Analyse zur Gerinnung (Clotting), Herzfunktion (Troponin, pro-BNP), Immunologie (Ephorese, IgG-A-M; IgE; ECP), Lymphozyten-Typisierung, Antikörperlast (viral u.a.), rheumatisch-rheumatoide Autoaggression (CCP; ANF mit Subsets), Muskel-Aktivierung (motorische Endplatte - Acetylcholinrezeptor-Antikörper muskelspezifische Rezeptortyrosinkinase Ak; MUSK-Gen Mutation) und zur Hypophysen-Neben-Nieren-Schilddrüsen-Achse (Hormon-Profil). Allenfalls Bestimmung neuronaler Autoantikörper (Aquaporin 4-AAk, NMDA-Rezeptor-AAk (IgG)m – NMDAR-Enzephalitis, Kaliumkanäle-AAk – LGI-1 (leucine-rich glioma inactivated 1), CASPR2 (contactin-associated protein related 2).
Guillain-Barrè-Syndrom – Myelin-AAk – Notwendigkeit zur Plasmapherese.
Anti-HuD-Antikörper – ahmt Botenstoffe Acetylcholin u. Adenosintrophosphate nach (TUM, Prof. M. Schemann, schemann@wzw.tum.de).

Covid-19 Rebounds in some Patients who take PAXLOVID
JAMA Network; Medical News & Perspectives, June 8, 2022

Paxlovid 150 mg PF-07321332 Nirmatrelvi and ritonavir – used for early treatment of mild to moderate covid-19 among people at high risk of progression to severe disease.
Unexpected rebound phenomenon of symptoms and positive PCR test confirming rapid antigen testing.
Nirmatrelvir is a protease inhibitor blocking SARS-CoV-2 from replicating, ritonavir boots Nirmatrelvir metabolism by increasing blood concentration. Wirkmechanismus sei unabhängig von der jeweiligen Coronavirus-Variante. 2 x 150 mg Nirmatrelvir und 1 x 100 mg Ritonavir Kps durch 5 Tage.
Nebenwirkungen: Dysgeusie, Durchfall, Kopfschmerzen, Erbrechen.
Relevante Wechselwirkungeng: Alfusozin, Amiodaron, Bepridil, Dronedaron, Propafenon, Statine, Astemizol, Colchicin, Sildenafil, Neratinib, Fusidinsäure, Diazepam, Midzolam, Clozpin u.a.

Molnupiravir (Lagevrio) is less effective in keeping patients out of the hospital.
Both received an EUA in Dec 2021 for treating mild to moderate COVID-19 in high-risk adults aged 18 years or older.
800 mg 12-stündig durch 5 Tage.
Molnupiravir liegt als Prodrug vor und wird zum Ribonukleosid-Analogon N-Hydroxy-Cytidin (NHC) metabolisiert. NHC verteilt sich in den Zellen und wird dort zum pharmakologisch wirksamen Ribonukleosid-Triphosphat (NHC-TP) phosphoryliert. Der Einbau von NHC-TP in die virale RNA durch die virale RNA-Polymerase führt zu einer Ansammlung von Fehlern im viralen Genom und dadurch zu einer Replikationshemmung. Dieser Mechanismus wird als virale Fehlerkatastrophe (viral error catastrophe) bezeichnet.

A study posted online May 26 but not peer-reviewed is one of the first to explore real-world effectiveness of **nirmatrelvir/ritonavir and molnupiravir** in vaccinated as well as unvaccinated patients infected with Omicron, according to its authors.
Conducted in Hong Kong, the retrospective cohort study focused on nearly 1.1 million nonhospitalized patients territory wide with confirmed SARS-CoV-2 infection during the Omicron BA.2.2 wave between February 26 and May 3, 2022. Among them, 5257 took molnupiravir and 5663 took nirmatrelvir/ritonavir. Both antivirals were associated with lower all-cause mortality risk—a 39% reduction for molnupiravir, 75% for

nirmatrelvir/ritonavir—compared with no antiviral use. Both also were associated with a lower risk of in-hospital disease progression—36% for molnupiravir and 53% for nirmatrelvir/ritonavir—compared with no antiviral use. Nirmatrelvir/ritonavir was associated with a 31% lower risk of hospitalization, while the hospitalization risk in patients who took molnupiravir was comparable with that of patients who didn't take an antiviral.
Neither drug was associated with as high a level of protection among the Hong Kong patients infected with Omicron as was seen in its clinical trial among unvaccinated patients infected by the Delta variant. (In its trial, molnupiravir reduced hospitalization risk by 30% compared with placebo, while nirmatrelvir/ritonavir reduced it by 88%.)
In the Hong Kong study, nirmatrelvir/ritonavir use was associated with greater and more consistent protection than molnupiravir use, and the protective effects of nirmatrelvir/ritonavir were similar regardless of vaccination status and age. However, the apparent superiority of nirmatrelvir/ritonavir to molnupiravir in the study could have been due in part to a higher proportion of patients older than 65 years and a lower proportion of fully vaccinated patients among those who received the latter drug, the authors noted.
The CDC's May 24 health advisory noted that "a brief return of symptoms may be part of the natural history of SARS-CoV-2…infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status."

Ronapreve (Casirivimab, Imdevimab) Kombination neuralisierender Antikörper, Injektins-Infusionslösung, zur wiederholten Präexpositionsprophylaxe monatlich
Casirivimab (IgG1κ) und Imdevimab (IgG1λ) sind zwei rekombinante humane monoklonaleAntikörper, die in den Fc-Regionen unverändert sind. Casirivimab und Imdevimab binden an nicht überlappende Epitope der Spike-Protein-Rezeptor-Bindungsdomäne (RBD) von SARS-CoV-2. Dies verhindert die RBD-Bindung an den humanen ACE2-Rezeptor und damit das Eindringen des Virus in die Zellen.

Neue Konzepte – Überlegungen zu
Long Covid-19 Syndrom – post vaccination syndrome
ME/CFS myalgic encephalomyelitis/chronic fatigue syndrome

Infekt-Folgen, Vaccination mit überschießender Ak-Bildung
Langzeit-Schäden durch *persistierend aktivierte Gerinnung* – Coagulation im micro-vasculären Bereich (Muskulatur, Gehirn u.a.)
Auto-Anti-Körper-Bildung gegen Muskulatur (Gefäße, motorische Endplatten), Nerven - Gehirn (Jonenkanäle– anti-neuronale Ak), Herzmuskel (Arhythmien, Myokarditis), Lunge (Diffusions-Perfusions-Störung), Nebennieren (Unterfunktion – Cortison-Mangel)
persistierende virale Bruchstücke - Irritation des Immunsystems, Immunaktivierung, Autoaggression (LE-ähnliche Bilder)

Kreuzreaktion von SARS-CoV-2-neutralisierneden Antikörpern mit Säugetier-Proteinen zur Stimulierung von anti-neuralen Autoantikörpern – Unterformen von Gedächtnisstörungen, Fatigue, Depression

Bekämpfung der Inflammation	einfach (Entzündungshemmer), aggressiv (IL-Blocker)
gegen Immun-over-shoot	Steroide, Apherese, MTX, Cyclophosphamid, Depletion von B-Zellen (CD20/CD19), Reduktion von Plasmazellen (Bortezomib), chimäre Autoantikörper-Rezeptor (CAAR)-T-Zellen

long covid-19 syndrome - post vaccination syndrome
ME/CFS myalgic encephalomyelitis/chronic fatigue syndrome

side effects of the infection, vaccination and surplus of antibody formation
long-term alteration/damage due to **persistent activated coagulation**, coagulation in the micro-vascular bed (muscular structure, brain tissue) → check markers of thrombosis, embolism
autoantibody formation directed against muscular structure (vessel wall, neuro-muscular junction), nerves, brain (ion channel-linked receptors, anti-neural antibodies), heart muscle (arrhythmias, myocarditis), lungs (disturbance of diffusion and perfusion, mismatch), suprarenal organ (impaired functional capacity, deficit of cortisol)
persistent viral fragments (nuclear acid): irritating the immune system, over-activation, auto-aggression (LE-like disease)

cross-over reaction of SARS-CoV-2 neutralizing antibodies with mammalian proteins cause stimulation of anti-neural autoantibodies: symptoms of mental disorder, loss of memory, cognitive dysfunction, fatigue, depression

fight inflammation	simple intervention (anti-oxidation, oxygen radicals) with ASS, Perfalgan, Mesalazin, aggressive with interleukin blockers (Baricitinib, Tocilizumab)
and immune over-shoot	steroids, apheresis, MTX Methotrexate, Cyclophosphamide, depletion of B-cells (CD20/CD19), depletion of plasma cells (Bortezomib), chimeric autoantibody-receptor- (CAAR)-T-cells

Antikörper-vermittelte Erkrankungen des Nervensystems – von Enzephalitis bis Demenz

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Autoantikörper sind in den letzten Jahren als relativ häufige Ursache eines breiten Spektrums neurologischer und psychiatrischer Erkrankungen identifiziert worden. Die Isolierung Patienten-spezifischer monoklonaler Antikörper hat es ermöglicht, die Krankheitsmechanismen zu verstehen, immunologische Signalkaskaden und Triggerfaktoren zu klären und ebnet den Weg für neue Herangehensweisen, z. B. Antikörper-spezifische Immuntherapien.

Schlüsselwörter: Pathogene Autoantikörper, Neuropsychiatrie, NMDA-Rezeptor-Enzephalitis, Diagnostik, selektive Therapie, post-viral

Noch vor 10–15 Jahren hätte niemand gedacht, dass durch die Entdeckung immer neuer antineuronaler Autoantikörper ein fundamentales Umdenken in der Neurologie und Psychiatrie eingeleitet werden würde. Seither sind etliche Krankheiten in ihrem Wesen aufgeklärt worden, die zuvor unter fraglichen Diagnosen wie Enzephalitis ohne Erregernachweis, nichtinfektiöse Enzephalopathie oder unter psychosomatischen Erklärungsmodellen behandelt wurden [1]. Allen gemeinsam ist, dass sich bei diesen Erkrankungen aus zum Teil noch ungeklärter Ursache Autoantikörper bilden, die eigenes Hirn- oder Nervengewebe angreifen.

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–	Klinische Zeichen	Besonderheiten	Altersverteilung	Tumor
NMDA-Rezeptor	schizophreniforme Psychosen, periorale Dyskinesien, epileptische Anfälle, Koma, Dystonie, Hypoventilation	zerebrales MRT oft unauffällig, meist Pleozytose im Liquor, Verlangsamung im EEG	alle Altersgruppen im Kindes- und Jugendalter, 75% Frauen	Bei Frauen oft Ovarial-Alteration
LGI1	faziobrachiale dystone Anfälle, Amnesie, Psychose	mesiotemporale Hyperintensität im MRT, Hyponatriämie	ältere Patienten (> 40 Jahre)	Selten
Caspr2	Neuromyotonie, Morvan-Syndrom	Ähnlich LGI1, keine Hyponatriämie	ältere Patienten	Thymom möglich
AMPA-Rezeptor	epileptische Anfälle, Gedächtnisstörungen, Psychose	Liquor meist auffällig	Erwachsene	Selten (Thymom)
GABAB-Rezeptor	epileptische Anfälle sind führend, Gedächtnisstörungen	Pleozytose, MRT-Veränderungen	Erwachsene	Vor allem kleinzelliges Bronchialkarzinom
mGluR5	Wesensänderung, emotionale Instabilität	Ophelia-Syndrom	Junge Erwachsene	Hodgkin-Lymphom
Glyzin- Rezeptor	kognitive Defizite, Hyperexzitabilität	PERM, Stift-Person- Syndrom	Ältere Erwachsene	Selten

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Inflammasom Signaling und chronische Entzündungsreaktionen
X-chromosomale TLR7-Expression bei Frauen und Prädisposition zu Lupusassoziierter Autoimmunität
Die G-Protein-gekoppelte Signaltransduktion im Immunsystem
Mutationen im JAK-STAT-Signalweg und ihre klinischen Konsequenzen

Inflammasom Signaling und chronische Entzündungsreaktionen
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Inflammasome sind Multiproteinkomplexe, die typischerweise aus drei Proteinentitäten – einem Sensor, einem Adaptor und Caspase 1 – bestehen. Sie werden als Antwort auf die Erkennung von Pathogen-assoziierten molekularen Strukturen (PAMPs) oder Gefahren-assoziierten molekularen Strukturen (DAMPs) gebildet. Eine Schlüsselrolle im Inflammasom-Signalweg spielt dabei das Zymogen Pro-Caspase 1, das zunächst selbst durch Autoprozessierung aktiviert werden muss. Aktive Caspase 1 prozessiert die Vorstufen der pro-inflammatorischen Interleukine (IL) IL-1beta (IL-1β) und IL-18, die daraufhin sekretiert werden. Caspase 1 schneidet zusätzlich Gasdermin D proteolytisch, was eine spezielle, pro-inflammatorische Form des Zelltods – Pyroptose – induziert. Durch die Sekretion der pro-inflammatorischen Interleukine und Pyroptose wird eine starke Entzündungsreaktion ausgelöst. Das Ausmaß einer Inflammasom-vermittelten chronischen Entzündungsreaktion wird bei Patienten mit „gain-of-function"-Mutationen deutlich, bei denen es zu einer Überaktivierung der Inflammasom-Sensoren kommt. Diverse Mutationen in Genen, die einzelne Sensoren der Inflammasome kodieren, lösen chronische Entzündungs- und Autoimmunerkrankungen aus, die unbehandelt tödlich verlaufen können. Viele Studien haben uns gezeigt, wie essentiell präzise Regulations- und Aktivierungsmechanismen sind, um eine effektive Bekämpfung von Pathogenen zu ermöglichen und gleichzeitig unkontrollierte und damit schädliche Entzündungsreaktionen zu verhindern. Dieser Review-Artikel fasst die allgemein anerkannten Konzepte der Inflammasomforschung zusammen und gibt Einblicke in die Aktivierungsprozesse von Inflammasome-Sensoren und die Bildung von Inflammasom-Komplexen.

Die G-Protein-gekoppelte Signaltransduktion im Immunsystem
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Die mit Abstand größte Familie der Membranrezeptoren bilden die G-Protein-gekoppelten Rezeptoren (GPCR). Dabei handelt es sich um heptahelikale Transmembranproteine, deren extrazelluläre Schleifen der Ligandenbindung dienen und deren größte intrazelluläre Schleife mit einem heterotrimeren G-Protein assoziiert ist. GPCR kommen in zahlreichen Formen auf unterschiedlichen Zellen des menschlichen Körpers vor und spielen eine zentrale Rolle in einigen grundlegenden physiologischen Vorgängen, beispielsweise der Muskelkontraktion, dem Zellstoffwechsel durch Bindung von Hormonen, der optischen und olfaktorischen Wahrnehmung sowie der Regulation des Immunsystems. Aufgrund ihrer stark verbreiteten Expression und vielfältigen Wirkungsweisen ist es kaum verwunderlich, dass einige GPCR auch mit pathophysiologischen Vorgängen des menschlichen Körpers assoziiert sind. Im Folgenden werden die verschiedenen Signaltransduktionswege der G-Protein-gekoppelten Rezeptoren und ihre Bedeutung hinsichtlich der Regulation von Immunzellen vorgestellt. Anhand von ausgewählten Beispielen wird in diesem Kontext die klinische Relevanz einzelner GPCR verdeutlicht und diskutiert.

Mutationen im JAK-STAT-Signalweg und ihre klinischen Konsequenzen
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Der JAK-STAT-Signalweg spielt eine entscheidende Rolle bei der Zytokin-Signalübertragung in den Bereichen Entwicklung, Immunkompetenz und Tumorgenese für fast jeden Zelltyp. Aufgrund der übersichtlichen Mechanismen der Signaltransduktion erscheint dieser Signalweg auf den ersten Blick wenig komplex. Bei genauerer Betrachtung finden sich jedoch viele verschiedene Faktoren, die die JAK- und STAT-Proteine beeinflussen, aber dennoch die Vielfalt der Zellantworten auf die große Anzahl von Zytokinen nicht ausreichend erklären können. Alle beteiligten Moleküle, angefangen vom Zytokin und seinem Rezeptor über die Tyrosinkinasen und die STAT-Moleküle bis hin zu molekularen Feedbackmechanismen (z. B. SOCS- und PIAS-Proteine) und dazugehörigen epigenetischen Veränderungen, können in ihrer Funktion ausfallen und damit die Ursache für die Entstehung vieler verschiedener Krankheiten darstellen. Der JAK-STAT-Signalweg war und ist Gegenstand der Grundlagenforschung und bietet über den Einsatz von JAK-Inhibitoren hinaus ein enormes Potential für die Entwicklung neuer Methoden der personalisierten Medizin und damit der Translation von molekularer Grundlagenforschung in die klinische Praxis.