Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study
https://www.sciencedirect.com/science/article/pii/S2095809920300631?via%3Dihub&fbclid=IwAR30B6VVTfABSxJIXQZVjRsZSt0dj_WqvmNJfTZ_EbYznbgxBPRAzb9Diro
Journal: Engineering *Published Online: 18 March 2020*
Authors from: China

Herein, the authors examine the effects of **Favipiravir (FPV) versus Lopinavir (LPV)/ritonavir (RTV)** for the treatment of COVID-19. Patients with laboratory-confirmed COVID-19 who received **oral FPV** (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) **plus interferon (IFN)-α by aerosol inhalation** (5 million U twice daily) were included in the FPV arm of this study, whereas patients who were treated with **LPV/RTV** (Days 1–14: 400 mg/100 mg twice daily) **plus IFN-α by aerosol inhalation** (5 million U twice daily) were included in the control arm. Changes in chest computed tomography (CT), viral clearance, and drug safety were compared between the two groups. **For the 35 patients enrolled in the FPV arm and the 45 patients in the control arm**, all baseline characteristics were comparable between the two arms. A **shorter viral clearance time was found for the FPV** arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) d versus 11 (8–13) d, $P < 0.001$). The FPV arm also showed **significant improvement in chest imaging** compared with the c ontrol arm, with an improvement rate of 91.43% versus 62.22% ($P = 0.004$). After adjustment for potential confounders, the FPV arm also showed a significantly **higher improvement rate in chest imaging**. Multivariable Cox regression showed that FPV was independently associated with faster viral clearance. In addition, **fewer adverse reactions were found in the FPV** arm than in the control arm. In this open-label nonrandomized control study, FPV showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance; if causal, these results should be important information for establishing standard treatment guidelines to combat the SARS-CoV-2 infection.

Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro
https://www.nature.com/articles/s41421-020-0156-0?fbclid=IwAR00SZmlr8i4s_GeGQHBRKFHrgLy3fOEc7X5VLrC4ecfF9Yypiba6eI2EBA
Journal: Cell Discovery *Published Online: 18 March 2020*
Authors from: China

Chloroquine (CQ) appears to be the drug of choice for large-scale use due to its availability, proven safety record, and a relatively low cost. Hydroxychloroquine (HCQ) sulfate, a derivative of CQ, was demonstrated to be much less (~40%) toxic than CQ in animals. More importantly, HCQ is still widely available to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Both CQ and HCQ are weak bases that are known to elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes, essential for membrane fusion. In addition, CQ could inhibit SARS-CoV entry through changing the glycosylation of ACE2 receptor and spike protein. Whether HCQ is as efficacious as CQ in treating SARS-CoV-2 infection still lacks the experimental evidence.

To this end, the authors evaluated the antiviral effect of HCQ against SARS-CoV-2 infection in comparison to CQ in vitro. Taken together, the data suggest that the **anti-SARS-CoV-2 activity of HCQ seems to be less potent compared to CQ**, at least at certain multiplicities of infection (MOIs).
It has been reported that oral absorption of CQ and HCQ in humans is very efficient. In animals, both drugs share similar tissue distribution patterns, with high concentrations in the liver, spleen, kidney, and lung reaching **levels of 200–700 times higher than those in the plasma**. It was reported that safe dosage (6–6.5 mg/kg per day) of HCQ sulfate could generate serum levels of 1.4–1.5 μM in humans. **Therefore, with a safe dosage, HCQ concentration in the above tissues is likely to be achieved to inhibit SARS-CoV-2 infection**.
Clinical investigation found that high concentration of cytokines were detected in the plasma of critically ill patients infected with SARS-CoV-2, suggesting that **cytokine storm** was associated with disease severity. Other than its direct antiviral activity, HCQ is a **safe and successful anti-inflammatory agent** that has been used extensively in autoimmune diseases

2019 Novel Coronavirus Disease (COVID-19): Paving the Road for Rapid Detection and Point-of-Care Diagnostics

https://www.mdpi.com/2072-666X/11/3/306
Journal: Micromachines Published Onl*ine: 14 March 2020*
Authors from: Denmark

Point-of-care (PoC) device for the rapid detection of the 2019 novel Coronavirus (SARS-CoV-2) is crucial and urgently needed. With this perspective, the authors give suggestions regarding a potential **candidate for the rapid detection** of the coronavirus disease 2019 (COVID-19), as well as factors for the preparedness and response to the outbreak of the COVID-19. In order to overcome the current time-consuming and laborious detection technique using RT-qPCR, an **alternative molecular amplification technique** should be deployed. **Loop-mediated isothermal amplification (LAMP)** reaction is a novel nucleic acid amplification technique that amplifies DNA with high specificity, efficiency, and rapidity under isothermal conditions. This method uses a **set of four specially designed primers**, and a **DNA polymerase with strand displacement activity** to synthesize target **DNA up to 109 copies in less than an hour** at a constant temperature of 65 °C. The final products are stem-loop DNAs with multiple inverted repeats of the target, bearing structures with a cauliflower-like appearance. LAMP has high specificity and sensitivity and is simple to perform; hence, soon after its initial development it became an enormously popular isothermal amplification method in molecular biology, with application in pathogen detection**. LAMP uses strand-displacement polymerases instead of heat denaturation to generate a single-stranded template;** hence, it has the advantage of running at a constant temperature, simultaneously reducing the cumbersomeness of a thermocycler as well as the energy required. LAMP technology is proven to be more stable and more sensitive in detection compared to PCR.

Professional and Home-Made Face Masks Reduce Exposure to Respiratory Infections among the General Population

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0002618
Journal: PLoS One *Published Online: July 9, 2008*
Authors from: Netherlands, USA

Face-masks worn by the general population could be an accessible and affordable intervention, if effective when worn under routine circumstances. The authors assessed transmission reduction potential provided by personal respirators, surgical masks and home-made masks when worn during a variety of activities by healthy volunteers and a simulated patient.
All types of masks reduced aerosol exposure, relatively stable over time, unaffected by duration of wear or type of activity, but with a high degree of individual variation. **FFP2** masks provided adults with about **50 times as much protection as home made masks**, and **25 times as much protection as surgical masks**. The increase in protection for children was less marked, about 10 times as much protection by FFP2 versus home-made masks and 6 times as much protection as surgical masks.
Any type of general mask use is likely to decrease viral exposure and infection risk on a population level, in spite of imperfect fit and imperfect adherence.

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19
https://www.nejm.org/doi/full/10.1056/NEJMoa2001282?query=TOC&fbclid=IwAR25Alrvzf81k67-FL_bYH7W4HZpISlK-LEsneY-CxggAgaNtoPSv50H_EU
Journal: NEJM *Published Online: March 18, 2020*
Authors from: China, UK, USA

A **randomized, controlled, open-label trial** involving 199 hospitalized adult patients with confirmed SARS-CoV-2 infection and an oxygen saturation (Sao2) of **94% or less on air** or a **ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg.** Patients were randomly assigned in a 1:1 ratio to receive **either lopinavir–ritonavir** (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, **or standard care** alone. The primary endpoint was **time to clinical improvement,** defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first and **was not met** (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). **Mortality at 28 days was similar** in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). The percentages of patients with **detectable viral RNA at various time points were similar**. Gastrointestinal adverse events were more common in the lopinavir–ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events. In hospitalized adult patients with severe Covid-19, **no benefit was observed with lopinavir–ritonavir treatment beyond standard care**.
COVID-19 induced Renin–Angiotensin System (RAS) imbalance may drive acute lung injury: the evidence and therapeutic options

https://www.bmj.com/content/368/bmj.m406/rr-19?fbclid=IwAR1HJU9UgRNeruggL2yi7eo-I3sFmhys7ckJq3Lg4fmoETSce_XfExg9sSg
Journal: BMJ Published On*line: 12 March 2020*
Authors from: USA

Several authors have debated the potential role of **angiotensin converting enzyme inhibitors** (ACEi) and **angiotensin receptor blockers** (ARBs) in treatment of COVID-19, based on the evidence that ACE2 has been identified as the host receptor for the SARS-CoV-2 virus. The authors of the present article support the hypothesis that **dysregulation of the renin angiotensin system (RAS) may serve a central role in the pathophysiology of COVID-19 associated acute lung injury (ALI)/acute respiratory distress syndrome (ARDS).**
Angiotensin I is converted to angiotensin II (AngII) by ACE. AngII mediates vasoconstrictive, pro-inflammatory and pro-oxidative effects through agonism at AngII receptor type 1 (AT1). ACE2 converts AngII to angiotensin 1-7 (Ang1-7), which through binding Mas receptor (MasR) mediates anti-inflammatory, anti-oxidative and vasodilatory effects. Hence, the ACE2/Ang1-7/MasR axis opposes the actions of the ACE/AngII/AT1 axis.
COVID-19 **appears more severe in patients with hypertension, cardiovascular disease and diabetes** . These disorders are associated with decreased baseline levels of ACE2 expression. We postulate here that **SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity**, further skewing the ACE/ACE2 balance to a state of predominant ACE/AngII/AT1 axis signaling, in which **AngII causes pulmonary vasoconstriction, and inflammatory and oxidative organ damage**, ultimately progressing towards ALI/ARDS.
This theory is supported by a recent publication by Liu et al, demonstrating that **serum AngII levels in patients with COVID-19 were significantly higher** than in non-infected individuals, and more importantly, were **linearly associated with viral load and lung injury**.
As such, we believe that RAS modulation may have a potential role in treatment of selected patients with severe COVID-19 at risk for ALI/ARDS. Since ACEi can lead to cough secondary to accumulation of bradykinin, we believe ARBs, recombinant ACE2 or Ang1-7 may be more favorable treatment options. Of note, a **pilot clinical trial of recombinant ACE2 in ARDS showed that the treatment was well tolerated and led to decreased serum AngII and increased serum Ang1-7 levels**. To further evaluate the role of RAS modulation in COVID-19, datasets should be analyzed to investigate if **use of ACEi and ARBs on admission could be associated with ALI/ARDS and/or mortality** in patients with diabetes, hypertension and cardiovascular disease.

SARS-CoV-2 Infection in Children
https://www.nejm.org/doi/full/10.1056/NEJMc2005073?fbclid=IwAR2RHQj3K9K8G3d0K87Vbs4bs9GTtM8rBWuAhII-xtSVP74YPskAjGijyys
Journal: NEJM *Published Online: March 18, 2020*
Authors from: China, USA

A recent review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that **less than 1% of the cases were in children younger than 10 years** of age.

The authors evaluated children infected with SARS-CoV-2 and treated at the Wuhan Children's Hospital, the only center assigned by the central government for treating infected children under 16 years of age in Wuhan. Both symptomatic and asymptomatic children with known contact with persons having confirmed or suspected SARS-CoV-2 infection were evaluated. Nasopharyngeal or throat swabs were obtained for detection of SARS-CoV-2 RNA.
Of the 1391 children assessed and tested from January 28 through February 26, 2020, a total of **171 (12.3%) were confirmed to have SARS-CoV-2 infection**, median age was 6.7 years. **Fever was present in 41.5%** of the children at any time during the illness. Other common signs and symptoms included **cough** and **pharyngeal erythema**. **15.8% did not have any symptoms** of infection or radiologic features of pneumonia. A total of **12 patients had radiologic features of pneumonia but did not have any symptoms of infection**. During the course of hospitalization, **3 patients required intensive care** support and invasive mechanical ventilation; **all had coexisting conditions** (hydronephrosis, leukemia [for which the patient was receiving maintenance chemotherapy], and intussusception). **Lymphopenia (lymphocyte count, <1.2×109 per liter) was present in 6 patients (3.5%)**. The most common radiologic finding was **bilateral ground-glass opacity (32.7%).** As of March 8, 2020, there was **one death**. A 10-month-old child with intussusception had multiorgan failure and died 4 weeks after admission. A total of 21 patients were in stable condition in the general wards, and 149 have been discharged from the hospital.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial
https://drive.google.com/file/d/186Bel9RqfsmEx55FDum4xY_IlWSHnGbj/view
Journal: Méditerranée Infection *Published Online: March 18, 2020*
Authors from: France, Vietnam

French Confirmed COVID-19 patients were included in a **single arm protocol** from early March to March 16th, to receive **600mg of hydroxychloroquine daily**. **Viral load** in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, **azithromycin** was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as **negative controls**. Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. **Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls** (primary endpoint), and much lower average carrying duration than reported of untreated patients in the literature. **Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.** Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1
https://www.nejm.org/doi/full/10.1056/NEJMc2004973?query=RP

Journal: NEJM *Published Online: March 17, 2020*
Authors from: USA

The authors evaluated the stability of SARS-CoV-2 and SARS-CoV-1 in aerosols and on various surfaces and estimated their decay rates using a Bayesian regression model. The data consisted of 10 experimental conditions involving the two viruses in five environmental conditions (**aerosols, plastic, stainless steel, copper, and cardboard**). All experimental measurements are reported as means across three replicates.
SARS-CoV-2 remained viable in aerosols throughout the duration of our experiment (3 hours), with a reduction in infectious titer from 103.5 to 102.7 TCID50 per liter of air. This reduction was similar to that observed with SARS-CoV-1, from 104.3 to 103.5 TCID50 per milliliter.
SARS-CoV-2 was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was detected **up to 72 hours after application to these surfaces**, although the virus titer was greatly reduced. The stability kinetics of SARS-CoV-1 were similar. On copper, no viable SARS-CoV-2 was measured after 4 hours and no viable SARS-CoV-1 was measured after 8 hours. On cardboard, no viable SARS-CoV-2 was measured after 24 hours and no viable SARS-CoV-1 was measured after 8 hours. Both viruses had an exponential decay in virus titer across all experimental conditions. The stability of SARS-CoV-2 was similar to that of SARS-CoV-1 under the experimental circumstances tested. This indicates that differences in the epidemiologic characteristics of these viruses probably **arise from other factors**, including high viral loads in the upper respiratory tract and the potential for persons infected with SARS-CoV-2 to shed and transmit the virus while asymptomatic. The results indicate that **aerosol and fomite transmission of SARS-CoV-2 is plausible**.

Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection

https://pubs.rsna.org/doi/10.1148/radiol.2020200463?fbclid=IwAR0BB9BP3a2Xu7dorbFLCM55IF2FB4Sl1B6FJ2SK7hsap6RgaIRfJeTMc0g
Journal: Radiology *Published Online: Feb 20 2020*
Authors from: USA, China

In this **retrospective** study, **chest CTs of 121 symptomatic patients** infected with coronavirus disease-19 (COVID-19) from four centers in China from January 18, 2020 to February 2, 2020 were reviewed for common CT findings in relationship to the **time between symptom onset and the initial CT scan** (i.e. early, 0-2 days (36 patients), intermediate 3-5 days (33 patients), late 6-12 days (25 patients)). The hallmarks of COVID-19 infection on imaging were **bilateral and peripheral ground-glass and consolidative pulmonary opacities**. Notably, **56% of early patients had a normal CT**. With a longer time after the onset of symptoms, CT findings were more frequent, including consolidation, bilateral and peripheral disease, greater total lung involvement, linear opacities, “crazy-paving” pattern and the “reverse halo” sign. **Bilateral lung involvement was observed in 28% of early patients, 76% of intermediate patients and 88% of late patients.**

Teicoplanin: An Alternative Drug for the Treatment of Coronavirus COVID-19?

https://www.sciencedirect.com/science/article/pii/S0924857920300947?via%3Dihub
Journal: International Journal of Antimicrobial Agents *Published Online: 13 March 2020*
Authors from: France

Due to the lack of efficient and specific treatments and the need to contain the epidemic, **drug repurposing** appears to be the best tool to find therapeutic solution. Teicoplanin, a glycopeptide antibiotic used to treat staphylococci infection, previously **showed efficacy against various viruses** including ebola, influenza virus, flavivirus, hepatitis C virus, HIV virus and on coronavirus such as MERS-CoV and SARS-CoV. According to Zhou and colleagues, in coronaviruses, teicoplanin acts on the early step of the viral life cycle by **inhibiting the low pH cleavage of the viral spike protein by cathepsin L** in the late endosomes thereby **preventing the release of genomic viral RNA** and the continuation of virus replication cycle. A recent study by the same authors showed that this activity **was conserved on SARS-Cov-2**. These preliminary results need to be confirmed now by a randomized clinical trial.

COVID-19, ECMO, and lymphopenia: a word of caution
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30119-3/fulltext
Journal: The Lancet Respiratory Medicine Pub*lished Online: March 13, 2020*
Author from: USA

ECMO can serve as life-saving rescue therapy for refractory respiratory failure in the setting of acute respiratory distress syndrome, such as that induced by coronavirus disease 2019 (COVID-19). In the study by Yang and colleagues five (83%) of six patients receiving ECMO died. Although this sample was small, and specific baseline characteristics and disease courses were almost unknown, it raises concerns about potential **harms of ECMO therapy for COVID-19**. Lymphocyte count has been associated with increased disease severity in COVID-19. Patients who died from COVID-19 are reported to have had **significantly lower lymphocyte counts than survivors.** As such, we need to consider the potential compounding immunological insults involved with **initiation of an extracorporeal circuit** in these patients. During ECMO, substantial **decreases in the number and function of some populations of lymphocytes** is commonplace. As it might be hypothesised that repletion of lymphocytes could be key to recovery from COVID-19, **lymphocyte count should be closely monitored in these patients receiving ECMO.**
Ruan and colleagues also showed that **interleukin-6** (IL-6) concentrations differed significantly between survivors and non-survivors of COVID-19, with **non-survivors having up to 1.7-times higher values.** During ECMO, **IL-6 concentrations are consistently elevated and inversely correlated with survival in children and adults**. Those that survived ECMO were able to normalise their IL-6 concentrations, whereas those that died had persistently elevated values. Moreover, elevated IL-6 concentrations in lung induced by initiation of ECMO have been convincingly shown to be associated with parenchymal damage in animal models of venovenous ECMO. **While not to discourage the use of ECMO**, based on the abovementioned observations, **the immunological status of patients should be considered when selecting candidates for ECMO**.

Arbidol Combined With LPV/r Versus LPV/r Alone Against Corona Virus Disease 2019:a Retrospective Cohort Study
https://pubmed.ncbi.nlm.nih.gov/32171872/?from_term=covid+19&from_sort=date&from_page=27&from_pos=9
Journal: Journal of Infection *Published Online: March 11, 2020*
Authors from: China

Retrospective cohort study to compare **arbidol and lopinavir/ritonavir** (LPV/r) treatment for adults with COVID-19 **with LPV/r only** included patients without invasive ventilation, diagnosed between Jan 17, 2020, and Feb 13, 2020. Patients were given treatment for 5-21 days. The primary endpoint was a **negative conversion rate of coronavirus from the date of COVID-19 diagnosis (day7, day14)**, and assessment whether the pneumonia was progressing or improving by chest CT (day7). The SARS-CoV-2 could not be detected for 12 **(75%)** of 16 patients' nasopharyngeal specimens in the combination group **after seven days**, compared with 6 **(35%)** of 17 in the monotherapy group (p<0•05). **After 14 days**, 15 **(94%)** of 16 and 9 **(52.9%)** of 17, respectively, SARS-CoV-2 could not be detected (p<0.05). The **chest CT scans were improving for** 69% vs. 29% after 7 days.

Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis
https://www.sciencedirect.com/science/article/pii/S0033062020300554?via%3Dihub
Journal: Progress in Cardiovascular Diseases Published Online: *10 March 2020*
Authors from: Italy, USA, Spain

The authors performed an analysis of the current scientific literature to investigate whether the measurement of cardiac troponin I (cTnI) or cardiac troponin T (cTnT) may help predict clinical severity in patients with COVID-19. Overall 4 studies were included in the meta-analysis. Three studies used high-sensitivity **cTnI** and one cTnI. All studies were set in China, included a total number of 341 patients (123 with severe disease; 36%). Although the heterogeneity was considerably high, **the values of cTnI were found to be significantly increased in COVID-19 patients with severe disease than in those without.** Recent literature data has shown that cTnI concentration is only marginally increased in all patients with SARS-CoV-2 infection, whereby values exceeding the 99th percentile in the upper reference limit (URL) can only be observed in 8–12% of positive cases. Nonetheless, what seems to emerge from our results is that cTnI values are significantly increased in patients with severe SARS-CoV-2 infection compared to those with milder forms of disease. It is hence reasonable to hypothesize that initial measurement of cardiac damage biomarkers immediately after hospitalization for SARS-CoV-2 infection, as well as longitudinal monitoring during hospital stay, **may help identifying a subset of patients with possible cardiac injury.** Urgent studies shall also be planned to define whether or not echocardiographic testing and other adjunctive cardioprotective therapies may be advisable in patients with significant elevation of cardiac injury biomarkers.

The convalescent sera option for containing COVID-19
https://www.jci.org/articles/view/138003

Journal: The Journal of Clinical Investigation Published *Online: March 13, 2020*
Authors from: USA

Human convalescent serum is an option for prevention and treatment of COVID-19 disease. The anticipated mechanism of action by which passive antibody therapy would mediate protection is **viral neutralization**. However, other mechanisms may be possible, such as antibody-dependent cellular cytotoxicity and/or phagocytosis. Possible sources of antibody for SARS-CoV-2 are human convalescent sera from individuals who have recovered from COVID-19, mAbs, or preparations generated in certain animal hosts, such as genetically engineered cows that produce human antibodies. Although many types of preparations are or will soon be under development, the only antibody type that is **currently available for immediate use is that found in human convalescent sera**. As more individuals contract COVID-19 and recover, the number of potential donors will continue to increase. A general principle of passive antibody therapy is that it is **more effective when used for prophylaxis** than for treatment of disease. When used for therapy, antibody is **most effective when administered shortly after the onset** of symptoms. However, those who recover from viral disease **may not have high titers** of neutralizing antibodies . Consistent with this point, an analysis of 99 samples of convalescent sera from patients with SARS showed that only 87 had neutralizing antibodies. One of the risks of the therapy is that it may prevent disease in a manner that attenuates the immune response, leaving such individuals **vulnerable to subsequent reinfection.**

There is some experience with the method from the SARS outbreak. The largest study involved the treatment of 80 patients in Hong Kong. Patients treated before day 14 had **improved prognosis** defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. There is also some anecdotal information on the use of convalescent serum in **seriously ill individuals**. Three patients with SARS in Taiwan were treated with 500 mL convalescent serum, resulting in a reduction in serum virus titer, and each survived. There are also reports that convalescent serum was used for therapy of patients with COVID-19 in China **during the current outbreak.** Although few details are available from the epidemic in China and published studies involved small numbers of patients, the available information suggests that convalescent serum administration **reduced viral load** and **was safe**.

At least one pharmaceutical company, Takeda, is gearing up to generate antibody preparations against SARS2-CoV-2 from COVID-19 convalescent sera. Producing highly purified preparations containing a high titer of neutralizing antibodies against SARS2-CoV-2 is preferable to convalescent sera given that these are safer and have higher activity. Unfortunately, such preparations will not be available for many months, whereas locally produced convalescent sera could be available much sooner.

How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital
https://link.springer.com/article/10.1007%2Fs00134-020-05993-9
Journal: Intensive Care Medicine Published Online: *11 March 2020*
Authors from: China

The article describes AMI protocols in Sichuan Provincial People's Hospital during the SARS-CoV-2 outbreak. According to this document, patients with AMI accompanied by fever, especially respiratory symptoms, should first go to a fever outpatient clinic. Combined with epidemiological history and body temperature screening, if suspected of SARS-CoV-2 infection, they will be admitted to the hospital isolation ward for rapid nucleic acid test. **The test can significantly delay the time of STEMI emergency reperfusion.** Patients suspected or diagnosed with SARS-CoV-2 infection **should be isolated and begin thrombolytic therapy immediately, if within reperfusion time**. After the patient has recovered from COVID-19 pneumonia and test of nucleic acid is twice negative, elective PCI should be considered. High-risk patients with contraindications for thrombolysis need to assess the risk of infection and the benefit of PCI. **Perform PCI only for culprit vessel**. The door-to-balloon time in **NSTEMI** patients is less strict than that in STEMI patients. Therefore, the SARS-CoV-2 infection should be excluded first. The confirmed case should be transferred to the isolation ward until patient recovery and then it was assessed whether further invasive interventions are needed. Very few NSTEMI patients may present hemodynamic instability and fatal arrhythmia who cannot wait for the results of nucleic acid tests, and then, the isolated intervention surgery should be the first choice.

Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines

https://www.sciencedirect.com/science/article/pii/S1673852720300278?via%3Dihub

Journal: Journal of Genetics and Genomics *Published Online:* 13 February 2020

Authors from: China

The ~306 aa long **main protease** (Mpro) is a **key enzyme for coronavirus replication**. Studies have shown that the Mpros of different coronaviruses are highly conserved in terms of both sequences and 3D structures. These features, together with its functional importance, have made Mpro an attractive target for the design of anticoronaviral drugs A previous attempt to predict drugs for the Mpro of SARS-CoV has identified two HIV-1 protease inhibitors, namely **lopinavir and ritonavir**, as potential candidates, both of which bind to the same target site of Mpro.

The authors performed virtual docking to screen for commercial medicines in the DrugBank database that could bind to the above mentioned pocket site of 2019-nCoV Mpro, and identified 10 candidate clinical medicines (**colistin, valrubicin, icatibant, bepotastine, epirubicin, epoprostenol, vapreotide, aprepitant, caspofungin, perphenazine**). Compared to lopinavir/ritonavir, most of these predicted drugs could form more hydrogen bonds with 2019-nCoV Mpro, thus may have higher mutation tolerance than lopinavir/ritonavir. It should be noted that these results were obtained solely by in silico predictions, further experiments are needed to validate the efficacy of these drugs.

Timely development of vaccines against SARS-CoV-2

https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1737580

Journal: Emerging Microbes and Infections *Published Online: 08 March, 2020*
Authors from: USA

The good news now is that many entities have taken actions. **CEPI (Coalition for Epidemic Preparedness Innovations)** announced the funding to three platform vaccine technologies, DNA, mRNA, and "molecular clamp", to develop vaccines against SARS-2. The **US NIAID Vaccine Research Centre (VRC)** is drawing on broad research experience with coronaviruses, combined with a wide network of collaborators from academia, other government agencies, and industry, on the development of various SARS-2 vaccine candidates. **Biotech and traditional vaccine companies** in many countries are joining. **China** demonstrated confidence in developing a vaccine against this viral infection. More recently, the official announcement by the Chinese Health Commission indicated that at least five vaccine technologies will be explored: inactivated vaccine, subunit protein vaccine, nucleic acid vaccine, adenoviral vector vaccine, and recombinant influenza viral vector vaccine. China vaccine developers are expected to announce multiple leading candidate vaccines in the near future.
Given the unique requirements of a vaccine against the rapidly spreading emerging viral infection, vaccine technologies **with previous human study experience** will have the advantage, especially for the consideration of safety. Furthermore, whether the developer can quickly move its vaccine technology into a **scale-up** GMP production for potentially 10-million doses is another challenge. Anyone with an existing facility and the experience of such production will be in a much more favourable position. The immunopathogenesis plays a major role in SARS-2 infection and thus it is important to ensure that vaccines against this virus **should not elicit the same type of detrimental immune responses**. Finally, the planning should start now on how to let the world have **equal access** to a successful SARS-2 vaccine if the need is global.

SARS-CoV-2: a potential novel etiology of fulminant myocarditis
https://link.springer.com/article/10.1007%2Fs00059-020-04909-z
Journal: Herz *Published Online: 05 March 2020*
Authors from: China

Although **elevated cardiac troponin** I (cTnI) levels and **arrhythmia** were recorded, no specific investigation of the effects of SARS-CoV‑2 infection on the cardiovascular system was reported. The pathophysiology of SARS-CoV‑2 has not been completely understood. Studies have suggested the **cytokine storm** might affect the disease severity. The authors of the present study noticed that the plasma **IL‑6 level was increased** dramatically in SARS-CoV-2-infected patients with cardiac injury. Moreover, death was associated with the cardiac damage induced by **fulminant myocarditis** (FM). Considering that a cytokine storm is also the core pathophysiological mechanism in FM—which is often fatal, especially in patients with severe multiple organ dysfunction—**SARS-CoV-2-associated FM should be given more attention**. FM is a rare clinical syndrome with features of cardiac inflammation and a reported high mortality rate of approximately 40–70%. FM can be categorized into the histologically defined entities of lymphocytic, eosinophilic, and giant cell myocarditis and sarcoid heart disease. The lymphocytic forms are subdivided into those of infective and noninfective origin. The treatment

regimen includs an early application of sufficient doses of **immune-modulation drugs**, e.g., sufficient doses of steroids and i.v. immunoglobulins, neuraminidase inhibitors, and active mechanical life-support treatments. The life-support treatments comprised the application of mechanical respirators and circulatory support systems, of which **intra-aortic balloon pulsation** (IABP) or **Impella implantation** or **ECMO**, as well as **cardiac pacemaker** are part of the current therapeutic armamentarium These measures follow the hemodynamic principle of **unloading the inflamed myocardium**.

Arguments in favour of remdesivir for treating SARS-CoV-2 infections

https://www.sciencedirect.com/science/article/pii/S0924857920300832?via%3Dihub

Journal: International Journal of Antimicrobial Agents Published Online: March 6, 2020
Authors from: Taiwan, France

Remdesivir is a **nucleotide analogue inhibitor of RNA-dependent RNA polymerases**. It was developed by Gilead Science Inc. and has not been licensed or approved anywhere so far, but has been recommended for the treatment of cats with feline infectious peritonitis, which is uncommon but fatal and is caused by a feline coronavirus. An in vitro study has demonstrated that remdesivir - structurally a nucleoside triphosphate - works as an incorporation competitor with adenosine triphosphate, confuses viral RdRp, acts as a delayed RNA chain terminator against Ebola virus, evades proofreading by viral exoribonuclease, and causes a decrease in viral RNA production. Recently, the antiviral activity of remdesivir was demonstrated at the stage after virus entry into Vero E6 cells, supporting its antiviral mechanism as a nucleotide analogue. In 2016. The **first case of COVID-19 in Washington, USA**, was treated with **i.v. remdesivir** for the progression of pneumonia on Day 7 of hospitalisation. Interestingly, **the patient's condition improved and no obvious adverse effects were observed**. Of note, real-time reverse transcription PCR testing for SARS-CoV-2 in nasopharyngeal and oropharyngeal swabs remained positive at 4 days after the administration of remdesivir, but the authors noted a **trend in the decline of viral load** . The oropharyngeal swab tested negative for SARS-CoV-2 on Day 13. **There are two phase 3, randomised, double-blind, placebo-controlled multicentre clinical trials** currently ongoing in China - NCT04252664 and NCT04257656. The number of cases planned to be enrolled is 308 and 452, respectively. A 10-day regimen of remdesivir treatment is as follows: 200 mg loading dose on Day 1, followed by 100 mg once-daily maintenance doses for 9 days in both studies.

Guidelines for pregnant women with suspected SARS-CoV-2 infection

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30157-2/fulltext

Journal: The Lancet Infectious Diseases *Published Online: March 03, 2020*
Authors from: Switzerland, China, France, USA

Coronaviruses responsible for SARS and MERS can cause severe adverse pregnancy outcomes, such as miscarriage, premature delivery, intrauterine growth restriction, and maternal death. Vertical transmission of the virus responsible for COVID-19 has not yet been detected, whereas perinatal transmission has been suspected in one case (to the date of publication of

the present study). In the algorithm, we suggest that any pregnant woman who has **travelled in a country affected** by SARS-CoV-2 within the **previous 14 days** or who has had **close contact** with a patient with confirmed SARS-CoV-2 infection **should be tested** with a SARS-CoV-2 nucleic acid amplification test, **even if asymptomatic**. Pregnant women with laboratory-confirmed SARS-CoV-2 infection who are **asymptomatic should be self-monitored at home** for clinical features of COVID-19 for at least 14 days. These patients and those recovering from mild illness should be monitored with **bimonthly fetal growth ultrasounds and Doppler assessments** because of the potential risk for intrauterine growth restriction. Pregnant women with **COVID-19 pneumonia** should be managed by a **multidisciplinary team at a tertiary care centre**. When qSOFA criteria are met, the patient should be transferred to an intensive care unit. For pregnant women with confirmed infection, the **choice of delivery timing should be individualised depending on the week of gestation and maternal, fetal, and delivery conditions**. Whenever possible, **vaginal delivery via induction of labour**, with eventual instrumental delivery to avoid maternal exhaustion, **should be favoured to avoid unnecessary surgical complications** in an already sick patient. Septic shock, acute organ failure, or fetal distress should prompt **emergency cesarean delivery** (or termination if legal before fetal viability). **Newborns** of mothers positive for SARS-CoV-2 **should be isolated for at least 14 days** or until viral shedding clears, during which time **direct breastfeeding is not recommended**.

Therapeutic options for the 2019 novel coronavirus (2019-nCoV)
https://www.nature.com/articles/d41573-020-00016-0
Journal: Nature Reviews Drug Discovery *Published Online: February 10, 2020*
Authors from: China, Belgium

Similar to SARS and MERS, the 2019-nCoV genome encodes non-structural proteins (such as **3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase**), structural proteins (such as **spike glycoprotein**) and accessory proteins
The four non-structural proteins mentioned above are key enzymes in the viral life cycle, and the spike glycoprotein is indispensable for virus–cell receptor interactions during viral entry. These five proteins were therefore recognized as attractive targets to develop antiviral agents against SARS and MERS. Because the four structural proteins are highly conserved across 2019-nCoV, SARS and MERS it is reasonable to consider repurposing existing MERS and SARS inhibitors for 2019-nCoV. **Favipiravir and ribavirin** and experimental nucleoside analogues (**remdesivir and galidesivir**) may have potential against 2019-nCoV. Nucleoside analogues in the form of adenine or guanine derivatives target the RNA-dependent RNA polymerase and block viral RNA synthesis in a broad spectrum of RNA viruses. Approved protease inhibitors including **disulfiram, lopinavir and ritonavir** have been reported to be active against SARS and MERS. Disulfiram, an approved drug to treat alcohol dependence, has been reported to inhibit the papain-like protease of MERS and SARS in cell cultures, but clinical evidence is lacking. The spike glycoprotein is also a promising target. **Griffithsin**, a red-alga-derived lectin, binds to oligosaccharides on the surface of various viral glycoproteins, including HIV glycoprotein 120 and SARS-CoV spike glycoprotein. **Pegylated interferon alfa-2a and -2b**, could be used to stimulate innate antiviral responses in patients infected with 2019-nCoV,

and trials involving interferons have been initiated. However, it is unclear whether a pegylated interferon and a nucleoside compound could act synergistically against 2019-nCoV. An approved immune modulator, **chloroquine,** shows inhibitory effects against 2019-nCoV and is being evaluated in an open-label trial. **Nitazoxanide**, approved for diarrhea treatment, could also inhibit 2019-nCoV in vitro. **Phase III trials of remdesivir** have been initiated, and many other trials are being established in China to test various treatment options such as umifenovir, oseltamivir and ASC09F. In addition, more than 50 existing MERS and/or SARS inhibitors, such as galidesivir, the protease inhibitors GC813 and compound 3k, the helicase inhibitor SSYA10- 001 and the nucleoside analogue pyrazofurin could be screened against 2019-nCoV by facilities that have appropriate biocontainment capability.

Broad Spectrum Antiviral Agent Niclosamide and Its Therapeutic Potential
https://pubs.acs.org/doi/10.1021/acsinfecdis.0c00052
Journal: ACS Infectious Diseases *Published Online: March 10, 2020*
Authors from: USA

Through a series of drug repurposing screening campaigns, **niclosamide, an FDA-approved anthelminthic drug,** was found to be effective against various viral infections with nanomolar to micromolar potency such as SARS-CoV, MERS-CoV, ZIKV, HCV, and human adenovirus, indicating its potential as an antiviral agent.

COVID-19 – what should anaethesiologists and intensivists know about it?
https://www.termedia.pl/COVID-19-what-should-anaethesiologists-and-intensivists-know-about-it-,118,40133,1,1.html
Journal: Anaesthesiology Intensive Therapy *Published Online: March 16, 2020*
Authors from: Poland

A review article discussing etiology and pathogenesis, epidemiology, diagnostics (clinical, laboratory tests, radiological features) and treatment of COVID-19. In severe cases, lung-protective ventilation should be used – **tidal volumes should not exceed 4–6 mL kg-1 predicted body weight** (PBW), and r**espiration rates should be as low as possible** – allowing to maintain a **pH greater than 7.2**. A tidal volume of up to 8 mL kg-1 of PBW is acceptable if adverse events occur (e.g. dyssynchrony, pH < 7.15). It is recommended to **use high or very high PEEP**, determined by means of titration, so as to obtain satisfactory saturation with the lowest feasible FiO2, without generating too much pulmonary vascular resistance at the end of inspiration. In practice, the PEEP values range between 13 and 24 cm H_2O. In patients with severe COVID-19-related ARDS, the lung compliance is usually high, so inspiratory pressures rarely exceed 13 cm H_2O, and plateau pressures are not higher than 25–27 cm H_2O (unpublished information from Prof. Paolo Pelosi). The use of ventilation in the **prone position** provides good results in patients unresponsive to conventional methods of respiratory therapy. However, the time the medical team needs to put on protective clothing should be considered. It is recommended to keep the patient in the prone position **over 12 hours a day**, provided that his/her clinical condition allows it. Avoid disconnecting the ventilator system. **The WHO guidelines refer relatively positively to the use ECMO**, but some experts

are more sceptical. Specific pharmacological treatment for the new 2019-nCoV coronavirus is not available. Some centres are using **empirical antiviral therapy with darunavir or lopinavir in combination with ritonavir and oseltamivir and hydroxychloroquine** . Moreover, no data have been reported regarding the use of **aerosolised interferon-α**. Preventive administration of antibiotics should not take place **without microbiologically confirmed bacterial superinfection**. In confirmed bacterial infections, broad-spectrum empirical antibiotic therapy should be avoided; rather **targeted antibiotic** therapy should be used with de-escalation of treatment as early as possible. In patients with circulatory insufficiency, the use of **noradrenaline** is recommended to maintain organ perfusion at the expense of possibly restrictive fluid therapy. **Glucocorticosteroids should not be given to patients routinely.** Only in septic shock resistant to vasopressor therapy, 50 mg intravenous hydrocortisone every 6 hours is recommended. **The neuromuscular block should be limited exclusively to cases of significant patient-ventilator dyssynchrony** preventing the achievement of the set tidal volumes, or to cases of rapidly progressing hypoxaemia or hypercapnia.

Anesthesia procedures that carry a **high risk of infection** include those during which aerosol is formed, which may penetrate the respiratory tract or the conjunctival sac of the medical personnel. These are **tracheal intubation, replacement of the endotracheal/tracheostomy tube, bronchial fibroscopy**, all activities related to **disconnection of the ventilator system**, etc. Disconnection of the system can happen accidentally, e.g. when turning a patient for ventilation in prone position, therefore special precautions must be taken in such circumstances. **Planned removal** of the endotracheal tube is also a dangerous moment for the personnel and requires protection with PPE. The intubation itself should be "planned" or "semi-planned", before the patient's condition necessitates "rescue" instrumentation of the respiratory tract, when there is no time to apply PPE accurately. It is worth considering putting on **two pairs of gloves**, so that immediately after intubation the outer glove could be used as a cover for the laryngoscope, which must be put in a resealable bag together with it; the inner gloves should be replaced as soon as possible. One must remember **not to touch the environment with dirty gloves**(the ventilator, the anesthesia apparatus, the tables), which often happens right after intubation and extubation.

Moreover, another situation has to be mentioned, which poses a huge threat to ICU staff and is most often performed by anaesthesiologists, i.e. cardiopulmonary resuscitation (CPR). It may concern a patient with already confirmed infection, an isolated one, or not yet diagnosed one. The main hazard for staff is the **aerosol formed during ventilation with a self-inflating bag;** another problem is associated with quick protection with PPE, which can be problematic, almost certainly when resuscitation is carried out somewhere in a hospital and not in an isolated room. The number of **persons involved in CPR should be reduced to minimum**, with minimal, ideally none, involvement of other personnel.
Based on previous experience, it is known that the ways to reduce personnel exposure include **apnoeic oxygenation** or **careful ventilation through a mask by two staff members, one of whom presses it tightly against the patient's face** (with filter protection).
Early intubation is recommended. Use of mechanical chest compression devices reduces strain and minute ventilation in the personnel, which, in turn, reduces risk of inhalation of

infectious aerosol; the risk of the protective mask shifting/slipping or hair getting out from under the cap is also reduced. For patients already mechanically ventilated, in order not to disconnect the system and ventilate the lungs with a self-inflating bag, you can **put the ventilator into a volume-controlled ventilation mode,** with high peak inspiratory pressure (PIP) alarm threshold.

Association of Radiologic Findings With Mortality of Patients Infected With 2019 Novel Coronavirus in Wuhan, China
https://pubmed.ncbi.nlm.nih.gov/32191764/?from_term=covid+19&from_sort=date&from_page=5&from_pos=9
Journal: PLoS One *Published Online: 19 March, 2020*
Authors from: China

Radiologic characteristics of 2019 **novel coronavirus infected pneumonia** (NCIP) which had not been fully understood are especially important for diagnosing and predicting prognosis. The authors retrospectively studied **27 consecutive patients** (12 men, median age 60 yrs) who were confirmed NCIP. The clinical characteristics and CT image findings were collected, and the association of radiologic findings with mortality of patients was evaluated. 17 patients discharged in recovered condition and 10 patients died in hospital. The **median age of mortality group was higher** compared to survival group (68 (IQR 63–73) vs 55 (IQR 35–60), P = 0.003). 80% of those who died had comorbidities. The predominant CT characteristics consisted of **ground glass opacity** (67%), **bilateral sides involved** (86%), **both peripheral and central distribution** (74%), **and lower zone involvemen**t (96%). The **median CT score** of mortality group was higher compared to survival group (30 (IQR 7–13) vs 12 (IQR 11–43), P = 0.021), with more frequency of **consolidation** (40% vs 6%, P = 0.047) and **air bronchogram** (60% vs 12%, P = 0.025). An optimal **cutoff value of a CT score of 24.5 had a sensitivity of 85.6% and a specificity of 84.5% for the prediction of mortality.**

Coronavirus disease 2019: the harms of exaggerated information and non- evidence- based measures
https://onlinelibrary.wiley.com/doi/abs/10.1111/eci.13222
Journal: European Journal of Clinical Investigation *Published Online: March 19,2020*
Author from: USA

Opinion paper on the importance of unbiased data regarding COVID-19 epidemics: “The evolving COVID-19 is certainly cause for concern. Proper communication and optimal decision-making is an ongoing challenge, as data evolve. The challenge is compounded, however, by exaggerated information. This can lead to inappropriate actions. It is important to differentiate promptly the true epidemic from an epidemic of false claims and potentially harmful actions”.

COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics
https://www.tandfonline.com/doi/full/10.1080/21645515.2020.1735227
Journal: Human Vaccines and Immunotherapeutics *Published Online: March 18, 2020*

Authors from: India

Efforts have been made to develop vaccines against human coronavirus (CoV) infections such as MERS and SARS in the past decades. However, to date, no licensed antiviral treatment or vaccine exists for MERS and SARS. Most of the efforts for developing CoV vaccines and drugs target the **spike glycoprotein or S protein**, the **major inducer of neutralizing antibodies**. Although a few candidates have shown efficacy in in vitro studies, not many have progressed to randomized animal or human trials, hence may have limited use to counter COVID-19 infection. This article highlights ongoing **advances in designing vaccines and therapeutic**s to counter COVID-19 while also focusing on such experiences and advances as made with earlier SARS- and MERS-CoVs, which together could enable efforts to halt this emerging virus infection.

Coronavirus in pregnancy and delivery: rapid review
https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/uog.22014
Journal: Ultrasound in Obstetrics and Gynecology *Published Online: March 17, 2020*
Authors from: UK

There are **limited case series** reporting the impact on women affected by coronaviruses (CoV) during pregnancy. In women affected by SARS and MERS, the **case fatality rate appeared higher in women affected in pregnancy** compared with non-pregnant women. The authors conducted a rapid review to guide health policy and management of women affected by COVID-19 during pregnancy, which was used to develop the **RCOG guidelines on COVID-19 infection in pregnancy**. 23 relevant studies (case reports and case series) were identified. From reports of **32 women to date affected by COVID-19 in pregnancy**, delivering 30 babies (one set of twins, three ongoing pregnancies), seven **(22%) were asymptomatic** and **two (6%) were admitted to the ICU** (one of whom remained on extracorporeal membrane oxygenation). No maternal deaths have been reported to date. **Delivery was by Cesarean section in 27 cases and by vaginal delivery in two, and 15 (47%) delivered preterm,** which may put considerable pressure on neonatal services if the UK's reasonable worst-case scenario of 80% of the population being affected is realized**.** There was **one stillbirth and one neonatal death**. In 25 babies, **no cases of vertical transmission** were reported; 15 were reported as being tested with RT-PCR after delivery. Compared with SARS and MERS, **COVID-19 appears less lethal in this clinical setting.** Based on the information, the recommendation is as follows: delivery mode should be determined **primarily by obstetric indication** and the data is **against routine separation of COVID-19-affected mothers and babies.**

Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on ST-Segment–Elevation Myocardial Infarction Care in Hong Kong, China
https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.120.006631
Journal: *Circulation: Cardiovascular Quality and Outcomes* Published Online: March 17, 2020
Authors from: Hong Kong (China)

Systems of care have been established to expedite PCI workflow to **minimize ischemic time**. The authors describe the impact of the COVID-19 outbreak on STEMI care in Hong Kong through a handful of recent cases of patients with STEMI who underwent PCI at a single center. Indications for PCI were according to the international guidelines.The center has offered 24/7 PCI service to all eligible patients presenting with acute STEMI per standard protocol. When STEMI is diagnosed, a PCI team is activated after cardiology evaluation. Data on key time points in STEMI care are recorded in a clinical registry. From January 25, 2020, to February 10, 2020, the authors observed **changes in time components of STEMI care** among the aggregate group of 7 consecutive patients who underwent PCI. These 7 patients did not suffer from COVID-19 infection, and 6 out of 7 presented to the hospital during regular work hours. Median times were longer in all components when compared with historical data from the prior year. The largest time difference was in the **time from symptom onset to first medical contact**, door to device and cathlab arrival to device times were also prolonged. Precautions such as detailed travel and contact history, symptomatology, and chest X-ray, therefore, are taken before transferring patients to the catheterization laboratory. Although these are essential measures for containing COVID-19 infection, this could increase delays in diagnosis, staff activation and transfer if healthcare systems are not prepared. Similarly, even after patients arrived in the catheterization laboratory, staff may need more time to wear protective gear to prepare the patients and interventional cardiologists may not be used to performing PPCI while in full protective gear, leading to longer treatment.

Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis
https://pubmed.ncbi.nlm.nih.gov/32186894/?from_term=covid+19&from_sort=date&from_page=12&from_pos=4
Journal: American Journal of Roentgenology
Published: April 2020, available ahead of print
Authors from: China

The authors reviewed the clinical data and CT examinations of **15 consecutive pregnant women** with COVID-19 pneumonia in one hospital from January 20, 2020, to February 10, 2020. A semiquantitative CT scoring system was used to estimate pulmonary involvement and the time course of changes on chest CT. **Eleven patients had successful delivery (10 cesarean deliveries and one vaginal delivery)** during the study period, and four patients were still pregnant (three in the second trimester and one in the third trimester) at the end of the study period. **No cases of neonatal asphyxia, neonatal death, stillbirth, or abortion** were reported. The most common early finding on chest CT was **ground-glass opacity** (GGO). With disease progression, **crazy paving pattern and consolidations were seen on CT**. The abnormalities showed absorptive changes at the end of the study period for all patients. The most common onset symptoms of COVID-19 pneumonia in pregnant women were fever (13/15 patients) and cough (9/15 patients). The most common abnormal laboratory finding was lymphocytopenia (12/15 patients). CT images obtained before and after delivery showed **no signs of pneumonia aggravation after delivery**. The four patients who were still pregnant at the end of the study period were not treated with antiviral drugs but had achieved good

recovery.Pregnancy and childbirth did not aggravate the course of symptoms or CT features of COVID-19 pneumonia. All the cases of COVID-19 pneumonia in the pregnant women in the study were mild type. All the women in this study—some of whom did not receive antiviral drugs—achieved good recovery from COVID-19 pneumonia.

Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19
https://academic.oup.com/jtm/advance-article/doi/10.1093/jtm/taaa041/5809509
Journal: Journal of Travel Medicine *Published Online: March 18, 2020*
Author from: USA

Intravenous infusions of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in experimental animals **increase the numbers of angiotensin-converting enzyme 2 (ACE2) receptors in the cardiopulmonary circulation.** ACE2 receptors serve as binding sites for SARS-CoV-2 virions in the lungs. Patients who take ACEIs and ARBS **may be at increased risk of severe disease** outcomes due to SARS-CoV-2 infections. Future case-control studies in patients with COVID-19 infections are recommended to further confirm chronic therapy with ACEIs or ARBs as a risk factor for more severe disease outcomes. The hypothesis may also explain mild course of disease in children, who have fewer ACE2 receptors in their lower respiratory tracts to attract the binding S proteins of the beta coronaviruses.

COVID-19: consider cytokine storm syndromes and immunosuppression
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext
Journal: The Lancet *Published Online: March 16, 2020*
Authors from: UK

Current focus has been on the development of novel therapeutics, including antivirals and vaccines. Accumulating evidence suggests that a **subgroup of patients with severe COVID-19 might have a cytokine storm syndrome**. The authors recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.
Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality. **Secondary haemophagocytic lymphohistiocytosis** (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a **fulminant and fatal hypercytokinaemia** with multiorgan failure. In adults, sHLH is most commonly triggered by viral infections and occurs in 3.7–4.3% of sepsis cases. Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients. A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterised by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α. **Predictors of fatality** from a recent retrospective, multicentre study of

150 confirmed COVID-19 cases in Wuhan, China, included **elevated ferritin and IL-6** , suggesting that mortality might be due to virally driven hyperinflammation.

Corticosteroids are not routinely recommended and might exacerbate COVID-19-associated lung injury. **However, in hyperinflammation, immunosuppression is likely to be beneficia**l. Re-analysis of data from a phase 3 randomised controlled trial of IL-1 blockade **(anakinra)** in sepsis, showed significant survival benefit in patients with hyperinflammation, without increased adverse events. A multicentre, randomised controlled trial of **tocilizumab** (IL-6 receptor blockade, licensed for cytokine release syndrome in the UK), has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China. Janus kinase (JAK) inhibition could affect both inflammation and cellular viral entry in COVID-19.

COVID-19: combining antiviral and anti-inflammatory treatments
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30132-8/fulltext
Journal: The Lancet Infectious Diseases *Published Online: February 27, 2020*
Authors from: UK

Both COVID-19 and SARS are characterised by an overexuberant inflammatory response and, for SARS, viral load is not correlated with the worsening of symptoms. Arteficial inteligence was already used by the same group in the past for identification of a target and a potential therapeutic against SARS coronavirus 2 (SARS-CoV-2; the causative organism in COVID-19). Group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells was identified. 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. **Baricitinib** could be of use in countering SARS-CoV-2 infections, subject to appropriate clinical testing. To take this work further the authors re-examined the affinity and selectivity of all the approved drugs to identify those with **both antiviral and anti-inflammatory properties**. **Baricitinib, fedratinib, and ruxolitinib** are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. 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.

Positive RT-PCR Test Results in Patients Recovered From COVID-19
https://pubmed.ncbi.nlm.nih.gov/32105304/?from_term=covid+19&from_sort=date&from_page=84&from_pos=10
Journal: JAMA *Published Online: February 27, 2020*
Authors from: China

One hospitalized patient and 3 patients (all **medical personnel**) quarantined at home with COVID-19 were treated at Zhongnan Hospital of Wuhan University and evaluated RT-PCR tests for COVID-19 nucleic acid to determine if they could return to work. Two were male and the age range was 30 to 36 years. All the following criteria had to be met for hospital discharge or discontinuation of quarantine: normal temperature lasting longer than 3 days, resolved

respiratory symptoms, substantially improved acute exudative lesions on chest computed tomography (CT) images, and 2 consecutively negative RT-PCR test results separated by at least 1 day. Initially, all patients **had positive RT-PCR test results and CT imaging** showed ground-glass opacification or mixed ground-glass opacification and consolidation. The severity of disease was mild to moderate. Antiviral treatment (75 mg of oseltamivir taken orally every 12 hours) was provided for the 4 patients. For 3 of the patients, all clinical symptoms and CT imaging abnormalities had resolved. The CT imaging for the fourth patient showed delicate patches of ground-glass opacity. **All 4 patients had 2 consecutive negative RT-PCR test results.** The time from symptom onset to recovery ranged from 12 to 32 days. After hospital discharge or discontinuation of quarantine, the patients were asked to continue the quarantine protocol at home for 5 days. **The RT-PCR tests were repeated 5 to 13 days later and all were positive**. **All patients had 3 repeat RT-PCR tests performed over the next 4 to 5 days and all were positive.** An additional RT-PCR test was performed using a kit from a different manufacturer and the results were also positive for all patients. The patients continued to be asymptomatic by clinician examination and chest CT findings showed no change from previous images. They did not report contact with any person with respiratory symptoms. No family member was infected. These findings suggest that **at least a proportion of recovered patients still may be virus carriers.**

A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS coronavirus-A Possible Reference for Coronavirus disease-19 Treatment Option
https://pubmed.ncbi.nlm.nih.gov/32104907/?from_term=covid+19&from_sort=date&from_page=85&from_pos=7
Journal: Journal of Medical Virology *Published Online: February 27, 2020*
Authors from: China

There are no specific antiviral therapies for COVID-19. However, there are agents that were used during the SARS and MERS epidemics. **Lopinavir** (LPV) is an effective agent that **inhibits the protease activity of coronavirus**. In this review, the authors discuss the literature on the efficacy of LPV in vitro and in vivo, especially in patients with SARS and MERS, so that they might clarify the potential for the use of LPV in patients with COVID-19. Additional studies are needed to gain further insights into the origin, tropism, and pathogenesis of COVID- 19. Most in vitro studies have shown that SARS- CoV could be inhibited by LPV and that the EC50 of LPV is acceptable. Furthermore, **two retrospective matched cohort studies of SARS patients** revealed that LPV/r (lopinavir/ritonavir) plays an **essential role in the clinical outcome**, especially in the early stage. LPV/r- treatment alone or in combination with interferon had improved clinical outcomes in some MERS patient. However, we need to wait for more clinically valid evidence to confirm the positive value of LPV for COVID- 19 treatment. A retrospective study of MERS showed that the most common symptoms and laboratory tests of LPV/r PEP were diarrhea (40.9%), nausea (40.9%), stomatitis (18.2%), fever (13.6%), anemia (45.0%), leukopenia (40.0%), and hyperbilirubinemia (100%). However, the symptoms and laboratory tests returned to normal after LPV therapy ceased.

Non-invasive respiratory support for patients with novel coronavirus pneumonia

clinical efficacy and reduction in risk of infection transmission

https://journals.lww.com/cmj/Citation/publishahead/Non_invasive_respiratory_support_for_patients_with.99377.aspx

Journal: Chinese Medical Journal *Published Online: February 24, 2020*

Authors from: China

Noninvasive respiratory support systems, including various conventional oxygen therapies, **non-invasive positive pressure ventilation** (NPPV), and **high-flow nasal cannula** (HFNC), are most commonly used. However, their efficacy and safety in the treatment of COVID-19 remain unclear, and whether they **increase the risk of aerosol dispersion** and disease transmission is particularly controversial. In vitro simulation experiments have shown that NPPV can lead to the dispersion of exhaled aerosols within 1 m of patients. In addition, the dispersion range increases with increased air leakage and increased inspiratory pressure. However, clinical studies on the use of NPPV for SARS did not clearly demonstrate that NPPV increases the risk of infection transmission between infected patients and medical staff.

NPPV can **reduce the rate of tracheal intubation** and theoretically the risk of infection of medical personnel during tracheal intubation. A recent retrospective epidemiological study of 99 COVID-19 pneumonia patients in China revealed that NPPV is the **most commonly used mechanical ventilation method for acute respiratory failure.** The rates of using non-invasive and invasive mechanical ventilation are 13% and 4%, respectively; however, the efficacies of these ventilation methods need to be further investigated. However, current evidence and Chinese clinical guidelines **do not recommend NPPV for treating acute hypoxic respiratory failure and pandemic viral illness**. Therefore, the authors believe that NPPV should currently not be used as a first-line treatment to correct respiratory failure in patients with COVID-19 pneumonia. For **strictly selected early-stage** patients with mild-to-moderate (partial pressure of arterial oxygen [PaO2]/fraction of inspired oxygen [FiO2] > 200 mmHg) hypoxic respiratory failure and especially for units **with limited numbers of invasive ventilators**, it is recommended that NPPV be **attempted for short periods of time** (1–2 hours) and to intubate immediately if no improvement is observed. NPPV should be avoided in patients with hemodynamic instability, multiple organ failure, disorders of consciousness, or mucus drainage disorders.

No clinical data exist regarding the use of HFNC for SARS, MERS, or COVID-19, and the clinical efficacy of HFNC needs to be further investigated. However, for patients with non-infectious mild-to-moderate hypoxic respiratory failure, compared with conventional oxygen therapy, **HFNC can reduce the rate of tracheal intubation and Mortality**. Therefore, HFNC treatment for COVID-19 pneumonia can be attempted when hypoxemia cannot be treated using conventional oxygen therapy devices, NPPV cannot be tolerated. HFNC should be avoided in patients with hemodynamic instability, multiple organ failure, or disorders of consciousness. The therapeutic response should be closely monitored (1–2 hours) after HFNC treatment.

Virus against virus: a potential treatment for 2019-nCov (SARS-CoV-2) and other RNA viruses

https://www.nature.com/articles/s41422-020-0290-0

Journal: Cell Research *Published Online: February 18, 2020*

Authors from: USA, Italy

The analysis of SARS-CoV-2 RNA genome from 19 patients in China, USA and Australia reveals that these viruses have differences in sequence. These differences are mostly single nucleotide variations. The evidence from patient samples suggests that the virus is **actively acquiring new mutations** that may enable it to escape antiviral drugs. The authors propose a use of **CRISPR/Cas13d system** as a potentially a straightforward, flexible, and rapid novel approach for the treatment and prevention of RNA virus infection. The advantage is that it can be tailored to target specific strains of the virus regardless of the mutations. Future studies determining the safety and efficacy of this system in eliminating 2019-nCov (SARS-CoV-2) and other viruses in animal models are needed before its therapeutic application to patients. If proven to be effective, this therapeutic approach will provide patients worldwide with more options to fight against life-threatening viruses that have the potential to evolve and develop resistance rapidly.

Potent Binding of 2019 Novel Coronavirus Spike Protein by a SARS Coronavirus-Specific Human Monoclonal Antibody

https://pubmed.ncbi.nlm.nih.gov/32065055/?from_term=covid+19&from_sort=date&from_page=102&from_pos=10

Journal: Emerging Microbes and Infections *Published Online: January 27, 2020*

Authors from: China

Considering the relatively genomically conserved receptor-binding domain (RBD) in 2019-nCoV and SARS-CoV, it is urgent to assess the cross-reactivity of anti-SARS CoV antibodies with 2019-nCoV spike protein, which could have important implications for rapid development of vaccines and therapeutic antibodies against 2019-nCoV. In the present study the authors report **that a SARS-CoV-specific human monoclonal antibody, CR3022, could bind potently with 2019-nCoV RBD**. The epitope of CR3022 does not overlap with the ACE2 binding site within 2019-nCoV RBD. These results suggest that **CR3022 may have the potential to be developed as candidate therapeutic**, alone or in combination with other neutralizing antibodies, for the prevention and treatment of 2019-nCoV infections. Interestingly, some of the most potent SARS-CoV-specific neutralizing antibodies (e.g. m396, CR3014) that target the ACE2 binding site of SARS-CoV failed to bind 2019-nCoV spike protein, implying that the difference in the RBD of SARS-CoV and 2019-nCoV has a critical impact for the cross-reactivity of neutralizing antibodies.

Persistence of Coronaviruses on Inanimate Surfaces and Their Inactivation With Biocidal Agents

https://pubmed.ncbi.nlm.nih.gov/32035997/?from_term=covid+19&from_sort=date&from_page=111&from_pos=8

Journal: The Journal of Hospital Infection *Published Online: March 2020*
Authors from: Germany

Human-to-human transmissions of 2019-nCoV have been described with incubation times between 2-10 days, facilitating its spread via **droplets, contaminated hands or surfaces**. The authors therefore reviewed the literature on all available information about the persistence of human and veterinary coronaviruses on inanimate surfaces as well as inactivation strategies with biocidal agents used for chemical disinfection, e.g. in healthcare facilities. The **analysis of 22 studies** reveals that human coronaviruses such as SARS and MERS coronaviruses or endemic human coronaviruses (HCoV) can **persist on inanimate surfaces like metal, glass or plastic for up to 9 days**, but can be efficiently inactivated by surface disinfection procedures with **62–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute**. Other biocidal agents such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective.

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

https://www.nature.com/articles/s41422-020-0282-0

Journal: Cell Resears *Published Online: February 4, 2020*
Authors from: China

In the present study, the authors evaluated the antiviral efficiency of five FDA-approved drugs including **ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine** and two well-known broad-spectrum antiviral drugs **remdesivir (GS-5734) and favipiravir** (T-705) against a clinical isolate of 2019-nCoV in vitro. Standard assays were carried out to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates of 2019-nCoVs. Among the seven tested drugs, high concentrations of three nucleoside analogs including ribavirin, penciclovir and favipiravir were required to reduce the viral infection. However, favipiravir has been shown to be 100% effective in protecting mice against Ebola virus challenge, suggesting further in vivo studies are recommended to evaluate this antiviral nucleoside. Nafamostat, a potent inhibitor of MERS-CoV, which prevents membrane fusion, was inhibitive against the 2019-nCoV infection. Nitazoxanide, a commercial antiprotozoal agent with an antiviral potential against a broad range of viruses including human and animal coronaviruses, inhibited the 2019-nCoV at a low-micromolar concentration Further in vivo evaluation of this drug against 2019-nCoV infection is recommended. Notably, two compounds **remdesivir** and **chloroquine** potentl**y blocked virus infection at low-micromolar concentration and showed high selectivity index.** The preliminary data showed that remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV.

Overview of planned or ongoing studies of drugs for the treatment of COVID-19

https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx

Vytvořeno ve spolupráci s Terezou Rádl a Czech Health Interactive, s.r.o.