INFOLETTER 3 – COVID-19

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Recent epidemiological publications and summaries – Content overview

Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic: From ACC's Interventional Council and SCAI

https://www.sciencedirect.com/science/article/pii/S0735109720345666?via%3Dihub
Journal: Journal of the American College of Cardiology *Published Online: March 16, 2020*
Authors from: USA

The purpose of this joint statement from the ACC Interventional Council and SCAI is to discuss issues facing catheterization laboratory personnel during this time. **Elective patients:** Under any circumstance, to preserve hospital bed capacity, it would seem reasonable to **avoid elective procedures on patients with significant comorbidities** or in whom the **expected length of stay is >1 to 2 days (or anticipated to require the intensive care unit)**. In addition, the definition of truly elective requires clinical judgment, because in some cases deferral of patients may have independent deleterious effects.
STEMI patients: A recent **report from China outlines a protocol that relies on rapid nucleic acid testing and reliance on fibrinolytic therapy**. This is a controversial subject especially in the United States where primary PCI is the routine for STEMI patients. Furthermore, it is complicated by the fact that access to rapid testing is limited. However, in the patient with known COVID-19 and STEMI, the balance of staff exposure and patient benefit will need to be weighed carefully. **Fibrinolysis can be considered an option for the relatively stable STEMI patient with active COVID-19.**
NSTEMI patients: For most patients with NSTEMI and suspected COVID-19, timing should **allow for diagnostic testing for COVID-19** prior to cardiac catheterization, and allow for a more informed decision regarding infection control. It has been suggested that in appropriately selected cases of patients with known COVID-19 and NSTEMI, (e.g., particularly for patients with type 2 MI) **conservative therapy may be sufficient.**
It is important to note that recent reports suggest that **acute cardiac injury is present in ~7% of patients with COVID-19** and may represent either **type 2 MI or myocarditis**.

Viral dynamics in mild and severe cases of COVID-19

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30232-2/fulltext
Journal: The Lancet Infectious Diseases *Published Online: March 19, 2020*
Authors from: China

The authors previously reported that the viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) **peaks within the first week** of disease onset. In the present study, 76 patients from one hospital were included. All patients were confirmed to have COVID-19 at the time of admission by RT-PCR. The viral loads of their nasopharyngeal swab samples were estimated with the **DCt method** (Ctsample – Ctref). 61% of individuals were classified as mild cases and 39% were classified as severe cases. No patient died from the infection. 77% of 30 severe cases received ICU treatment. We noted that the DCt values of severe cases were significantly lower than those of mild cases at the time of admission. **The mean viral load of severe cases was around 60 times higher than that of mild cases**, suggesting that higher viral loads might be associated with

severe clinical outcomes. We further stratified these data according to the day of disease onset at the time of sampling. The DCt values of severe cases remained significantly lower for the first 12 days after onset than those of corresponding mild cases. **Mild cases were found to have an early viral clearance, with 90% of these patients repeatedly testing negative on RT-PCR by day 10 post-onset.** By contrast, all severe cases still tested positive at or beyond day 10 post-onset. Overall, our data indicate that, similar to SARS in 2002–03, patients with severe COVID-19 tend to have a high viral load and a long virus-shedding period. This finding suggests that the **viral load of SARS-CoV-2 might be a useful marker for assessing disease severity and prognosis.**

Prolonged presence of SARS-CoV-2 viral RNA in fecal samples

https://www.thelancet.com/journals/langas/article/PIIS2468-1253(20)30083-2/fulltext
Journal: The Lancet Gastroenterology and Hepatology *Published Online: March 19, 2020*
Authors from: China, USA

The authors collected respiratory and fecal samples from 98 patients from one hospital throughout the course of their illness and obligated quarantine period and analyzed them for the presence of the SARS-CoV-2 by RT-PCR. Respiratory and fecal samples were collected every 1–2 days until two sequential negative results were obtained.
Both respiratory and fecal samples were obtained from 76% of patients. **Fecal samples from 45% of the patients were negative** for SARS CoV-2 RNA, while their respiratory swabs remained positive for a mean of 15.4 days from the first symptom onset. Of the 55% of 74 patients with fecal samples that were positive, respiratory samples remained positive for SARS-CoV-2 RNA for a mean of 16.7 days and **fecal samples remained positive for a mean of 27,9 days**. Notably, one patient had **positive fecal samples for 33 days continuously after the respiratory samples became negative**, and one patient tested positive in their fecal sample for **47 days after the first symptom onset**. The presence of gastrointestinal symptoms was not associated with fecal sample viral RNA positivity (p=0.45); disease severity was not associated with extended duration of fecal sample viral RNA positivity (p=0.60); however, antiviral treatment was positively associated with the presence of viral RNA in fecal samples (p=0.025;). These associations should be interpreted with caution because of the possibility of confounding. The data suggest the possibility of an **extended duration of viral shedding in feces**. Although knowledge about the viability of SARS-CoV-2 is limited. the virus could remain viable in the environment for days, which could lead t**o fecal-oral transmission**.

Use of antiviral drugs to reduce COVID-19 transmission

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30114-5/fulltext
Journal: The Lancet Global Health *Published Online: March 19, 2020*
Authors from: Spain

The current COVID-19 emergency warrants the urgent development of potential strategies to protect people at high risk of infection—particularly **close contacts and health-care workers**. Pre-

exposure prophylaxis and postexposure prophylaxis (PEP) with antimicrobial drugs are routinely used for some infections. Furthermore, antiviral drugs administered shortly after symptom onset can **reduce infectiousness to others** by reducing viral shedding in the respiratory secretions of patients (SARS-CoV-2 viral load in sputum peaks at around 5–6 days after symptom onset and lasts up to 14 days), and **targeted prophylactic treatment of contacts** could reduce their risk of becoming infected.

For feasible prophylaxis, the stockpile of drugs must be adequate, the safety of treatment must be very high, and costs should ideally be low. **Hydroxychloroquine** has a history of being safe and well-tolerated at typical doses. Notably, the drug shows antiviral activity in vitro against coronaviruses, and specifically, SARS-CoV-2. Pharmacological modeling based on observed drug concentrations and in vitro drug testing suggest that prophylaxis with hydroxychloroquine at approved doses could prevent SARS-CoV-2 infection and ameliorate viral shedding.

The authors are planning a **multicentre randomized controlled trial** (NCT04304053) to evaluate the **efficacy of antiviral treatment in anyone found to be infected**, and the **efficacy of prophylactic hydroxychloroquine in preventing secondary SARS-CoV-2 infections**. The objective is to evaluate the reduction in transmissibility of SARS-CoV-2 and in disease progression among the contacts of an index case.

COVID-19 Infection Implications for Perioperative and Critical Care Physicians

https://pubmed.ncbi.nlm.nih.gov/32195698/?from_term=covid+19&from_sort=date&from_page=12&from_pos=10

Journal: Anesthesiology *Published Online: March 19, 2020*
Authors from: USA

The authors draw on literature from other viral epidemics, treatment of acute respiratory distress syndrome, and recent publications on COVID-19, as well as guidelines from major health organizations. This review provides a comprehensive summary of the evidence currently available to guide the management of critically ill patients with COVID-19.

SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19?

https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa235/5810479

Journal: European Heart Journal *Published Online: March 20, 2020*
Authors from: Switzerland

In a rapid response published online by the British Medical Journal, Sommerstein and Gräni pushed forward the hypothesis that angiotensin-converting enzyme inhibitors (ACE-Is) could act as a **potential risk factor for fatal COVID-19 by up-regulating ACE2.** According to the translational evidence for diverse roles of the renin-angiotensin-aldosterone system (RAAS), the opposite hypothesis could be also formulated, stating that **inhibition of the RAAS might be protective in**

COVID-19. Diabetes, hypertension, and cardiovascular diseases are highly prevalent among SARS-CoV2 infected patients and may be associated with poor outcome. Patients with these conditions are frequently treated with ACE-Is, angiotensin II type 1 receptor blockers (ARBs), or mineralocorticoid receptor antagonists (MRAs).

SARS-CoV2 utilizes **ACE2 as a receptor for viral cell entry**. In the RAAS, ACE2 catalyzes the conversion of angiotensin II to angiotensin 1–7, which acts as a vasodilator and exerts protective effects in the cardiovascular system.

Although ACE2 is thought to be mandatory for SARS-CoV infection, the absence of SARS-CoV was observed in some ACE2 expressing cell types, whereas infection was present in cells apparently lacking ACE2, suggesting that **additional co-factors might be needed**.
Importantly, in a mouse model of SARS-CoV infection and pulmonary disease, a key pathophysiological role was shown for ACE, angiotensin II, and angiotensin II receptor type 1. SARS-CoV or **SARS-CoV spike protein led to the down-regulation of ACE2 and more severe lung injury** in mice that **could be attenuated by the administration of an ARB.** These findings suggest a protective role of ARB in SARS-CoV associated lung injury and give rise to the hypothesis that primary activation of the RAAS in cardiovascular patients, rather than its inhibition, renders them more prone to a deleterious outcome. Clearly, much more research is needed to clarify the multifaceted role of the RAAS in connection with SARS-CoV2 infection.
Nevertheless, based on the work by Josef Penninger et al., who proposed to therapeutically use the dual function of ACE2 as viral receptor and gatekeeper of RAAS activation, a **pilot trial using soluble human recombinant ACE2 (APN01) in patients with COVID-19** has recently been initiated (Clinicaltrials.gov #NCT04287686). Such therapy could have the potential to lower both the viral load and the deleterious effects of angiotensin II activity.
In conclusion, based on currently available data and in view of the overwhelming evidence of mortality reduction in cardiovascular disease, **ACE-I, and ARB therapy should be maintained or initiated** in patients with heart failure, hypertension, or myocardial infarction according to current guidelines as tolerated, irrespective of SARS-CoV2. Withdrawal of RAAS inhibition or preemptive switch to alternate drugs at this point seems not advisable since it **might even increase cardiovascular mortality in critically ill COVID-19 patients.**

American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients with Suspected or Confirmed COVID-19 Infection

https://journals.lww.com/bronchology/Citation/publishahead/American_Association_for_Bronchology_and.99785.aspx
Journal: Journal of Bronchology and Interventional Pulmonology
Published Online: March 18, 2020
Authors from: USA

The collection of upper respiratory samples via **nasopharyngeal and oropharyngeal swabs** is the primary and preferred method for diagnosis. Respiratory specimen collection is recommended in

suspected COVID-19 regardless of the time of onset of symptoms. Induced Sputum Collection is NOT recommended. Because it is an aerosol-generating procedure that poses a substantial risk to patients and staff, **bronchoscopy should have an extremely limited role** in the diagnosis of COVID-19 and only be considered in intubated patients if upper respiratory samples are negative and another diagnosis is considered that would significantly change clinical management. Alternative respiratory specimen collection in the intubated patient can include tracheal aspirates and non-bronchoscopic alveolar lavage (N-BAL). If bronchoscopy is being performed for COVID 19 sample collection, a minimum of 2- 3 ml of the specimen into a sterile, leak-proof container for specimen collection is recommended. Only essential personnel should be present. **Disposable bronchoscopes** should be used first-line when available Follow standard disinfection protocol of durable re-usable video monitors Follow standard High-Level Disinfection for re-usable bronchoscopes. Bronchoscopy is relatively CONTRAINDICATED in patients with suspected and confirmed COVID-19 infections. The only role for bronchoscopy would be when less invasive testing to confirm COVID-19 are inconclusive, suspicion for an alternative diagnosis that would impact clinical management is suspected, or an **urgent life-saving intervention** as cited below. Bronchoscopy for any elective reason should be postponed until after full recovery and the patient is declared free of infection. Elective indications include a lung mass, bronchial mass, mediastinal or hilar lymphadenopathy, lung infiltrates and mild to moderate airway stenosis. If immediate testing is not available, bronchoscopy should be deferred if possible. Bronchoscopy (Flexible and Rigid) for urgent/emergent reasons should be considered only if a lifesaving bronchoscopic intervention is deemed necessary. **Indications include massive hemoptysis, benign or malignant severe airway stenosis or suspicion of an alternative or secondary infectious etiology or malignant condition with resultant significant endobronchial obstruction.**

Exuberant Plasmocytosis in Bronchoalveolar Lavage Specimen of the First Patient Requiring Extracorporeal Membrane Oxygenation for SARS-CoV-2 in Europe

https://www.jto.org/article/S1556-0864(20)30201-X/pdf

Journal: Journal of Thoracic Oncology *Published Online: March 16, 2020*

Authors from: Italy

The arrival of the COVID-19 epidemic to Europe introduced a new scenario in the differential diagnosis of infectious diseases that pathologists may encounter in **cytologic specimens, such as those in bronchoalveolar lavage (BAL)**. On February 17, a 66- year-old male patient presented to the emergency department of a hospital in the north of Italy with a 2-day history of fatigue and fever. He had no respiratory symptoms, and his chest radiograph result was negative. The day after, he progressively developed respiratory distress and hypoxia, and a new chest radiograph image revealed bilateral infiltrates. After a failed noninvasive ventilation trial, he was sedated and endotracheally intubated. Computed tomography scan images revealed bilateral consolidation with ground-glass attenuation in the nondependent areas. **Progressive worsening of hypoxemia** (up to 47 mm Hg of the ratio of the partial pressure of arterial oxygen to fraction of inspired oxygen) was also observed in the patient. **ECMO** team was called to retrieve the patient. The patient was transferred to the center after starting **venovenous extracorporeal support.** Real-time polymerase

chain reaction on the BAL specimen revealed positivity for SARS-CoV-2. The BAL specimen was sent for pathologic examination as well. The fluid was cytospinned and stained by May-Grünwald-Giemsa, Papanicolaou, and Perls (Prussian blue) methods. A cell block was produced for immunohistochemical staining (CD3, CD138, CD20, and kappa and lambda immunoglobulin light chains on a Dako Omnis platform, Glostrup, Denmark). The morphologic analysis revealed **fibrinohematic material with scattered alveolar macrophages and a predominantly large number of activated plasma cells** (CD138þ) with occasional plasmablastic features, admixed with T lymphocytes (CD3þ) and scattered B cells (CD20þ). Desquamated pneumocytes, multinucleated syncytial cells, and hyaline material were not appreciated; however, occasional alveolar macrophages revealing nuclear clearing or intranuclear cytopathic inclusions attributable to SARS-CoV-2 were easily found. Common morphologic features of viral infection include cytomegaly, syncytia formation, and intracytoplasmic and intranuclear inclusions, but different viruses (adenovirus, respiratory syncytial virus, influenza, parainfluenza, herpes simplex virus, cytomegalovirus, varicella-zoster virus, and measles) may cause overlapping cytomorphologic changes. In the COVID-19 BAL specimen, dramatically activated plasma cells revoked immune elements frequently found in extrinsic allergic alveolitis, drug-induced pneumonia, aspergillosis, and specific subgroups of lymphomas, such as lymphomatoid granulomatosis or primary effusion lymphoma. At the moment, there are no specific therapeutics approved by the Food and Drug Administration, but the **peculiar abundance of CD138þ plasma cells in COVID-19 may be a relevant feature**; indeed COVID-19 and SARS, both caused by coronaviruses, are characterized by an overexuberant inflammatory response. On the basis of this finding, the empiric combined use of antivirals and anti-inflammatory drugs is under study, even though previous studies on the 2009 influenza A virus subtype H1N1 have not reported evidence of beneficial effects of corticosteroids, which are often administered to patients with acute respiratory distress syndrome secondary to viral pneumonia

The potential added value of FDG PET/CT for COVID-19 pneumonia

https://link.springer.com/article/10.1007%2Fs00259-020-04767-1
Journal: European Journal of Nuclear Medicine and Molecular Imaging
Published Online: March 21, 2020
Authors from: China

Nucleic acid testing (RT-PCR) is the gold standard for the diagnosis of COVID-19 infection, but with a high false-negative rate, which is easy to miss the diagnosis and cause the spread of the epidemic. Chest high-resolution CT is the routine-preferred method for screening, diagnosis, course severity assessment, and efficacy monitoring of COVID-19 pneumonia. As for the FDG PET/CT imaging results after COVID-19 infection, there are only four patients with highly suspected COVID-19 infection having been reported so far by Qin et al. They found **lung lesions characterized by increased FDG uptake** and **evidence of lymph node** involvement. In fact, as a non-invasive imaging method, FDG PET/CT plays an important role in evaluating inflammatory and infectious pulmonary diseases, monitoring disease progression and treatment effect, and improving patient management. In acute inflammation or chest infection, **activated neutrophils are heavily**

dependent on anaerobic glycolysis, requiring increased glucose and resulting in high FDG uptake. Although lymph node enlargement on CT is rare, lymphadenopathy is present in more than 1% of patients. Considering that CT is less sensitive to host reactions than FDG PET/CT, the actual percentage of lymph node involvement may be higher. From Qin et al.'s paper, we can roughly see that **patients with higher FDG uptake in lung lesions take longer to heal** and are positively correlated with the value of the erythrocyte sedimentation rate. Another advantage of FDG PET/CT is that it may be more appropriate when viral infections are associated with other factors. As the disease progresses, it may cause damage to the gastrointestinal tract, kidneys, heart, bone marrow, and other organs. As mentioned above, FDG PET/CT is a sensitive method to detect and monitor inflammatory diseases, such as viral pneumonia, monitor disease progression, and treatment outcomes.

Point-of-Care RNA-Based Diagnostic Device for COVID-19

https://www.mdpi.com/2075-4418/10/3/165
Journal: Diagnostics *Published Online: March 18, 2020*
Authors from: Taiwan

Currently, there are two primary methods for diagnosing COVID-19: a **lateral flow immunoassay**, which is a common point-of-care (POC) diagnostic approach that detects antibodies against specific viruses and a **molecular-based assay**. The current standard approach for screening COVID-19 requires a **reverse real-time PCR assay (rRT-PCR),** which can be carried out using a variety of clinical specimens, including bronchoalveolar lavage fluid, fibrobronchoscope brush biopsies, sputum, nasal swabs, pharyngeal swabs, feces, or blood.
This approach relies on expensive facilities, well-trained staff, and is often time-consuming. An alternative, rapid, inexpensive, easy-to-use, and sensitive COVID-19 diagnostic tool must be developed **for use by nonclinical individuals in their homes**. A recent study conducted by Song et al at the University of Pennsylvania in mid-February of 2020 describes a **novel closed-tube COVID-19 assay**. To improve COVID-19 diagnostic test sensitivity, Song's group developed a **closed-tube Penn-RAMP, a two-stage isothermal dsDNA amplification method that utilized both recombinase polymerase amplification (RPA) and loop-mediated isothermal amplification (LAMP) techniques in a single tube.** In order to make the detection process simpler, they used leucocrystal violet (LCV) dye as a chromogenic reagent, providing an obvious, deep violet color change that could be observed with the naked eye. The entire diagnostic process was relatively simple and required only a single tube for the reaction. In this process, the RPA mixture was loaded onto the inside of the tube lid and the LAMP mixture was placed within the tube itself. The tube was subsequently sealed and incubated at 38 degrees Celsius for 15–20 min to facilitate the RPA reaction. The tube was then inverted several times and incubated at 63 degrees Celsius for 40 min. The Penn-RAMP process provided greater sensitivity than RT-PCR or LAMP alone. When using a limited viral load, Penn-RAMP provided 100 times better sensitivity than a single LAMP test. Compared to a LAMP assay, which requires sophisticated equipment and must be run at a fixed temperature, the Penn-RAMP process requires less energy cost, is easier to execute, and can be completed in clinical or home settings.

The concept for the new tool is derived from previous research on **paper-based nucleic acid detection employing RT-LAMP assay amplification**. The potential rapid and easy-to-use paper-based LAMP assay for COVID-19 could be used in combination **with a smartphone application** to facilitate test results recording/sharing. Using this tool, a home-quarantined individual could easily self-collect a nasal swab sample; perform a LAMP assay; and observe a visible, colorimetric test result that could then be recorded and shared with clinicians or healthcare professionals via the internet.

Is there a role for lung ultrasound during the COVID-19 pandemic?

https://onlinelibrary.wiley.com/doi/abs/10.1002/jum.15284
Journal: Journal of Ultrasound in Medicine *Published Online: March 20, 2020*
Authors from: Italy

See full article for an image library and a clinical algorithm.
The analysis of the available CT data from patients with Covid 19 pneumonia shows largely bilateral lesions, patchy, also confluent, appearing as ground glass or with the mixed consolidative and ground-glass pattern. 10% of lesions with a crazy-paving appearance are reported. The lesions often have a wedge-like appearance with a pleural base. Major consolidations may show air bronchograms. Pleural effusion is absent. Patchy or confluent lesions tend to be distributed along the pleura. The lobe most frequently affected is the lower right lobe, followed by the upper and lower left lobes. The posterior lung is involved in 67% of cases. Given that lung ultrasound (LUS) can identify changes in the physical state of superficial lung tissue, which correlate with histopathology and that can be identified in CT, but remain hidden in a large percentage of chest radiographs, the role of LUS can be relevant in the context of the Covid 19 epidemic. It should also not be underestimated that, in experimental models of ARDS, **LUS has proved capable of detecting lung lesions before the development of hypoxemia.** LUS may be useful for prehospital and in-hospital **triage and diagnosis**, prognostic **stratification,** and monitoring, **management of ICU patients** with regard to ventilation and weaning, **monitoring the effect** of therapeutic measures (antiviral or others) and **reducing the number of healthcare professionals** exposed during patient stratification (a single clinician would be necessary to perform an objective medical examination).

Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy

https://jamanetwork.com/journals/jama/fullarticle/2763667
Journal: JAMA *Published Online: March 23, 2020*
Authors from: Italy

The fatality rate was defined as a number of deaths in persons who tested positive for SARS-CoV-2 divided by a number of SARS-CoV-2 cases. The overall fatality rate of persons with confirmed COVID-19 in the Italian population, based on data up to March 17, was 7.2% (1625 deaths/22 512 cases). This rate is higher than that observed in other countries and may be related to 3 factors.

The demographic characteristics of the Italian population differ from other countries. In 2019, approximately 23% of the Italian population was aged 65 years or older. When data were stratified by age group, the case-fatality rate in Italy and China appear very similar for age groups 0 to 69 years, but rates are higher in Italy among individuals aged 70 years or older, and in particular among those aged 80 years or older. A second possible explanation for the high Italian case-fatality rate may be how COVID-19–related deaths are identified in Italy. COVID-19–related deaths are those occurring in patients who test positive for SARS-CoV-2 via RT-PCR, independently from preexisting diseases that may have caused death. A third possible explanation is the different strategies used for testing. After an initial, extensive testing strategy of both symptomatic and asymptomatic contacts of infected patients in a very early phase of the epidemic, more stringent testing policies were issued. This recommendation prioritized testing for patients with more severe clinical symptoms who were suspected of having COVID-19 and required hospitalization.
A subsample of 355 patients underwent a detailed chart review. The mean age was 79.5 years 30.0% were women. 30% had ischemic heart disease, 35.5% had diabetes, 20.3% had active cancer, 24.5% had atrial fibrillation, 6.8% had dementia, and 9.6% had a history of stroke. The mean number of preexisting diseases was 2.7. **Overall, only 3 patients (0.8%) had no disease**, 25.1% had a single disease, 25.6% had 2 diseases, **and 48.5% had 3 or more underlying diseases**.

TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib

https://www.sciencedirect.com/science/article/pii/S1684118220300657?via%3Dihub
Journal: Journal of Microbiology, Immunology, and Infection Published Online: March 11, 2020
Authors from: USA, China

The authors reviewed TH17 responses in patients with SARS-CoV-2 and proposed an **FDA approved JAK2 inhibitor fedratinib** for reducing mortality of patients with TH17 type immune profiles. ARDS in COVID-19 is associated with a cytokine storm, manifesting elevated serum levels of various molecules. Compared with non-ICU patients, ICU patients have even higher levels of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα. Amongst these, several cytokines are involved in **TH17 type** responses. **IL-1β and TNFα (TH17 and TH1 cells highly express TNFα), both promote TH17 responses and vascular permeability and leakage**. **TH17 cells themselves produce IL-17**, which has broad pro-inflammatory effects on the induction of cytokines. This stimulation eventually contributes to the formation of **life-threatening edema enriched with mucins and fibrin**. Targeting the TH17 pathway may benefit patients with TH17 dominant immune profiles. There are several **antibody-based TH17 blockades** (anti-IL-17, anti-IL-17R, and anti-IL-12/23p40) available; however, the antibody-based treatment is expensive and has only a narrow spectrum of effects. **STAT3**, a transcription factor, mediates IL-6 and IL-23 signals for TH17 cell initial differentiation and effector function. **Both IL-6 and IL-23 activate STAT3 through JAK2.** The authors postulate that **JAK2 inhibitors** can be used to restrict the proinflammatory function of existing TH17 cells. In addition to JAK2 inhibitors, several FDA approved **STAT3 inhibitors** are also promising but may affect IL-21 signals in B cells.

The authors tested Fedratinib, a JAK2 inhibitor approved by FDA for myeloproliferative neoplasms, on TH17 cell cytokine production. Fedratinib treatment d**ecreased the expression of IL-17 by murine TH17 cells**, and this suppressive effect was even more profound when IL-23 was added. In addition, Fedratinib also **inhibited the expression of IL-22 by TH17 cells**. Fedratinib only has marginal effects on IL-21 expression, suggesting that Fedratinib does not compromise IL-21 mediated B cell function. Because JAK2 inhibition is reversible, transient treatment with this inhibitor before the disease transition from serious to critical or during the critical phase would not affect TH17 responses essential for innate immune responses and immunity against extracellular pathogens.

Policies on the use of respiratory protection for hospital health workers to protect from coronavirus disease (COVID-19)

https://www.sciencedirect.com/science/article/pii/S0020748920300523?via%3Dihub
Journal: International Journal of Nursing Studies *Published Online: March 13, 2020*
Authors from: Australia, USA

The lack of agreement on the selection and use of masks and respirators (N95/P2/FFP2 or equivalent) is reflected in **inconsistent and conflicting policies worldwide.** The World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC) and other leading health organizations have different recommendations for the selection of respiratory protection. For example, the WHO recommends **using masks to protect health workers from COVID-19 during routine care and respirators during aerosol-generating procedures.** In contrast, the US CDC and the European Center for Disease Prevention and Control recommend **using respirators during both routine care of COVID19 patients and high-risk situations**. While all organizations recommend using N95/ P2/FFP2 or equivalent respirators, Public Health England (UK) recommends using filtering facepiece 3 (FFP3) respirators for all cases and the European Center for Disease Prevention and Control recommends using FFP3 during aerosol-generating procedures. Australian guidelines also recommend **powered air-purifying respirators while performing aerosol-generating procedures on multiple patients.**
The guidelines simultaneously state that **community use of masks has no benefit**. Yet there are more **randomized controlled clinical trials supporting the use of masks in the community** than for source control. The community trials show a benefit of face masks with or without hand hygiene, conditional on compliance. Like other coronavirus diseases (e.g. SARS and MERS), COVID-19 is believed to be transmitted through droplet and contact modes however other transmission modes, such as airborne, are likely given the virus is found in higher concentrations in the lungs than the upper respiratory tract. In Canada, initially, masks were recommended, but this recommendation was later changed to respirators due to the deaths of health workers. A recent study demonstrated the presence of coronavirus in anal swabs from infected patients and the possibility of transmission through the faecal-oral route. Transmission dynamics for COVID-19 are still unclear and pharmaceutical control measures are not yet available, therefore **N95 or higher respirators should be offered to health workers who are working at the frontline**. Health workers and other first responders in high coronavirus transmission areas (e.g. Wuhan) should use respirators during

routine care of coronavirus cases. Health workers and first responders in low-risk countries should use a respirator when encountering a suspected or confirmed case of coronavirus. If respirators are not available, then masks should be used. **Extended use and reuse are high-risk practices and may lead to self-contamination to the wearer and should be avoided.** In case of shortage, extended use should be balanced against the risk of infections and **the wearer should not remove masks between patient's encounters.**

Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases

https://linkinghub.elsevier.com/retrieve/pii/S2213260020301211

Journal: The Lancet Respiratory Medicine *Published Online: March 20, 2020*

Authors from: Singapore, USA, France, Australia

WHO interim guidelines recommend offering ECMO to eligible patients with ARDS related to COVID-19. The number of patients with COVID-19 infection who might develop severe ARDS that is refractory to maximal medical management and require this level of support is currently unknown. Available evidence from similar patient populations suggests that carefully selected patients with severe ARDS who do not benefit from conventional treatment might be **successfully supported with venovenous ECMO**. The need for ECMO is relatively low and its use is mostly restricted to specialized centers globally. Providing complex therapies such as ECMO during outbreaks of emerging infectious diseases has unique challenges. Careful planning, judicious resource allocation, and training of personnel to provide complex therapeutic interventions while adhering to strict infection control measures are all crucial components of an ECMO action plan. ECMO can be initiated in specialist centers, or patients can receive ECMO during transportation from a center that is not specialized for this procedure to an expert ECMO center. Ensuring that systems enable safe and coordinated movement of critically ill patients, staff, and equipment is important to improve ECMO access. ECMO preparedness for the COVID-19 pandemic is important in view of the high transmission rate of the virus and respiratory-related mortality.

Once the patient is safely administered ECMO, it is important to ensure that an **ultra-protective mechanical ventilation strategy** is used. There is no consensus on the most appropriate ventilatory strategy for ECMO. **Two randomized trials of ventilation during ECMO** for patients with ARDS (**EOLIA**; *plateau pressure of ≤24 cm H2O while applying a positive end-expiratory pressure of at least 10 cm H2O; the respiratory rate of 10–30 breaths per min*) and conventional ventilatory support versus ECMO for severe adult respiratory failure (**CESAR**; *peak inspiratory pressure 20–25 cm H2O; positive end-expiratory pressure 10 cm H2O; the respiratory rate of 10 breaths per min*) could serve as useful guides pending further evidence on ventilation strategies for ECMO in patients with ARDS. **Prone positioning** could be considered during ECMO, although there are little data to support this practice. The benefits of ECMO for ARDS largely stem from its ability to **confer lung protection,** which is associated with decreased adverse outcomes. It should be noted that although extracorporeal CO2 removal for lung-protective ventilation is feasible, it is neither evidence-based nor is it universally available. Occasionally, patients develop **concomitant or**

discrete cardiac failure—mainly from myocarditis, myocardial infarction, or sepsis-related cardiomyopathy—and might need venoarterial ECMO. The provision of ECMO in the setting of both pulmonary and cardiac dysfunction is particularly complex and, where possible, requires close liaison with an expert extracorporeal life support center before ECMO initiation. **ECMO-assisted cardiopulmonary resuscitation** (ECPR) can be considered in carefully selected patients who develop cardiac arrest. However, given the likelihood of poor outcomes and the considerable risk of infection to staff responding to these patients, ECPR should be undertaken with great caution.

Treatment for severe acute respiratory distress syndrome from COVID-19

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30127-2/fulltext#%20

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Authors from: USA

Before endotracheal intubation, it is important to consider a **trial of high-flow nasal oxygen** for patients with moderately severe hypoxemia. This procedure might avoid the need for intubation and mechanical ventilation because it provides high concentrations of humidified oxygen, low levels of positive end-expiratory pressure, and can facilitate the elimination of carbon dioxide. Close monitoring for clinical deterioration is required in order to avoid emergent intubation with an increased risk of spread of infection.
For patients with COVID-19 who require endotracheal intubation, use of **low tidal volume** (6 mL/kg per predicted bodyweight) with a **plateau airway pressure of less than 30 cm H2O**, and **increasing the respiratory rate to 35 breaths per min** as needed, is the mainstay of lung-protective ventilation. If the hypoxemia progresses to a PaO2: FiO2 ratio of less than 100–150 mm Hg, there are several therapeutic options. The **level of positive end-expiratory pressure can be increased by 2–3 cm H2O every 15–30 min** to improve oxygen saturation to 88–90%, with the goal of maintaining a plateau airway pressure of less than 30 cm H2O. **Lower driving pressures** (plateau airway pressure minus positive end-expiratory pressure) with a target of 13–15 cm H2O can also be used. If the patient is not responding to adjustment of the level of positive end-expiratory pressure, additional strategies might stabilize them. **Recruitment maneuvers probably have little value**, but moderate pressures of approximately 30 cm H2O for 20–30 s can be applied in the presence of a physician to monitor hemodynamics. If there is no improvement in oxygenation or driving pressure, or if the patient develops hypotension or barotrauma, the recruitment maneuvers should be discontinued. If there is considerable dyssynchrony with positive pressure ventilation, accompanied by increased plateau airway pressures and refractory hypoxemia, then **deep sedation should be used** followed by the prompt institution of **neuromuscular blockade with cisatracurium**. Additionally, **prone positioning** should be instituted, unless there is a specific contraindication, and can be initiated along with the interventions already described.
For persistent refractory hypoxemia even with prone positioning, neuromuscular blockade, and efforts to optimize positive end-expiratory pressure therapy, there are additional options. **Inhaled 5–20 ppm NO** might improve oxygenation. **Insertion of an oesophageal balloon** to measure transpulmonary pressures to set an optimal positive end-expiratory pressure can be considered in patients with moderate-to-severe obesity, although a 2019 trial in patients with ARDS did not show

the benefit of this procedure in most patients. **Fluid management** is important to consider as a measure to reduce pulmonary edema. In the absence of shock, fluid conservative therapy is recommended to achieve a **negative fluid balance of 0.5 to 1.0 L per day.** In the presence of shock, the fluid balance might be achieved with **renal replacement therapy**, especially if there is associated acute kidney injury and oliguria. Antibiotics should be considered since **secondary bacterial infections** have been reported in patients with COVID-19. **Glucocorticoids should be avoided** in view of the evidence that they can be harmful in cases of viral pneumonia and ARDS from influenza. Rescue therapy with **high-dose vitamin C** can also be considered. Finally, **ECMO** should be considered using the inclusion and exclusion criteria of the EOLIA trial.
There are some research groups working to coordinate and disseminate key information, including information on patients who have been treated with ECMO for COVID-19, although an accurate estimate of the number of such patients is not currently available. The Extracorporeal Life Support Organization is an international non-profit consortium that plans to maintain a registry of patients to facilitate an improved understanding of how ECMO is being used for patients with COVID-19.

Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine

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Authors from: USA, China

The CoV spike (S) protein plays the most important role in viral attachment, fusion, and entry, and serves as a target for the development of antibodies, entry inhibitors, and vaccines. In the present study, the authors identified the receptor-binding domain (RBD) in SARS-CoV-2 S protein and found that the **RBD protein bound strongly to human and bat angiotensin-converting enzyme 2 (ACE2) receptors**. SARS-CoV-2 RBD exhibited significantly higher binding affinity to ACE2 receptor than SARS-CoV RBD and RBD block inhibited attachment of the virus and therefore infection. **SARS-CoV RBD-specific antibodies could cross-react with SARS-CoV-2 RBD protein**, and SARS-CoV RBD-induced antisera could cross-neutralize SARS-CoV-2, suggesting the potential to develop **SARS-CoV RBD-based vaccines** for prevention of SARS-CoV-2 and SARS-CoV infection.

Fair Allocation of Scarce Medical Resources in the Time of Covid-19

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Authors from: USA, Canada, UK

Rationing is already here. For example, physicians in Italy have proposed directing crucial resources such as intensive care beds and ventilators to patients who can benefit most from treatment. The authors of the present study provide recommendations for fair resource allocation.

Recommendation 1: In the context of a pandemic, the **value of maximizing benefits is most important**. Priority for limited resources should aim both at saving the most lives and at maximizing improvements in individuals' post-treatment length of life. Saving more lives and more years of life is a consensus value across expert reports. Whatever the balance between saved lives and life-years is chosen must be applied consistently. Encouraging all patients to document in an advance care directive what future quality of life they would regard as acceptable and when they would refuse ventilators or other life-sustaining interventions can be appropriate. Because maximizing benefits is paramount in a pandemic, the authors believe that removing a patient from a ventilator or an ICU bed to provide it to others in need is also justifiable and that patients should be made aware of this possibility at admission. **Recommendation 2:** Critical Covid-19 interventions — testing, PPE, ICU beds, ventilators, therapeutics, and vaccines — should **go first to front-line health care workers** and others who care for ill patients and who keep critical infrastructure operating. These workers should be given priority not because they are somehow more worthy, but because of their instrumental value: they are essential to the pandemic response. Priority for critical workers must not be abused by prioritizing wealthy or famous persons or the politically powerful above first responders and medical staff — as has already happened for testing. Such abuses will undermine trust in the allocation framework. **Recommendation 3:** For patients with similar prognoses, **equality should be invoked and operationalized through random allocation**, such as a lottery, rather than a first-come, first-served allocation process. First-come, first-served medication or vaccine distribution would encourage crowding and even violence during a period when social distancing is paramount. Finally, first-come, first-served approaches mean that people who happen to get sick later on, perhaps because of their strict adherence to recommended public health measures, are excluded from treatment, worsening outcomes without improving fairness. **Recommendation 4:** Prioritization **guidelines should differ by intervention and should respond to changing scientific evidence.** For instance, younger patients should not be prioritized for Covid-19 vaccines, which prevent disease rather than cure it. Epidemiologic modeling is even more relevant in setting priorities for coronavirus testing. Conversely, ICU beds and ventilators are curative rather than preventive - which may mean giving priority to younger patients and those with fewer coexisting conditions. **Recommendation 5:** People who **participate in research to prove the safety and effectiveness of vaccines and therapeutics should receive some priority** for Covid-19 interventions. Their assumption of risk during their participation in research helps future patients, and they should be rewarded for that contribution. Research participation, however, should serve only as a tiebreaker among patients with similar prognoses. **Recommendation 6:** There should be **no difference** in allocating scarce resources **between patients with Covid-19 and those with other medical conditions.**

Can a Paper-Based Device Trace COVID-19 Sources with Wastewater-Based Epidemiology?

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Authors from: China, UK

Conventional SARS-CoV-2 testing is time and resource consuming. An alternative method utilizing **wastewater-based epidemiology** (WBE), may provide an effective approach to predict the potential spread of the infection by testing for infectious agents in wastewater. SARS-CoV-2 was isolated from the feces and urine of infected people, which would then enter the wastewater treatment system. Analysis of SARS-CoV-2 in community wastewater could trace COVID-19 sources through sewage pipe networks and determine **whether there are potential SARS-CoV-2 carriers in certain local areas**. Effective intervention can be taken as early as possible to restrict the movements of that local population, working to minimize the pathogen spread and threat to public health. For this to work, it is critical to develop efficient transportable and robust analytical tools to accurately and quickly trace low-level SARS-CoV-2 sources through WBE to confirm these suspected cases and screen asymptomatic infected cases without centralized laboratories. **Paper analytical devices** have emerged as powerful tools for rapid diagnosis. It is a small analytical tool with different functional areas printed with a wax printer that integrates all processes (extraction, enrichment, purification, elution, amplification, and visual detection) required for nucleic acid testing. The whole testing process can be completed through simple folding of a paper-based device in different ways in different steps without a pump or power supply, which overcomes the limitation of PCR and avoids multiple processes. Although wastewater is a complex matrix, paper-based devices have shown the potential to detect pathogens in wastewater.

Covid-19 mass testing facilities could end the epidemic rapidly

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Authors from: UK

There is an urgent need for increased capacity to test frontline healthcare workers serologically to verify their immunity to the COVID-19 virus. Even more urgent is the **capacity for weekly viral detection in the whole UK population.** This, together with intensive contact tracing, could enable the country to **resume normal life** immediately. Within the tested population, anyone infected would be detected within about a week (0 to 7 days plus sample transport and testing) of becoming infectious. Centrally organized facilities with the capacity to test the entire UK population weekly (in 6 days at 10 million tests per day) can be made available much **more quickly and cheaply than a vaccine,** probably within weeks. This heroic but straightforward national effort would involve a crash program to enlist all existing PCR facilities, acquire or manufacture the PCR reagents, and agree on protocols including a laptop program for barcode reading in smaller laboratories. Processing capacity equivalent to **4000 Roche COBAS 8800 systems is needed**. All patients registered with a GP would be **sent a test kit** (a swab for throat and nasal self-sample, and a transport tube labeled with their name, NHS number, and a barcode). Homeless people and other

disadvantaged groups would be **served by charities.** The Post Office, Amazon, and other companies already have the capacity to collect swabs from everyone with an address. **Everyone should be tested weekly**. All households and care homes would return self-taken swabs from all residents together. In most homes, all residents would test negative and they could resume normal life immediately. An identification card certifying date and result of latest test (positive, negative, negative contact of a positive case) might be useful for policing arrangements. By the time the first test is done there may be more than a million infected people who must be treated or remain quarantined at home or in care until all residents at the address test negative. This emergency system would only be needed for about 2 months but could be rapidly **reintroduced to control any future epidemic** caused by a new virus.

Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic

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Authors from: USA

COVID-19 has significant implications for the cardiovascular care of patients. First, those with COVID-19 and preexisting cardiovascular disease (CVD) have an **increased risk of severe disease and death**. Second, the infection has been associated with multiple direct and indirect cardiovascular complications including **acute myocardial injury, myocarditis, arrhythmias and venous thromboembolism**. Third, therapies under investigation for COVID-19 may have **cardiovascular side effects**. Fourth, the response to COVID-19 can compromise the rapid triage of **non-COVID-19 patients with cardiovascular conditions**. Finally, the provision of cardiovascular care may place **health care workers** in a position of vulnerability as they become host or vectors of virus transmission.

It is crucial to determine whether or not a concomitant cardiogenic component is present when considering mechanical respiratory and circulatory support ECMO or other techniques, as this may lead to changes in device selection (e.g. **venovenous vs. venoarterial ECMO cannulation**). Regardless, in the most severe of infections with ARDS and necrotizing pneumonia, the patient prognosis may be poor even with ECMO support. In a case series of 52 critically ill patients with COVID-19, 83.3% (5/6) of patients who were treated with ECMO did not survive. Further studies regarding the utility of ECMO support in advanced COVID-19, including which patients may (or may not) benefit and whether concomitant left ventricular venting should be done, are warranted.

A number of theories exist regarding the elevated risk of adverse events for patients with CVD who develop COVID-19. In particular, a better understanding of the **relationship between the ACE2 protein, antihypertensive agent use, and COVID-19 prognosis** will have important implications for patients with both COVID-19 and CVD. In this regard, an ongoing randomized trial evaluating recombinant ACE2 in the setting of COVID-19 may help provide mechanistic information in patients infected with this virus (ClinicalTrials.gov Identifier: NCT04287686).

High-flow nasal-oxygenation-assisted fibreoptic tracheal intubation in critically ill patients with COVID-19 pneumonia: a prospective randomised controlled trial

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Authors from: China

Tracheal intubation for invasive mechanical ventilation is the mainstay therapy to correct hypoxemia in COVID-19. Direct laryngoscopy, inadequate sedation, coughing during laryngoscopy, and manual ventilation are consistently associated with increased risk of transmission as a result of the generation of natural aerosols. Furthermore, the previous study reported that 23% of patients had Spo2 <90% during intubation. The authors performed a randomized clinical trial evaluating the efficacy and safety of **high-flow nasal oxygenation (HFNO) during fibreoptic bronchoscopic intubation** in critically ill patients with COVID-19 pneumonia compared with standard mask oxygenation (SMO). **60 patients** were placed in the head-up supine position and oxygen was administered for 4 min, either via HFNO at 50 L/min with heated and humidified oxygen at 37°C, or by standard bag-valve-mask at 15 L/min. All patients were then instructed to take deep breaths before general anesthesia was induced with propofol followed by rocuronium. Fibreoptic tracheal intubation was attempted after one minute. During attempts at tracheal intubation, HFNO was maintained for the HFNO group, whereas no oxygen was administered for the SMO group. After the removal of the bronchoscope, successful intubation was confirmed by capnography. If Spo2 <90% occurred during intubation, bronchoscopy was terminated and face-mask ventilation was initiated to correct desaturation. **Intubation time was significantly shorter in the HFNO group** (69 vs 76 s). The l**owest Spo2 during the procedure was in the HFNO group higher** (94% vs. 91%) and **rescue face-mask ventilation was performed less often** (4% vs 27%). There was no significant difference in the proportion of patients with minimum Spo2 >95% during intubation, in the incidence of Spo2 <80% during intubation, or in the incidence of 7-day mortality.

Lung Recruitability in SARS-CoV-2 Associated Acute Respiratory Distress Syndrome: A Single-center, Observational Study

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Authors from: China, Canada

For patients with ARDS, the specific characteristics of the syndrome, such as respiratory mechanics, remain unknown. In particular, an important clinical question for personalizing the management of these patients is whether the lungs are recruitable with high positive end-expiratory pressure (PEEP) for each individual patient.
Patients who received invasive mechanical ventilation and met criteria for ARDS were included in a **retrospective, observational study.** Subjects were under continuous infusion of sedatives and were assessed for respiratory mechanics including lung recruitability. Patients were ventilated in volume-controlled mode with **tidal volume at 6 mL/kg** of predicted body weight. Prone positioning

was performed over periods of 24 hours when PaO2/FiO2 was persistently lower than 150 mmHg. Measurements were performed at clinically set PEEP and were repeated every morning during the observation days, when possible. Total PEEP and plateau pressure were measured by a short end-expiratory and an end-inspiratory occlusion, respectively. Complete airway closure was assessed by performing a low-flow (6 L/min) inflation and by comparing it with circuit compliance. Potential for lung recruitment was assessed by the R/I ratio, which can be calculated automatically from a webpage (https://crec.coemv.ca).
A threshold of **0.5 was used for defining high recruitability** (R/I ratio ≥ 0.5). Note that recruitability can differ at different ranges of pressure. In the present study, the R/I ratio was measured from 15 to 5 cmH2O in all patients. **Twelve patients were enrolled** (7 males and 5 females, age 59±9 years). On the day of intubation, PaO2/FiO2 was 130±55 mmHg with PaCO2 57±27 mmHg. Of note, patients received various days of noninvasive or invasive ventilatory support before the 1st day of observation. During the 6-day period of observation, 7 patients received at least one session of prone positioning. Three patients received both prone positioning and ECMO. Three patients died (25%). Neither complete airway closure nor auto-PEEP was found in any patient. Among the 12 patients, **10 (83%) were poorly recruitable (R/I ratio: 0.21±0.14) on the first day of observation**. Patients who did not receive prone positioning had persistent poor recruitability (only 1 out of 17 daily measurements showed high recruitability). In contrast, **alternating body position between supine and prone positioning was associated with increased lung recruitability** (13 out of 36 daily measurements showed high recruitability; P=0.020 by chi-square test between two groups). In patients who received prone position, PaO2/FiO2 went from 120±61 mmHg at supine to 182±140 mmHg at prone (P=0.065 by paired t-test).

COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. What Is the Evidence?

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Authors from: USA

The increased mortality and morbidity of COVID-19 in patients with hypertension is an association that has been observed in a number of initial epidemiological studies - Wu et al found hypertension to have a hazard ratio of 1.70 for death and 1.82 for acute respiratory distress syndrome in 201 patients with COVID-19. The study was not adjusted for confounding variables. There has been a growing concern that this association with hypertension is confounded by treatment with specific antihypertensive medications: angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). The link with ACEIs and ARBs is because of the known association between angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2. ACE2 has been shown to be a co-receptor for viral entry for SARS-CoV-2. ACE2 has a broad expression pattern in the human body with strong expression in type II alveolar cells in the lungs. The concern that ACEIs and ARBs affect the severity and mortality of COVID-19 is 2-fold. One suggestion is that **ACEIs could directly inhibit ACE2**; however, ACE2 functions as a carboxypeptidase and is not inhibited by clinically prescribed ACEIs.

In addition, there is concern that the use of ACEIs and ARBs **will increase the expression of ACE2 and increase patient susceptibility** to viral host cell entry and propagation. There has been considerable evidence in animal models as well as some evidence in humans showing increased expression of ACE2 in the heart, brain, and even in urine after treatment with ARBs; however, there is limited evidence showing changes in serum or pulmonary ACE2 levels. More relevant, the significance of ACE2 expression on COVID-19 pathogenesis and mortality is not specifically known. **ACE2 primarily acts to counterbalance the effect of ACE**. As ACE generates angiotensin II from angiotensin I, ACE2 generates angiotensin (1-7) from angiotensin II which, shifts the balance from vasoconstriction with angiotensin II to vasodilation with Mas receptor activation in the affected vascular bed. **ACE2 and angiotensin (1-7) have been found to be protective in a number of different lung injury models.** In an acid lung injury model in mice, **ACE2 downregulation by SARS-CoV worsened lung injury that was improved by treatment with ARB**. Although these preclinical data suggest that increasing ACE2 expression can attenuate SARS-CoV-2–induced lung injury, **there is no direct clinical evidence** that has proven ACE2 to be an effective treatment for viral-induced lung injury.

Despite the lack of evidence, **there have been advocates for both the use and cessation of ACEIs, ARBs or both during the treatment for COVID-19 in patients with hypertension.** This has prompted some individuals to solicit changes in their hypertensive medications and growing uncertainty from physicians on what should be done. In response, the Council on Hypertension of the European Society of Cardiology made the following statement, "**The Council on Hypertension strongly recommends that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEIs or ARBs should be discontinued because of the COVID-19 infection**." This statement has been followed by similar statements from a number of different societies suggesting patients continue their current hypertensive medication regimen.

Covid-19: identifying and isolating asymptomatic people helped eliminate virus in Italian village

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Authors from: UK

Italian village Vo'Euganeo with 3000 inhabitants was closed off by authorities in mid-February, at which point **repeat RNA testing of the entire population began**. All those with positive tests were quarantined. The **number of people sick from COVID-19 fell from 88 to seven in less than 10 days**. 50-75% of the positively tested population was asymptomatic but represented "a formidable source" of contagion. Asymptomatic cases were particularly, but not only, among young people. Isolation of asymptomatics is essential for controlling the spread of the virus and the seriousness of the epidemic. Another big group is formed by health workers who might unwittingly pass the virus to colleagues or patients.

Decisions not to test doctors and nurses if they're not developing symptoms are widespread. But in the light of the results, this decision could be dangerous; **hospitals risk becoming zones with high infection rates in which infected people are not isolated.**"

COVID-19 infection: the perspectives on immune responses

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Authors from: China, USA, Italy

Not all people exposed to SARS-CoV-2 are infected and not all infected patients develop a severe respiratory illness. Accordingly, SARS-CoV-2 infection can be roughly divided into three stages: stage I, an **asymptomatic incubation period** with or without detectable virus; stage II, **non-severe symptomatic period** with the presence of virus; stage III, a **severe respiratory symptomatic stage with high viral load.** Among over 1000 patients analyzed in Wuhan, except occasionally in children and adolescence, it infects all the other age groups evenly. About 15% of the confirmed cases progress to the severe phase, although there is a higher chance for patients over 65. One of the biggest unanswered questions is why some develop severe disease, whilst others do not. Clinically, the immune responses induced by SARS-CoV-2 infection are **two-phased.** During the incubation and non-severe stages, a **specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages**. Therefore, strategies to boost immune responses (anti-sera or pegylated IFNα) at this stage are certainly important. For the development of an endogenous protective immune response at the incubation and non-severe stages, the host should be in good general health and an appropriate genetic background (e.g. HLA) that elicits specific antiviral immunity. However, when a protective immune response is impaired, the virus will propagate The damaged cells induce innate inflammation in the lungs that is largely mediated by pro-inflammatory macrophages and granulocytes. **Lung inflammation is the main cause of life-threatening respiratory disorders at a severe stage**. Once severe lung damage occurs, efforts should be made to **suppress inflammation and to manage the symptoms.**
The cytokine release syndrome (CRS) seems to affect patients with severe conditions. Since lymphocytopenia is often seen in severe COVID-19 patients, the CRS caused by the SARS-CoV-2 virus has to be mediated by leukocytes other than T cells. **Blocking IL-6 may be effective**. **Blocking IL-1 and TNF may also benefit patients.** Although various clinical sites in China have announced the use of **mesenchymal stromal/stem cells** (MSCs) in severe cases with COVID-19 infection, solid results have yet to be seen. One caveat is that MSCs need to be activated by IFNγ to exert their anti-inflammatory effects, which may be absent in severely affected patients as T cells are not well activated by SARS-CoV-2 infection. To enhance effectiveness, one could consider pretreating MSCs with IFNγ with/without TNF or IL-1. The **major-histocompatibility-complex (HLA**) is a prototypical candidate for genetic susceptibility to infectious diseases. Haplotype HLA-loci variability results from selective pressure during co-evolution with pathogens. Therefore, it is imperative to study whether specific HLA loci are associated with the development of anti-SARS-CoV-2 immunity and, if so, to identify the alleles, either class I or II, that demonstrate induction of protective immunity. Once the dominant alleles are identified, simple detection kits can be

developed. Such information is critical for (1) strategic clinical management; (2) evaluation of the efficacy of vaccination in different individuals in the general population; (3) assignment of clinical professional and managerial teams amid interactions with COVID-19 patients.
The innate immune response to tissue damage caused by the virus could lead to ARDS. Recent autopsies have confirmed that the lungs are filled with clear liquid jelly, much resembling the lungs of wet drowning. Although the nature of the clear jelly has yet to be determined, hyaluronan (HA) is associated with ARDS. Therefore, reducing the presence or inhibiting the production of HA holds a great promise in helping COVID-19 patients breathe. Doctors can simply provide patients with medical-grade hyaluronidase to reduce the accumulation of HA and thus to clear the jelly in the lung. Doctors can also use a clinically approved bile therapy drug, **Hymecromone** (4-Methylumbelliferone, 4-MU), an inhibitor of HAS2. The authors propose some simple but largely ignored, approaches to the treatment of COVID-19 patients. **Doctors should try to boost immune responses during the first phase while suppressing it in the second phase.** Since **Vitamin B3 is highly lung-protective**, it should be used as soon as coughing begins. When breathing difficulty becomes apparent, **hyaluronidase can be used intratracheally** and at the same time, **4-MU can be given to inhibit HAS2.**

Critical Organizational Issues for Cardiologists in the COVID-19 Outbreak: A Frontline Experience From Milan, Italy

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Authors from: Italy

In late February, one of the first measures adopted by the Lombardy Regional Health Service was to **reduce the number of elective hospitalizations by approximately 80%**. Under normal conditions, the waiting list allows patients with chronic coronary syndromes and clinical indications to **undergo coronary angiography within approximately 3 weeks**. After the decision to reduce the number of elective hospitalizations was implemented, maintaining the same waiting times was no longer possible. Already during the first week of restrictive measures, the authors had to postpone 80% of planned procedures. Therefore, they needed a strategy to select patients in whom clinical status would not allow postponement of their planned cardiac procedure. **Prioritization was based on risk stratification**, taking into account patient symptoms, evidence of a large area of ischemia, and the presence of known critical disease of the left main stem or of the proximal left anterior descending coronary artery at prior coronary angiogram or at coronary computed tomography angiography. In addition, patients with decompensated, symptomatic, **severe aortic stenosis** scheduled for transcatheter aortic valve replacement were prioritized. The impact on the patient prognosis of this inevitable decision is unknown. Outpatient clinics have been closed and available beds were limited to cardiovascular emergencies.

COVID-19 patients tend to be elderly and suffer from several comorbidities. Among these comorbidities, a history of ischemic heart disease and other cardiovascular risk factors is prevalent and is associated with worse outcomes. Along the same lines, **myocardial involvement**

has been described in COVID-19 patients; those with the most severe clinical presentation have elevated cardiac biomarkers coupled with impairment of left ventricular ejection fraction. In this context, cardiologists' clinical activities have been reorganized into two teams; those **taking care of cardiovascular emergencies** and those **focusing on the management of cardiovascular comorbidities** and myocardial involvement in critical COVID-19 patients.
The major goal is not to compromise the standard-of-care for the management of AMI patients. In order to continue to treat **AMI patients in line with current guidelines** while **preventing their exposure to SARS-CoV2, the Lombardy Regional Health Service restructured the AMI network.** Under normal conditions, Lombardy has 129 accredited hospitals, 55 of which are equipped with cardiac catheterization laboratories offering 24/7 service for AMI to approximately 10 million inhabitants. On March 8, 2020, the regional government passed a deliberation to reduce to **13 the hospitals with catheterization laboratories now acting as Hubs**, with the remaining hospitals acting as Spokes. Patients are now referred to a Hub on the basis of geographic proximity. The same model has been applied to other cardiovascular emergencies (e.g., stroke). The result of this measure has been to concentrate a large majority of AMI patients in a limited number of hospitals. Whether this will have an impact on timely reperfusion strategies is currently unknown.
Thus, key actions for cardiologists should include efforts to 1) Foster a **close collaboration** with other specialists involved in the management of COVID-19 patients; 2) Define pathways to appropriately manage **cardiovascular diseases in both COVID-19- positive and uninfected patients**, while guaranteeing the safety of healthcare professionals; 3) Enhance **cooperation between hospitals to centralize services** to treat cardiovascular diseases.

Functional exhaustion of antiviral lymphocytes in COVID-19 patients

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Authors from: China

Cytotoxic lymphocytes such as **cytotoxic T lymphocytes** (CTLs) and **natural killer** (NK) cells are necessary for the control of viral infection, and the functional exhaustion of cytotoxic lymphocytes is correlated with disease progression. The authors showed that the **total number of NK and CD8+ T cells was decreased** markedly in patients with SARS-CoV-2 infection. The function of NK and CD8+ T cells was exhausted with the increased expression of NKG2A in COVID-19 patients. Importantly, in patients convalescing after therapy, the number of NK and CD8+ T cells was restored with reduced expression of NKG2A. These results suggest that the **functional exhaustion of cytotoxic lymphocytes is associated with SRAS-CoV-2 infection**. Hence, **SARS-CoV-2 infection may break down antiviral immunity at an early stage.**