Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)

https://link.springer.com/article/10.1007%2Fs00134-020-06022-5

Journal: Intensive Care Medicine *Published Online: March 28, 2020*

Authors from: Canada, Denmark, USA, Saudi Arabia, The Netherlands, China, Italy, Korea...

The authors formed a **panel of 36 experts from 12 countries**. The panel proposed 53 questions that are relevant to the management of COVID-19 in the ICU. They searched the literature for direct and indirect evidence and identified relevant and recent systematic reviews on most questions related to supportive care. Certainty in the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, then generated recommendations based on the balance between benefit and harm, resource and cost implications, equity, and feasibility. Recommendations were either strong or weak or in the form of best practice recommendations. The Surviving Sepsis Campaign COVID-19 panel issued **54 statements, of which 4 are best practice statements, 9 are strong recommendations, and 35 are weak recommendations.** No recommendation was provided for 6 questions. The full rationale can be found on the link above. Recommendation summary table is enclosed below:

	Recommendation	**Strength**
INFECTION CONTROL AND TESTING		
1	For healthcare workers performing aerosol-generating procedures* on patients with COVID-19 in the ICU, we *recommend* using fitted respirator masks (N95 respirators, FFP2, or equivalent), as opposed to surgical/medical masks, in addition to other personal protective equipment (i.e. gloves, gown, and eye protection, such as a face shield or safety goggles)	Best practice statement
2	We *recommend* performing aerosol-generating procedures on ICU patients with COVID-19 in a negative pressure room	Best practice statement

3	For healthcare workers providing usual care for non-ventilated COVID-19 patients, we *suggest* using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e. gloves, gown, and eye protection, such as a face shield or safety goggles)	Weak
4	For healthcare workers who are performing non-aerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19, we *suggest* using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e. gloves, gown, and eye protection, such as a face shield or safety goggles)	Weak
5	For healthcare workers performing endotracheal intubation on patients with COVID-19, we *suggest* using video-guided laryngoscopy, over direct laryngoscopy, if available	Weak
6	For COVID-19 patients requiring endotracheal intubation, we *recommend* that endotracheal intubation be performed by the healthcare worker who is most experienced with airway management in order to minimize the number of attempts and risk of transmission	Best practice statement
7.1	For intubated and mechanically ventilated adults with suspicion of COVID-19: For diagnostic testing, we *suggest* obtaining lower respiratory tract samples in preference to the upper respiratory tract (nasopharyngeal or oropharyngeal) samples	Weak
7.2	For intubated and mechanically ventilated adults with suspicion of COVID-19: With regard to lower respiratory samples, we *suggest* obtaining endotracheal aspirates in preference to bronchial wash or bronchoalveolar lavage samples	Weak

HEMODYNAMICS		
8	In adults with COVID-19 and shock, we *suggest* using dynamic parameters skin temperature, capillary refilling time, and/or serum lactate measurement over static parameters in order to assess fluid responsiveness	Weak
9	For the acute resuscitation of adults with COVID-19 and shock, we *suggest* using a conservative over a liberal fluid strategy	Weak
10	For the acute resuscitation of adults with COVID-19 and shock, we *recommend* using crystalloids over colloids	Weak
11	For the acute resuscitation of adults with COVID-19 and shock, we *suggest* using buffered/balanced crystalloids over unbalanced crystalloids	Weak
12	For the acute resuscitation of adults with COVID-19 and shock, we *recommend against* using hydroxyethyl starches	Strong
13	For the acute resuscitation of adults with COVID-19 and shock, we *suggest against* using gelatins	Weak
14	For the acute resuscitation of adults with COVID-19 and shock, we suggest against using dextrans	Weak
15	For the acute resuscitation of adults with COVID-19 and shock, we *suggest against* the routine use of albumin for initial resuscitation	Weak

16	For adults with COVID-19 and shock, we *suggest* using norepinephrine as the first-line vasoactive agent, over other agents	Weak
17	If norepinephrine is not available, we *suggest* using either vasopressin or epinephrine as the first-line vasoactive agent, over other vasoactive agents, for adults with COVID-19 and shock	Weak
18	For adults with COVID-19 and shock, we *recommend against* using dopamine if norepinephrine is available	Strong
19	For adults with COVID-19 and shock, we *suggest* adding vasopressin as a second-line agent, over titrating norepinephrine dose, if target mean arterial pressure (MAP) cannot be achieved by norepinephrine alone	Weak
20	For adults with COVID-19 and shock, we *suggest titrating* vasoactive agents to target a MAP of 60-65 mmHg, rather than higher MAP targets	Weak
21	For adults with COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, we *suggest* adding dobutamine, over increasing norepinephrine dose	Weak
22	For adults with COVID-19 and refractory shock, we *suggest* using low-dose corticosteroid therapy (“shock-reversal”), over no corticosteroid *Remark*: A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses	Weak

VENTILATION		
23	In adults with COVID-19, we *suggest* starting supplemental oxygen if the peripheral oxygen saturation (SpO_2) is < 92%, and *recommend* starting supplemental oxygen if SpO_2 is < 90%	Weak Strong
24	In adults with COVID-19 and acute hypoxemic respiratory failure on oxygen, we *recommend* that SpO_2 be maintained no higher than 96%	Strong
25	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, we *suggest using* HFNC over conventional oxygen therapy	Weak
26	In adults with COVID-19 and acute hypoxemic respiratory failure, we *suggest* using HFNC over NIPPV	Weak
27	In adults with COVID-19 and acute hypoxemic respiratory failure, if HFNC is not available and there is no urgent indication for endotracheal intubation, we *suggest* a trial of NIPPV with close monitoring and short-interval assessment for worsening of respiratory failure	Weak
28	We were not able to make a recommendation regarding the use of helmet NIPPV compared with mask NIPPV. It is an option, but we are not certain about its safety or efficacy in COVID-19	No recommendation
29	In adults with COVID-19 receiving NIPPV or HFNC, we *recommend* close monitoring for worsening of respiratory status, and early intubation in a controlled setting if worsening occurs	Best practice statement

30	In mechanically ventilated adults with COVID-19 and ARDS, we *recommend* using low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predicted body weight), over higher tidal volumes (Vt > 8 mL/kg)	Strong
31	For mechanically ventilated adults with COVID-19 and ARDS, we *recommend* targeting plateau pressures (Pplat) of < 30 cm H_2O	Strong
32	For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, we *suggest* using a higher PEEP strategy, over a lower PEEP strategy. *Remarks*: If using a higher PEEP strategy (i.e. PEEP > 10 cm H_2O), clinicians should monitor patients for barotrauma	Strong
33	For mechanically ventilated adults with COVID-19 and ARDS, we *suggest* using a conservative fluid strategy over a liberal fluid strategy	Weak
34	For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, we *suggest* prone ventilation for 12–16 h, over no prone ventilation	Weak
35.1	For mechanically ventilated adults with COVID-19 and moderate to severe ARDS: we *suggest* using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA), over continuous NMBA infusion, to facilitate protective lung ventilation	Weak
35.2	In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, we *suggest* using a continuous NMBA infusion for up to 48 h	Weak

36	In mechanically ventilated adults with COVID-19 ARDS, we *recommend against* the routine use of inhaled nitric oxide	Weak
37	In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, we *suggest* a trial of inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off	Weak
38	For mechanically ventilated adults with COVID-19 and hypoxemia despite optimizing ventilation, we *suggest* using recruitment maneuvers, over not using recruitment maneuvers	Weak
39	If recruitment maneuvers are used, we *recommend against* using staircase (incremental PEEP) recruitment maneuvers	Strong
40	In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, we *suggest* using venovenous (VV) ECMO if available or referring the patient to an ECMO center *Remark*: Due to the resource-intensive nature of ECMO, and the need for experienced centers and healthcare workers, and infrastructure, ECMO should only be considered in carefully selected patients with COVID-19 and severe ARDS	Weak
THERAPY		
41	In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we *suggest against* the routine use of systemic	Weak

	corticosteroids	
42	In mechanically ventilated adults with COVID-19 and ARDS, we *suggest* using systemic corticosteroids, over not using corticosteroids *Remark:* The majority of our panel support a weak recommendation (i.e. suggestion) to use steroids in the sickest patients with COVID-19 and ARDS. However, because of the very low-quality evidence, some experts on the panel preferred not to issue a recommendation until higher quality direct evidence is available	Weak
43	In mechanically ventilated patients with COVID-19 and respiratory failure, we *suggest* using empiric antimicrobials/antibacterial agents, over no antimicrobials *Remark*: if the treating team initiates empiric antimicrobials, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology results and the patient's clinical status	Weak
44	For critically ill adults with COVID-19 who develop fever, we *suggest* using acetaminophen/paracetamol for temperature control, over no treatment	Weak
45	In critically ill adults with COVID-19, we *suggest against* the routine use of standard intravenous immunoglobulins (IVIG)	Weak
46	In critically ill adults with COVID-19, we *suggest against* the routine use of convalescent plasma	Weak

47.1	In critically ill adults with COVID-19: we suggest against the routine use of lopinavir/ritonavir	Weak
47.2	There is insufficient evidence to issue a recommendation on the use of other antiviral agents in critically ill adults with COVID-19	No recommendation
48	There is insufficient evidence to issue a recommendation on the use of recombinant rIFNs, alone or in combination with antivirals, in critically ill adults with COVID-19	No recommendation
49	There is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19	No recommendation
50	There is insufficient evidence to issue a recommendation on the use of tocilizumab in critically ill adults with COVID-19	No recommendation

EMA advice on the use of NSAIDs for Covid-19
https://dtb.bmj.com/content/early/2020/03/31/dtb.2020.000021
Journal: Drugs and Therapeutics Bulletin (BMJ) *Published Online: March 31, 2020*
Authors from: UK

The European Medicines Agency (EMA) has responded to reports questioning whether the use of ibuprofen or other NSAIDs could worsen COVID-19. **No scientific evidence has established a link between ibuprofen and the worsening of the disease**. The EMA has advised that there is no reason for patients who are taking NSAIDs for chronic diseases to stop taking them. However, many national treatment guidelines recommend using paracetamol as the first-line option for fever or pain.

Intranasal corticosteroids in allergic rhinitis in COVID-19 infected patients: An

ARIA-EAACI statement

https://onlinelibrary.wiley.com/doi/epdf/10.1111/all.14302

Journal: Allergy *Published Online: March 31, 2020*

Authors from: Germany, France, Spain, Australia, Brazil, Switzerland, Poland, Romania, Belgium, Italy

Whether **systemic corticosteroids** have a deleterious effect on COVID-19 infection is still a matter of discussion. Clinical evidence does not support corticosteroid treatment for SARS-CoV-2 pneumonia. Concerning **inhaled corticosteroids in asthma**, the Global Initiative for Asthma (GINA) recently stated the following: "Some sources have suggested that "corticosteroids" should be avoided during the for SARS-CoV-2 epidemic. This advice is about the use of oral corticosteroids unless there is a clear indication for their use. However, **patients with asthma should not stop their prescribed inhaled corticosteroid controller medication (or prescribed oral corticosteroids)**. Stopping inhaled corticosteroids often leads to potentially dangerous worsening of asthma, and avoiding oral corticosteroids during severe asthma attacks may have serious consequences. Long-term oral corticosteroids may sometimes be required to treat severe asthma, and **it may be dangerous to stop them suddenly**."
Regarding **intra-nasal corticosteroids**, ARIA-EAACI is issuing the following recommendations: With the current knowledge, in patients with COVID-19 infection, intranasal corticosteroid (including spray) **can be continued in allergic rhinitis** at the recommended dose. Stopping local intra-nasal corticosteroid is not advised. Suppression of the immune system has not been proven and **more sneezing after stopping means more spreading of the Coronavirus**. These recommendations are conditional since there is a paucity of data and they should be revised regularly with new knowledge.

Spinal anaesthesia for patients with coronavirus disease 2019 and possible transmission rates in anaesthetists: retrospective, single-centre, observational cohort study

https://bjanaesthesia.org/article/S0007-0912(20)30161-6/fulltext

Journal: British Journal of Anaesthesia *Published Online: March 28, 2020*

Authors from: China

The safety of performing **spinal anaesthesia** for both patients and anaesthetists alike in the **presence of active infection** with COVID-19 is unclear. The authors of the present retrospective study reported the clinical characteristics and outcomes for patients with COVID-19 and the anaesthetists. 49 patients with radiologically confirmed COVID-19 underwent spinal anaesthesia with 0.75% ropivacaine during Caesarean section (91%) or lower-limb surgery (9%). Clinical characteristics and perioperative outcomes were recorded. For anaesthesiologists exposed to patients with COVID-19 by providing spinal anaesthesia, the level of personal protective equipment (PPE) used clinical outcomes (pulmonary CT scans), and confirmed COVID-19 transmission rates by PCR were reviewed. Spinal anaesthesia was **not associated with cardiorespiratory compromise** intraoperatively. **No patients subsequently developed severe pneumonia.** Of 44 anaesthetists, 37 (84.1%) provided spinal anaesthesia using Level 3 PPE. Coronavirus disease 2019 infection was subsequently confirmed by PCR in 5/44 (11.4%) anaesthetists. **One (2.7%) of 37 anaesthetists who wore Level 3 PPE developed PCR-**

confirmed COVID-19 compared with 4/7 (57.1%) anaesthetists who had Level 1 protection in the operating theatre (relative risk reduction: 95.3% [95% confidence intervals: 63.7–99.4]; P<0.01). Spinal anaesthesia was delivered safely in patients with active COVID-19 infection, the majority of whom had Caesarean sections. Level 3 PPE appears to reduce the risk of transmission to anaesthetists who are **exposed to mildly symptomatic surgical patients**.

Italian Society of Interventional Cardiology (GISE) Position Paper for Cath lab- specific Preparedness Recommendations for Healthcare providers in case of suspected, probable or confirmed cases of COVID- 19

https://onlinelibrary.wiley.com/doi/abs/10.1002/ccd.28888

Journal: Core Curriculum *Published Online: March 29, 2020*
Authors from: Italy

The aim of this position paper is to provide standards on infection prevention and control during the management of **suspected and confirmed cases of COVID-19, accessing cath-lab**. The document represents the view of the Italian Society of Interventional Cardiology (GISE), and it is based on recommendations from WHO, ECDC as well as from the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI). **Recommendation on following topics can be found in the article full text:** Daily checklist in the cath lab, a daily checklist of a crash cart, general and cath-lab specific procedures for wearing (‘donning’) and safe removal (‘doffing’) of PPE and what to do before the arrival in cath-lab of a suspected or confirmed COVID-19 patient.

Periprocedural management of suspected or confirmed COVID-19 patients in cath-lab.

1. Keep the door closed for the whole duration of the procedure.
2. PPE-protected (but non-sterile) member staff put the patient on the operating table.
3. Avoid entry and exit from the room of the staff for bringing material (everything necessary should be planned in advance and stored inside).
4. Non-sterile staff members moving into the operating room during the procedure should minimize any contact with the surfaces. Before any contact (for example before opening a tray), he should change the external gloves (or put on another pair of cleaned gloves).
5. Keep the procedure as simple as possible (only culprit lesion revascularization).

Post-procedural requirements when a suspected or confirmed COVID-19 patient leaves the cath-lab.

1. Keep the door closed.
2. Supervised doffing as previously described; if no anteroom is available, doffing of PPE could be done inside the room, at the end of the procedure and when the patient has been transferred away. Only facial respirator must be removed outside the contaminated area.
3. Dispose of all waste according to protocols (do not squeeze contaminated material into the container).
4. Treat used tissues in accordance with standard procedures.
5. Get out of the operating room and keep the door closed for at least an hour prior to

performing a terminal clean (in particular for a neutral pressure room).
6. Re-useable equipment has to be decontaminated according to the manufacturer's instructions (i.e.lead apron).
7. Notification of any new confirmed case.
8. A record of all staff providing care for suspected or confirmed 2019-nCoV cases must be maintained.
9. If at any point a member of the staff feels as he/she has been exposed to the pathogen, follow facility protocols.
10. Staff who have been provided care to confirmed 2019-nCoV cases should be vigilant for fever and any respiratory symptoms in the 14 days following the last exposure to a confirmed case and follow internal protocols.

ECMO for ARDS due to COVID-19

https://www.heartandlung.org/article/S0147-9563(20)30100-X/fulltext

Journal: Heart and Lung *Published Online: March 26, 2020*

Author from: Mexico

In China, approximately 5% of critically ill patients with COVID-19 infection have presented with rapidly progressive respiratory failure, development of ARDS, and ICU admission. The prevalence of ARDS caused by COVID-19 is approximately 8.2%. Critically ill patients have required invasive mechanical ventilation, prone positioning, and, in some cases, ECMO. ECMO has been proposed as rescue therapy in severely hypoxemic patients with MERS caused by a coronavirus who failed conventional strategies. ECMO might not seem to be as much of a priority as personal protective equipment, refine processes, and check logistics in the global response to the COVID-19 outbreak. The **complexity of ECMO requires a well-qualified ICU team** to deliver care to critically ill patients with ECMO; therefore, the use may be limited to expert, high-volume centers. Annual ECMO mortality rates vary widely across ECMO centers, and the interquartile range reported by Barbaro et al. was 33 to 92% for adult patients treated with ECMO. **Although there little evidence on the outcomes of patients with ARDS due to COVID-19** supported with ECMO, the results of the studies published during the COVID19 outbreak show that the **mortality rate of adult patients with ARDS due to COVID-19 undergoing ECMO is approximately 82.3%**.

Table 1
Comparison of studies that reported Extra Corporeal Membrane Oxygenation (ECMO) as a rescue therapy for patients with acute respiratory distress syndrome (ARDS) due to COVID-19.

	Huang C et al.	Nanshan Chen et al.	Wang D et al.	Yang X et al.	Guan WJ et al.	Zhou F et al.
Study type	Cross-sectional	Retrospective, observational	Case series	Retrospective, observational	Cross-sectional	Retrospective, cohort study
n	41	99	138	710	1099	191
ICU admission, proportion,% (95% CI)	31.7 (18.08–48.08)	17.17 (10.33–26.06)	26.08 (18.98–34.24)	7.32 (5.51–9.49)	5.0 (3.79–6.46)	26,17 (20.09–33.01)
ARDS, proportion,% (95% CI)	29.26 (16.13–45.53)	17.17 (10.33–26.06)	19.56 (13.3–27.17)	4.93 (3.45–6.78)	3.36 (2.38–4.6)	30.89 (24.1–37.96)
Risk of death during ECMO support, relative risk (95% CI)	Data were unavailable to calculate	0.46 (0.09–2.39)	Data were unavailable to calculate)	0.89 (0.61–1.29)	2.88 (1.65–5.01)	0.96 (0.66–1.41)
Overall mortality rate, proportion,% (95% CI)	14.63 (5.56–29.17)	11.11 (5.67–19.01)	4.34(1.61–9.22)	4.50 (3.10–6.30)	1.36 (0.76–2.24)	28,27 (22.0–35.22)

The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2

https://academic.oup.com/cardiovascres/advance-article/doi/10.1093/cvr/cvaa078/5813131

Journal: Cardiovascular Research *Published Online: March 30, 2020*

Authors from: China

Cardiac injury is a prevalent complication of COVID-19 and is exacerbating the disease severity. ACE2, the **key host cellular receptor of SARS-CoV-2**, has been identified in multiple organs, but its cellular distribution in the human heart is not illuminated clearly. This study performed an analysis of the adult human heart and revealed that **pericytes with high expression of ACE2 might act as the target cardiac cell of SARS-CoV-2**. The pericytes injury due to virus infection may result in capillary endothelial cells dysfunction, inducing microvascular dysfunction. Patients with **baseline heart failure showed increased ACE2** expression at both mRNA and protein levels, meaning that if infected by the virus, these patients may have a higher risk of ACS or progression to the critical condition.

Performance of VivaDiagTM COVID- 19 IgM/IgG Rapid Test is inadequate for diagnosis of COVID- 19 in acute patients referring to emergency room department

https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25800

Journal: Journal of Medical Virology *Published Online: March 30, 2020*

Authors from: Italy

RT-PCR from respiratory samples is the current gold standard method for the diagnosis of COVID-19. However, molecular testing is time-consuming and requires specialized operators. Recently, an easy to perform serological assay has been assessed to differentiate COVID-19 positive patients from negative subjects. The authors herein report results of a **real-life study performed in an emergency department** in Italy to validate VivaDiagTM COVID-19 IgM/IgG Rapid Test lateral flow immunoassay (LFIA) for the diagnosis of COVID-19.

Overall 110 subjects were tested for COVID19-specific serological assay, including 30 healthy volunteers with documented negative RT-PCR, 30 admitted COVID-19-positive controls and finally, 50 patients presenting to the emergency with fever and respiratory symptoms. In the cohort of patients admitted to the emergency department, data from serological tests were compared to molecular results in order to define specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of the rapid serological test. As expected, **all 30 COVID-19 negative volunteers were negative for both IgG and IgM.** Serum samples were obtained at a **median day 7** after the first COVID-19 positive result from **30 hospitalized patients**. 63,3% were positive for both IgM and IgG, 16,7% were negative for both IgG and IgM, 16,7% were weakly positive for both IgM and IgG and only 3,3% was positive for IgM and negative for IgG. Thus, **the sensitivity of the rapid assay was suboptimal.** Focusing on the **acute patients enrolled from the emergency department,** 24% were negative for COVID-19 by RT-PCR. Of these, 8.3% (one person) showed a positive result for the VivaDiagTM COVID-19 IgM/IgG Rapid Test, while the others tested negative. On the other side, 38 patients were positive for COVID-19 by RT-PCR. Of these, **only 18.4% showed a positive or weak positive serology for IgM and/or IgG.** Thus, the sensitivity of the VivaDiagTM COVID-19 IgM/IgG Rapid Test was 18.4%, specificity was 91.7%, while NPV was 26.2% and PPV was 87.5% in patients enrolled from the emergency department.

Guidance for Cardiac Electrophysiology During the Coronavirus (COVID-19) Pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association

https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.047063

Journal: Circulation *Published Online: March 31, 2020*

Authors from: USA

In a recent report from Wuhan, China, 16.7% of hospitalized and 44.4% of ICU patients with COVID-19 had **arrhythmias**. In addition, there have been anecdotal reports of patients experiencing late myocardial dysfunction, as well as cardiopulmonary arrest with pulseless electrical activity or ventricular fibrillation during the recovery phase of their pulmonary illness. COVID-19 has the potential to cause **myocardial injury** with at least 17% found to have an elevated troponin and 23% noted to have heart failure in a study of 191 inpatients from Wuhan, China. Cases of **fulminant myocarditis** with cardiogenic shock have also been reported, with associated atrial and ventricular arrhythmias. Given that hypoxia and electrolyte abnormalities that are common in the acute phase of severe illness can potentiate cardiac arrhythmias, the exact arrhythmic risk related to COVID-19 in patients with less severe illness or those who recover from the acute phase of the severe illness is currently unknown. Improved understanding of this is critical, primarily in guiding the need for additional arrhythmia monitoring (e.g., mobile cardiac telemetry) post-discharge and whether an **implantable cardioverter-defibrillator** (ICD) or wearable cardioverter defibrillator will be needed in those with impaired left ventricular function thought secondary to COVID-19.

Urgent, or Emergent Procedures (access should be maintained):

- Ventricular tachycardia (VT) ablation for medically uncontrolled electrical storm in a hemodynamically compromised patient
- Catheter ablation of incessant, hemodynamically significant, severely symptomatic tachycardia (SVT/AF/atrial flutter) not responding to antiarrhythmic drugs, rate control, and/or cardioversion
- Catheter ablation for Wolff-Parkinson-White syndrome or preexcited AF with syncope or cardiac arrest
- Lead revision for malfunction in a pacemaker dependent patient or ICD patient receiving inappropriate therapy
- Generator change in pacemaker-dependent patients who are at elective replacement indicator (ERI) or at device end of life (EOL)
- Pacemaker or ICD generator change with minimal battery remaining, depending on specific clinical situations.
- Secondary prevention ICD
- Pacemaker implant for complete heart block, Mobitz II AV block, or high-grade AVB with symptoms or severe symptomatic sinus node dysfunction with long pauses
- Lead/device extraction for infection, including patients not responding to antibiotics or for endocarditis, bacteremia or pocket infection
- Cardiac resynchronization therapy in the setting of severe refractory heart failure in guideline indicated patients
- Cardioversion for highly symptomatic atrial arrhythmias or rapid ventricular rates not controlled with medications
- Transesophageal echocardiogram for patients who need urgent cardioversion. (Further guidance on this issue from the American Society of Echocardiography)

Semi-Urgent procedures (not emergent, yet clinically may need to be performed in a timely manner due to clinical circumstances.)

- VT ablation for medically refractory recurrent ventricular tachycardia
- SVT ablation, in patients with medically refractory SVT resulting in ED visits
- CIED generator replacement for ERI battery status that is not urgent or emergent d
- Primary prevention ICD in patients at particularly high risk of life-threating ventricular arrhythmia

Limit In-Person CIED Interrogation to those Considered Urgent or Time-Sensitive:

- Clinically actionable abnormality of CIED noted on remote monitoring, telemetry, or ambulatory monitoring
- ICD shocks, presyncope or syncope concerning for an arrhythmic event, to perform programming changes
- Evaluation of symptoms suspicious for arrhythmia or abnormal device function in patients who are not enrolled in remote monitoring
- Identified need for re-programming of the device
- For CIED patients needing urgent or emergent MRI scanning, consider performing a CT scan instead, if possible (to minimize the need for additional health care provider or device manufacturer representative contact); if not urgent, delay the MRI.

- Patients in the emergency department where remote monitoring is not available; remote monitoring should be used wherever possible

Safety guidance for clinicians using hydroxychloroquine (HCQ) may be requested of EP providers. HCQ is known to block Kv11.1 (HERG) and can cause **drug-induced LQT.** The clinical arrhythmic toxicity (syncope and torsade de pointes) is largely limited to chronic use (due to its long half-life of 40 days), use of multiple concomitant QT-prolonging medications (e.g. azithromycin), metabolic derangements, renal failure, or in the setting of an acute overdose. To date, it has been widely tolerated in most populations as an antimalarial and safely used in the rheumatoid arthritis and systemic lupus erythematosus populations without ECG monitoring. Because the proposed HCQ therapy for COVID-19 is relatively short (e.g. 5-10 days), the risk of arrhythmic toxicity is likely quite low. There are specific precautions to be considered for select patients, however: • Patients with known congenital Long QT Syndrome • Patients with severe renal insufficiency should have the dose reduced (50% for CrCl <10 mL/min) • Patients on QT-prolonging drugs • Electrolyte imbalances (e.g. hypokalemia, hypomagnesemia) must be corrected prior to use, with regular monitoring
None of the above conditions is an absolute contraindication if use of HCQ is warranted. It is reasonable to temporarily stop class III antiarrhythmic drugs, with use of a reasonable alternative if there is evidence of QT prolongation. Importantly, aggressive electrolyte correction can mitigate arrhythmic toxicity. ECG monitoring should be considered for patients on multiple QT-prolonging medications and avoidance or careful monitoring may be required for congenital LQT patients.

Analysis of heart injury laboratory parameters in 273 COVID- 19 patients in one hospital in Wuhan, China

https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25809
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Authors from: China

In the present study, the authors detected and analyzed the main laboratory indicators related to heart injury, **CK- MB, MYO, ultra- TnI and NT- proBNP**, in **273 COVID- 19 patients** and investigated the correlation between heart injury and severity of the disease. It was found that higher concentration in venous blood of CK- MB, MYO, ultra- TnI and NT- proBNP were associated with the severity and case- fatality rate of COVID- 19. Careful monitoring of the myocardiac enzyme profiles is of great importance in reducing the complications. Patients were divided into three groups: mild **(n=198), severe (n=60) and critical (n=15)**. There was **no significant difference in gender and age** among three groups in this study. The blood tests of patients on admission showed most patients had normal levels of CK-MB, myohe-myoglobin (MYO), ultra-TnI and NT-proBNP. The positive rate of CK-MB had no difference between groups. However, the positive rate of MYO, ultra-TnI and NT-proBNP was higher in severe and critical cases as compared to mild cases. **The overall case-fatality rate was 8.79% and 22.81% in the abnormal parameters group.**

Can Bioactive Lipids Inactivate Coronavirus (COVID-19)?

https://www.sciencedirect.com/science/article/abs/pii/S0188440920302927?via%3Dihub
Journal: Archives of Medical Research *Published Online: March 27, 2020*
Authors from: USA

SARS-CoV-2, SARS and MERS are all **enveloped viruses** that can cause acute respiratory syndrome. **Arachidonic acid** (AA) and other unsaturated fatty acids (especially **eicosapentaenoic acid, EPA and docosahexaenoic acid DHA**) are known to **inactivate enveloped viruses** and inhibit proliferation of various microbial organisms. The pro-inflammatory metabolites of AA and EPA such as **prostaglandins, leukotrienes and thromboxanes induce inflammation** whereas lipoxins, resolvins, protectins and maresins derived from AA, EPA and DHA not only suppress inflammation but also enhance wound healing and augment phagocytosis of macrophages and other immunocytes and decrease microbial load. In view of these actions, it is suggested that AA and other unsaturated fatty acids and their metabolites may serve as endogenous anti-viral compounds and **their deficiency may render humans susceptible to SARS-CoV-2**. Hence, **oral or intravenous** administration of AA and other unsaturated fatty acids may aid in enhancing resistance and recovery of COVID-19.

Diagnosis and Management of COVID-19 Disease

https://www.atsjournals.org/doi/10.1164/rccm.2020C1
Journal: American Journal of Respiratory and Critical Care Medicine
Published Online: March 30, 2020
Authors from: USA

Bullet-style crash course summary on biology, epidemiology, laboratory findings, imaging, isolation and infection control for confirmed and suspected cases, general treatment recommendations, management of hypoxemic respiratory failure, investigational therapies, prognosis and control strategies of COVID-19.

Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know

https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician
Journal: Annals of Internal Medicine *Published Online: March 31, 2020*
Authors from: USA

The antimalarials hydroxychloroquine (HCQ) and chloroquine (CQ) have demonstrated antiviral activity against SARS–CoV-2 **in vitro and in small, poorly controlled or uncontrolled clinical studies**. Normally, such research would be deemed hypothesis-generating at best. Data to support the use of HCQ and CQ for COVID-19 are limited and inconclusive. The drugs have some in vitro activity against several viruses, including coronaviruses and influenza, but previous randomized trials in patients with influenza have been negative. **In COVID-19, one small nonrandomized study from France** demonstrated benefit but had serious

methodological flaws, and a follow-up study still lacked a control group. Yet, another **very small, randomized study from China** in patients with mild to moderate COVID-19 found no difference in recovery rates. Sadly, reports of **adverse events have increased**, with several countries reporting poisonings. Antimalarial drugs can cause ventricular arrhythmias, QT prolongation, and other cardiac toxicity, which may pose a particular risk to critically ill persons. Given these serious potential adverse effects, the hasty and inappropriate interpretation of the literature by public leaders has potential to do serious harm. However, at the time of publication, **ten randomized clinical trials are underway**, and more information should be forthcoming within weeks. Physicians should educate themselves about the strength of available data regarding HCQ and CQ in treating COVID-19. They **should avoid misuse of HCQ and CQ for the prophylaxis of COVID-19**, because there are absolutely no data to support this. Public figures should refrain from promoting unproven therapies to the public, and instead provide clear messages around the uncertainties we face in testing and using experimental treatments during the current pandemic, including the risk for serious adverse events. Well-done, randomized clinical trials should be performed urgently to test potential therapies, including HCQ. In the meantime, physicians should remember that first, we must do **no harm to the patients with the rheumatic disease** for whom high-quality evidence shows that HCQ improves health and who may now face shortages of the drugs.

A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19
https://annals.org/aim/fullarticle/2764065/rush-judgment-rapid-reporting-dissemination-results-its-consequences-regarding-use
Journal: Annals of Internal Medicine *Published Online: March 30, 2020*
Authors from: USA, France, Canada, UK, Peru

The coronavirus disease 2019 (COVID-19) pandemic has placed the scientific and research communities under extraordinary pressure, to which they have responded with exceptional vigor and speed. This desire to quickly find safe and effective treatments may also lead to relaxed standards of data generation and interpretation, which may have undesirable downstream effects. The recent publication of a study **evaluating hydroxychloroquine** (HCQ) in COVID-19 highlights the challenges of conducting research during a pandemic. A scientific rationale existed for investigating HCQ in COVID-19 with in vitro activity being described in preclinical studies. In a **nonrandomized study, Gautret and colleagues** reported a higher frequency of SARS–CoV-2 clearance from the nasopharynx after 6 days of treatment with **HCQ, plus azithromycin (AZM)** if deemed necessary, versus an untreated control group (14 of 20 patients [70%] vs. 2 of 16 patients [13%]; $P < 0.001$). Given the urgency of the situation, some limitations of this study may be acceptable, including the small sample size, use of an unvalidated surrogate endpoint, and lack of randomization or blinding. However, other methodological flaws may affect the validity of the findings.

First, potentially substantial confounders may explain the findings. The HCQ + AZM treatment group was recruited from a single center. Instead of excluding patients who declined treatment, the researchers assigned them to the control group. The remainder of the control group was

recruited from other centers that could not contribute to the treatment group. In addition, **patients in the HCQ + AZM group had lower viral loads at the time of treatment initiation** compared with the control and HCQ groups. This problem may have been further exacerbated by issues with data measurement and imputation. Sites other than Marseille did not perform daily PCR testing, creating gaps in PCR data for control group patients that were later imputed with values from other days. Consequently, 75% (12 of 16 patients) of the control group lacked at least 1 PCR result. The handling of patients who were lost to follow-up also raises serious questions about scientific validity. Only 20 of 26 patients in the treatment group were included in the analysis despite meeting baseline eligibility criteria. Six patients were excluded because day 6 PCR data were missing, owing to early treatment cessation due to nausea (n = 1), hospital discharge (n = 1), intensive care unit transfer (n = 3), and death (n = 1). Therefore, **patients who had the most serious and clinically relevant outcomes, including intensive care unit transfer and death, were excluded from analysis.** These patients had treatment failure and should have been analyzed as such. Despite the study's substantial limitations, a simplification and probable overinterpretation of these findings was rapidly disseminated by the lay press and amplified on social media, ultimately endorsed by many government and institutional leaders. A major consequence has been an inadequate supply of HCQ for patients in whom efficacy is established.

Emerging prophylaxis strategies against COVID-19

https://monaldi-archives.org/index.php/macd/article/view/1289/1005

Journal: Monaldi Archives for Chest Disease *Published Online: March 30, 2020*
Authors from: India

A review of the possibilities of the prophylactic treatment for contacts of those infected with COVID-19, including **a list of the ongoing clinical trials** in this clinical setting. Currently, there is no recommendation for use of antiviral agents for prophylaxis of COVID-19. **Oseltamivir** is currently being investigated as a treatment option, but not specifically for prophylaxis against the coronavirus disease. Protease inhibitors and other agents are considered. **Chloroquine and its safer derivate hydroxychloroquine** are available and affordable drugs with proven chemoprophylaxis properties in malaria. Indian Council of Medical Research has recommended hydroxychloroquine for the prophylaxis of **all health care workers** who are involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals. **Asymptomatic household contacts** of laboratory-confirmed cases may be prescribed 400 mg twice a day on day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals. However, clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection is lacking from the American CDC due to absence of randomized clinical trials (RCTs).

Treating COVID-19 with Chloroquine

https://academic.oup.com/jmcb/advance-article/doi/10.1093/jmcb/mjaa014/5814655

Journal: Journal of Molecular Cell Biology *Published Online: April 1, 2020*
Authors from: China

22 patients were included in the clinical trial and randomized to the two groups: 10 patients, including 3 severe and 7 moderate cases, were treated with **Chloroquine 500mg orally twice daily for 10 days**; 12 patients, including 5 severe and 7 moderate cases, were treated with **Lopinavir/Ritonavir 400/100mg orally twice daily for 10 days**. RT-PCR showed that the first patient in the Chloroquine group became SARS-CoV-2 negative after 2 days of treatment. All patients from the same group were negative on the day 13. In comparison, the first patient in the Lopinavir/Ritonavir group became SARS-CoV-2 negative after 3 days, and 11 out of 12 turned negative on day 14. These results suggest that Chloroquine has a slight advantage over Lopinavir/Ritonavir based on RNA tests. By day 9, six patients (60%) in the Chloroquine group **reached lung clearance**, compared to three (25%) from the Lopinavir/Ritonavir group. In addition, consistent with the CT imaging data, patients treated with Chloroquine were **discharged from hospital faster** - all of them left the hospital by day 14, compared with only half of the patients being discharged from the control group. The most common adverse effect of chloroquine was vomiting and there were no serious adverse events.

Progress and Prospects on Vaccine Development against SARS-CoV-2

https://www.mdpi.com/2076-393X/8/2/153/htm

Journal: Vaccines *Published Online: March 31, 2020*

Authors from: China, USA

Several countries, companies, and institutions announced their programs and progress on vaccine development against the virus. While most of the vaccines are under design and preparation, there are some that have entered efficacy evaluation in animals and initial clinical trials. This review mainly focused on the progress and our prospects in the field of vaccine development against SARS-CoV-2. It comments on the possibilities in **antigen selection** and **describes different types of vaccines**.

The authors also stress several challenges. Typically, the development of novel vaccines generally takes 10–20 years, and the success rate is less than 10%, even for a vaccine that enters clinical trials. In the past 30 years, the US FDA has approved a total of nearly 3,000 clinical trials on vaccine applications and **less than 20 vaccines were approved for the market.** Recently, there is a report that **149 sites of mutations were identified** across the genome of 103 sequenced strains of SARS-CoV-2, and the virus had evolved into **two subtypes, termed L and S subtype**. The study also indicated that the two subtypes showed great differences in geographical distribution, transmission ability, and severity of disease, which add more difficulties for vaccine design.

Developing Covid-19 Vaccines at Pandemic Speed

https://www.nejm.org/doi/10.1056/NEJMp2005630

Journal: NEJM *Published Online: March 30, 2020*

Authors from: Norway

Coalition for Epidemic Preparedness Innovation (CEPI), an international nongovernmental organization funded by the Wellcome Trust, the Bill and Melinda Gates Foundation, the European Commission, and eight countries (Australia, Belgium, Canada, Ethiopia, Germany, Japan, Norway, and the United Kingdom), is supporting development of vaccines against five epidemic pathogens on the WHO priority list. An ideal platform would support development from viral sequencing to clinical trials in less than 16 weeks, demonstrate elicitation of consistent immune responses across pathogens, and be suitable for large-scale manufacturing. Multiple platforms are under development. Among those with the greatest potential for speed are **DNA- and RNA-based platforms,** followed by those for developing **recombinant-subunit vaccines**. RNA and DNA vaccines can be made quickly because they require no culture or fermentation, instead of using synthetic processes. Developers' and regulators' experience with these platforms for personal oncology vaccines can facilitate rapid testing and release. There are no approved RNA vaccines to date, but **RNA vaccines have entered clinical trials,** and regulators have experience in reviewing clinical trial applications and with associated manufacturing of the vaccines. Use of next-generation sequencing and reverse genetics may also cut development time of more conventional vaccines during epidemics.

Moderna's **mRNA-based SARS-CoV-2 candidate entered a phase 1 clinical trial** on March 16, less than 10 weeks after the first genetic sequences were released; the first phase 1 trial with a nonreplicating vector-based vaccine has regulatory clearance to start phase 1 studies in China. Other phase 1 trials of nucleic acid vaccines are expected to start in April. Despite the efforts, there are major challenges. First, although the virus's **spike protein** is a promising immunogen for protection, optimizing antigen design is critical to ensure optimal immune response. Debate continues over the best approach — for example, **targeting the full-length protein or only the receptor-binding domain**. Second, preclinical experience with vaccine candidates for SARS and MERS has raised **concerns about exacerbating lung disease**, either directly or as a result of antibody-dependent enhancement. Hence, rigorous safety monitoring will be critical. **Vaccine development is a lengthy, expensive process**. Developing a vaccine quickly requires a new pandemic paradigm, with a fast start and many steps executed in parallel before confirming a successful outcome of another step, hence resulting in elevated financial risk. For example, for platforms with experience in humans, phase 1 clinical trials may be able to proceed in parallel with testing in animal models. In a pandemic situation, once vaccine candidates are proved safe and effective, doses must be manufactured in large quantities. Though some high-income countries may pay for development and manufacture with their own populations in mind, there's **no global entity responsible** for financing or ordering vaccine manufacture.

Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2

https://www.ijbs.com/v16p1718.htm
Journal: International Journal of Biological Sciences *Published Online: March 15, 2020*
Authors from: China

The availability of therapeutic neutralizing antibodies (NAbs) against SARS-CoV-2 might offer benefits for the control of the current pandemic, as well as the possible reemergence of the virus in the future, and their development therefore remains a high priority. NAbs appear to be more specific for virions than the conventionally used or discussed therapeutic strategies. Understanding of action mechanisms of NAbs may provide valuable implications for the rapid development of antibody therapy and vaccine for SARS-CoV-2. However, the development of NAb-based therapeutics is a time-consuming and laborious process. To date, **no NAb agents for either SARS-CoV or MERS-CoV are available** in the market. Furthermore, a note of caution is that the effect of antibody immune response in protecting against pulmonary pathogenesis of SARS-CoV is controversial. Some patients who died of SARS showed strong NAb responses and pulmonary proinflammatory accumulation, suggesting NAbs could be associated with fatal acute lung injury. Therefore, it is important to take insight into humoral and cellular responses of SARS-CoV-2 when antiviral immunotherapy is developed.
The simplest and most direct approach to combating SARS-CoV-2 during the outbreak would be to use **plasma from convalescent patients**. These NAbs can provide passive immune responses to viral infection. However, the outcomes of passive plasma therapy are unpredictable due to the variability of sera in different patients.
The SARS-CoV-2 S protein is likely an important target for developing NAbs to block binding and fusion of SARS-CoV-2. SARS-CoV-2 seems to use the same cell entry receptor, ACE2, as the SARS-CoV because ACE2 shows binding to RBD of both SARS-CoV and SARS-CoV-2. However, a recent study demonstrates that SARS-CoV-2 S protein binds ACE2 with higher affinity than SARS-CoV (10- to 20-folder), suggesting its recognition to ACE2 could be different with SARS-CoV. **Although SARS-CoV-2 shows the high homology with SARS-CoV, antibody cross-reactivity is limited between the two virus S proteins.** Several published SARS-CoV NAbs do not have appreciable binding to SARS-CoV-2 S protein. A recent study shows that a SARS-CoV antibody, CR3022, binds to SARS-CoV-2 RBD, but its neutralization capability is uncertain. **Cocktail of NAbs,** targeting different epitopes, has shown stronger neutralization than alone in treatment of both Ebola and SARS viruses. This finding suggests that a cocktail antibody approach for SARS-CoV-2 could be undertaken.

Virological assessment of hospitalized patients with COVID-2019

https://www.nature.com/articles/s41586-020-2196-x

Journal: Nature *Published Online: April 1, 2020*

Authors from: Germany

The authors provide a detailed **virological analysis of nine cases**, providing proof of active virus replication in upper respiratory tract tissues. Pharyngeal **virus shedding was very high during the first week of symptoms** (peak at 7.11 × 108 RNA copies per throat swab, day 4). Infectious virus was readily isolated from the throat- and lung-derived samples, but not from stool samples, in spite of high virus RNA concentration. Blood and urine never yielded virus. Active replication in the throat was confirmed by viral replicative RNA intermediates in throat samples. Sequence-distinct virus populations were consistently detected in throat and lung samples from the same patient, proving independent replication. **Shedding of viral RNA from sputum outlasted the end of symptoms. Seroconversion** occurred after 7 days in 50% of

patients (14 days in all), but **was not followed by a rapid decline in viral load**. COVID-19 can present as a mild upper respiratory tract illness. Active virus replication in the upper respiratory tract puts the prospects of COVID-19 containment in perspective.

Clinical and virological data of the first cases of COVID-19 in Europe: a case series

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30200-0/fulltext
Journal: The Lancet Infectious Diseases *Published Online: March 27, 2020*
Authors from: France

In this case series, the authors followed **five patients** diagnosed with COVID-19 by semi-quantitative RT-PCR on nasopharyngeal swabs. They assessed **patterns of clinical disease and viral load** from different samples (nasopharyngeal and blood, urine, and stool samples), which were obtained once daily for 3 days since hospital admission, and once every 2 or 3 days until patient discharge. The patients were three men (aged 31 years, 48 years, and 80 years) and two women (aged 30 years and 46 years), all of Chinese origin, who had traveled to France from China. Three different clinical evolutions are described: two paucisymptomatic women diagnosed within a day of exhibiting symptoms, with **high nasopharyngeal titers of SARS-CoV-2 within the first 24 h of the illness onset** (5.2 and 7.4 log10 copies per 1000 cells, respectively) and viral RNA detection in stools; a two-step disease progression in two young men, with a **secondary worsening around 10 days after disease onset despite a decreasing viral load in nasopharyngeal samples**; and an 80-year-old man with a rapid evolution towards multiple organ failure and a **persistent high viral load in the lower and upper respiratory tract with systemic virus dissemination** and virus detection in plasma. The 80-year-old patient died on day 14 of illness, all other patients had recovered and were discharged.

Understanding COVID-19: what does viral RNA load really mean?

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30237-1/fulltext
Journal: The Lancet Infectious Diseases *Published Online: March 27, 2020*
Authors from: China (Hong Kong)

Previous studies in patients with SARS,MERS, and COVID-19 generally provide insufficient detail to allow examination of the relationship between individual patient clinical course and viral RNA load. The exception is a small French study by Lescure et al., where detailed clinical features of five patients with COVID-19 are aligned with the quantitative SARS-CoV-2 viral RNA load from nasopharyngeal and other sites.
Nevertheless, based on the assumption that viral RNA load correlates with high levels of viral replication, there are important insights to be gained from this time-course analysis. Currently, our understanding of the relationship between viral RNA load kinetics and disease severity in patients with COVID-19 remains fragmented. Zou and colleagues reported that patients with COVID-19 **with more severe disease requiring intensive care unit admission had high viral RNA loads** at 10 days and beyond, after symptom onset. Unfortunately, it is unknown when in the course of their disease these patients deteriorated. By contrast, Lescure and colleagues **report the viral RNA kinetics of two patients who developed late respiratory**

deterioration despite the disappearance of nasopharyngeal viral RNA. It would be interesting to know whether viral RNA load in lung tissue, or a surrogate sample such as tracheal aspirate, mirrors the decline in nasopharyngeal shedding. Nevertheless, this observation suggests that these **late, severe manifestations might be immunologically mediated** and has obvious implications for the potential to use immune-modulatory therapies for this subset of patients.

In a pandemic, prevention of disease transmission is key. Lescure and colleagues wisely note the implications for transmission **from patients with few symptoms but high viral RNA load** in the nasopharynx early in the course of disease. Equally worrying is the **persistently high nasopharyngeal viral RNA load**, and the detection of viral RNA in blood and pleural fluid, of the older patient (aged 80 years) with severe multi-organ dysfunction. This finding broadly correlates with the severely ill group data reported by Zou and colleagues.

It is noteworthy that the presence of viral RNA in specimens does not always correlate with viral transmissibility. For SARS coronavirus, viral RNA is detectable in the respiratory secretions and stools of some patients after onset of illness for more than 1 month, but live virus could not be detected by culture after week 3. The inability to **differentiate between infective and non-infective (dead or antibody-neutralized)** viruses remains a major limitation of nucleic acid detection. Despite this limitation, given the difficulties in culturing live virus from clinical specimens during a pandemic, using viral RNA load as a surrogate remains plausible for generating clinical hypotheses.

Protected Code Stroke: Hyperacute Stroke Management During the Coronavirus Disease 2019 (COVID-19) Pandemic

https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.029838

Journal: Stroke *Published Online: April 1, 2020*

Authors from: Canada

Hyperacute assessment and management of patients with stroke is a time-sensitive and high-stakes clinical scenario. In the context of the current Coronavirus Disease 2019 (COVID-19) pandemic, the **ability to deliver timely and efficacious care** must be balanced with **the risk of infectious exposure** to the clinical team. Furthermore, rapid and effective stroke care remains paramount to achieve maximal functional recovery for those needing admission and to triage care appropriately for those **who may be presenting with neurological symptoms but have an alternative diagnosis**. Available resources, COVID-19-specific infection prevention and control recommendations, and expert consensus were used to identify clinical screening criteria for patients and provide **modifyed conventional code stroke processes** to achieve a protected designation. A **protected code stroke algorithm** was developed and is enclosed below:

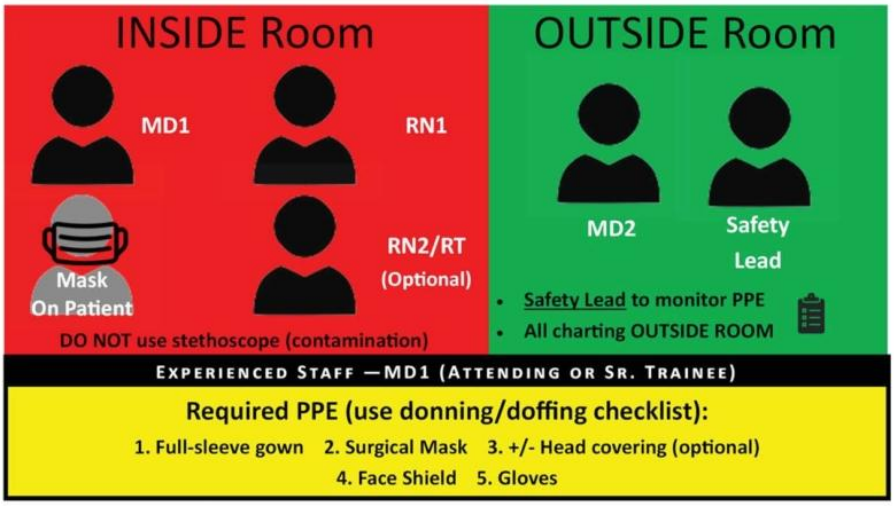
Protected Code Stroke

+ Positive Screen for COVID-19

Pre-notification screening: communication with paramedics or sending facility prior to arrival - Positive infection screen:

patient is exhibiting or has close contacts with infectious symptoms and/or travel history

Unclear or unable to obtain history: patient is obtunded or not able to communicate. History or exam features suggestive of an alternate diagnosis



EXPERIENCED STAFF — MD1 (ATTENDING OR SR. TRAINEE)

Required PPE (use donning/doffing checklist):

1. Full-sleeve gown 2. Surgical Mask 3. +/- Head covering (optional) 4. Face Shield 5. Gloves

Intubate EARLY for increasing O_2 requirements

Airway management for deteriorating patients OR increasing oxygen requirements $FiO_2 > 0.5$ - Preoxygenate with facemask, with filter, BVM WITHOUT MANUAL VENTILATIONS. AVOID BiPAP, CPAP, Nasal High Flow Therapy

Crisis Resource Management: Role designation and clarity, closed loop communication, optimized team size, avoid cross-contamination

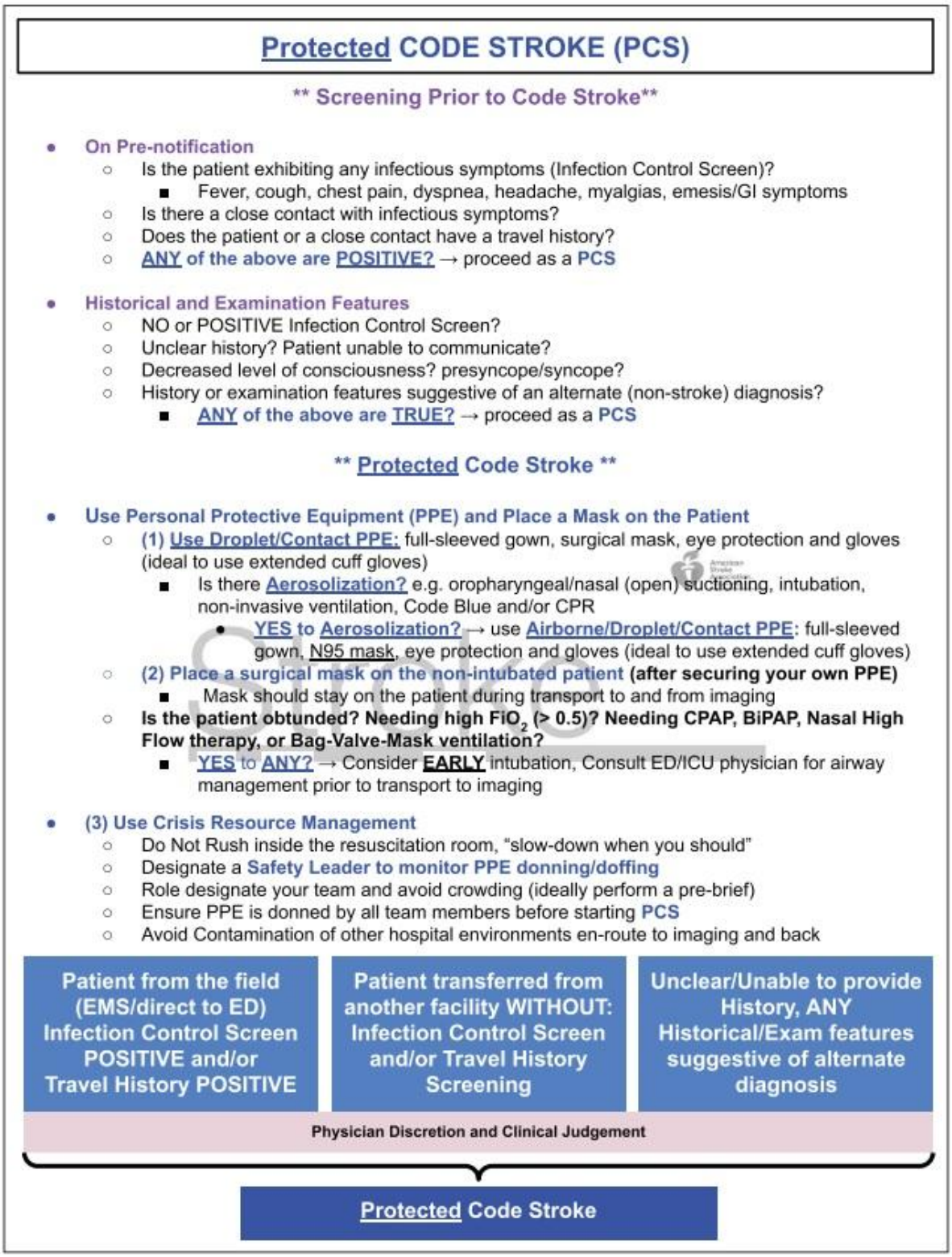


Figure 1. Protected code stroke (PCS) framework. Two key sections are outlined: screening and PCS operational parameters. These parameters are use of personal protective equipment (1) with and without aerosol-generating medical procedures, placing a surgical mask on the nonintubated patient (2), and utilization of crisis resource management principles (3).

The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality

https://www.sciencedirect.com/science/article/pii/S0924857920301047?via%3Dihub

Journal: International Journal of Antimicrobial Agents *Published Online: March 29, 2020*
Authors from: China

A large number of data suggest the important role of cytokine storms in the pathophysiology of a severe COVID-19. Therefore, the **treatment of the cytokine storm** has become an important part of therapeutic considerations. **IL-6** plays an important role in **cytokine release syndrome (CRS)**. The SARS-CoV-2 binds to alveolar epithelial cells and activates innate and adaptive immune systems. This results in the release of a large number of cytokines, including IL-6. Consequently, vascular permeability increases and a significant amount of fluid and blood cells move into the alveoli, resulting in dyspnea and even respiratory failure. **Tocilizumab** is a recombinant humanized monoclonal antibody against human interleukin 6 receptor.. Tocilizumab specifically binds soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits their signal transduction. In August 2017, the **FDA approved tocilizumab for the treatment of CRS caused by CAR-T** (Chimeric Antigen Receptor T-Cell Immunotherapy) therapy. The authors of the present review suggest that it should be considered in critically ill COVID-19 patients with significantly elevated IL-6.

COVID-19 and Diabetes: can DPP4 inhibition play a role?

https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(20)30375-2/fulltext

Journal: Diabetes Research and Clinical Practice *Published Online: March 23, 2020*
Authors from: USA

Type 2 diabetes (T2DM) is associated with a low-grade chronic inflammation induced by excessive visceral adipose tissue. Chronic hyperglycemia and inflammation can cause an abnormal and ineffective immune response. Recent data from Italy showed that more than two-thirds of those who died by COVID-19 had diabetes. The higher risk of mortality and complication among people with diabetes was similar in SARS and MERS. Remarkably, human **dipeptidyl peptidase 4** (DPP4) was identified as a **functional receptor for the spike protein of the MERS-Co-V**. MERS-CoV binds to the receptor-binding domain and interacts with T cells and nuclear factors, such as NF-κB, highly involved in the pathogenesis of inflammatory disorders. DPP4 enzyme is a type II transmembrane glycoprotein, expressed ubiquitously in many tissues, including the immune cells. Although its functions are not fully understood yet, **DPP4 plays a major role in glucose and insulin metabolism, as well as has an important role in immune regulation** by activating T cells and upregulating CD86 expression and NF-κB pathway. It can be summarized that DPP4 increases inflammation in type 2 diabetes via both catalytic and noncatalytic mechanisms.
In one study, mice were made susceptible to MERS-CoV by expressing human DPP4. Type 2 diabetes was induced by administering a high-fat diet. Upon infection with MERS-CoV, the mice developed weight loss, and had a prolonged phase of severe disease and delayed recovery when compared with non-diabetic animals. Interestingly, diabetic mice had fewer inflammatory monocyte/macrophages, CD4+ T cells, and lower expression of TNFα, IL-6, and Arg1

expression and demonstrated a delay in the initiation of inflammation in the lung characterized by reduced CD4+ T cell recruitment.
It is tempting to translate these data in humans and explore how these findings may be of interest in the context of the COVID-19 outbreak. Individuals with type 2 diabetes and obesity are commonly prescribed with DPP-4 inhibitors and/or GLP-1 receptor analogs. DPP4 inhibitors can be divided into mimetics, **sitagliptin, vildagliptin, saxagliptin** and not peptide mimetics, **alogliptin and linagliptin**. DPP4 inhibitors target the enzymatic activity of DPP4 and consequently block the breakdown of GLP-1. However, the **effects of DPP4 inhibition on the immune response is controversial**. When compared with placebo or active substance, risks of respiratory infection in patients treated with DPP4 inhibitors were all comparable. More data is needed, but **DPP4 may represent a potential target for preventing and reducing the risk and the progression of the acute respiratory complications that type 2 diabetes may add to the COVID-19 infection.**

Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19

https://www.ijbs.com/v16p1724.htm
Journal: International Journal of Biological Sciences *Published Online: March 15, 2020*
Authors from: China

One key element in viral infection is the process of viral entry into the host cells. In the last two decades, there is increasing understanding on the importance of the **endocytic pathway** and the autophagy process in viral entry and replication. As a result, the endocytic pathway including **endosome and lysosome** has become important targets for development of therapeutic strategies in combating diseases caused by coronaviruses. In this mini-review, the authors focus on the importance of the endocytic pathway as well as the autophagy process in viral infection. Several **inhibitors targeting the endocytic pathway** appear to have the therapeutic potential in treatment of COVID-19, including a **lysosomotropic agent chloroquine** and a **clathrin-mediated endocytosis inhibitor chlorpromazine**. Since both are FDA-approved and clinically available, clinical trials either as a single therapy or in combination with other antiviral drugs are much needed.

WHAT DOES ANDROGENETIC ALOPECIA HAVE TO DO WITH COVID-19? AN INSIGHT INTO A POTENTIAL NEW THERAPY

https://onlinelibrary.wiley.com/doi/epdf/10.1111/dth.13365
Journal: Dermatologic Therapy *Published Online: April 1, 2020*
Authors from: USA, Spain, Italy

Epidemiological reports unveiled a disproportionate **low rate of severe cases of COVID-19 among adult females compared to adult males**, 42% and 58%, respectively. Similarly, the rate of severe cases among pre-pubescent children was exceptionally low at 0.6%. An explanation is not yet clarified. The authors of the present study offer a theory. Male infants are more susceptible to respiratory distress syndrome and less likely to respond to prenatal glucocorticoid therapy. It was also demonstrated that a **sexual dimorphism in fetal**

pulmonary surfactant production is influenced by the androgen receptor (AR).
While severe COVID-19 symptoms are primarily manifested in older adults, the similar sexual dimorphism in the severity of respiratory disease is of interest. In addition, AR expression is low prior to pubertal maturation and may contribute to the low incidence of severe COVID-19 infection in children. The authors propose that the **lower rate of severe COVID-19 infection in female patients may be attributed to lower androgen receptor expression**. It was demonstrated that SARS-CoV-2 cell entry depends on priming of a viral spike surface protein by transmembrane protease serine 2 (**TMPRSS2**) present in the host. In type II pneumocytes, **TMPRSS2 expression is associated with an increase in AR expression.** Interestingly, ACE2 has been shown to have **reduced activity by the decrease of androgen hormones** (experimental orchidectomy). To test this hypothesis, it would be informative to study the **epidemiology of COVID-19 patients that are predisposed to either lower or higher AR expression**, such as, males suffering from androgenetic alopecia, benign prostatic hyperplasia or women suffering from polycystic ovary syndrome. Additionally, the activation of AR can be reduced androgen receptor antagonists, androgen synthesis inhibitors and antigonadotropins. For example, the FDA-approved **finasteride** demonstrated reduction of activation of AR in multiple tissues. Other potential drugs that could be studied include cyproterone acetate, megestrol acetate, chlormadinone acetate, spironolactone, medrogestone, oxendolone, osaterone, bifluranol acetate, flutamide, bicalutamide, nilutamide, topilutamide, enzalutamide, apalutamide, dienogest, drospirenone, medrogestone, nomegestrol acetate, promegestone, trimegestone, ketoconazole, abiraterone acetate, seviteronel, aminoglutethimide, dutasteride, epristeride, alfaestradiol and isotretinoin.

Inhibition of SARS-CoV-2 (Previously 2019-nCoV) Infection by a Highly Potent Pan-Coronavirus Fusion Inhibitor Targeting Its Spike Protein That Harbors a High Capacity to Mediate Membrane Fusion

https://www.nature.com/articles/s41422-020-0305-x
Journal: Cell Research *Published Online: March 30, 2020*
Authors from: China

To develop specific anti-coronavirus therapeutics and prophylactics, the molecular mechanism that underlies viral infection must first be defined. Therefore, the authors herein showed a superior **plasma membrane fusion capacity** of the SARS-CoV-2, compared to that of SARS-CoV. They described the X-ray crystal structure of **the six-helical bundle (6-HB) core** of the HR1 and HR2 domains in the SARS-CoV-2 S protein S2 subunit, revealing that several mutated amino acid residues in the HR1 domain may be associated with enhanced interactions with the HR2 domain. They previously developed a **pan-coronavirus fusion inhibitor, EK1,** which targeted the HR1 domain and could inhibit infection by divergent human coronaviruses tested, including SARS-CoV and MERS-CoV. In the present study, they synthesized a series of lipopeptides derived from EK1 and found that **EK1C4 was the most potent fusion inhibitor against SARS-CoV-2 S protein-mediated membrane fusion.** EK1C4 was also highly effective against membrane fusion and infection of other human coronavirus pseudoviruses tested, including SARS-CoV and MERS-CoV, and potently inhibited the replication of 5 live human coronaviruses examined, including SARS-CoV-2. **Intranasal application** of EK1C4 before or

after challenge with HCoV-OC43 **protected mice from infection**, suggesting that EK1C4 could be used for the prevention and treatment of infection by the currently circulating SARS-CoV-2 and other emerging SARSr-CoVs.

Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study

https://www.sciencedirect.com/science/article/pii/S0024320520303404?via%3Dihub

Journal: Life Sciences *Published Online: March 25, 2020*
Authors from: Egypt

In this study, the **RNA-dependent RNA polymerase (RdRp)** of the newly emerged coronavirus is modeled, validated, and then targeted using different approved anti-polymerase antiviral drugs. The results suggest **the effectiveness of Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir as potent drugs** against SARS-CoV-2 since they tightly bind to its RdRp. In addition, the results suggest **guanosine derivative (IDX-184), Setrobuvir, and YAK** as top seeds for antiviral treatments with high potential to fight the SARS-CoV-2 strain specifically.

Novel coronavirus treatment with ribavirin: Groundwork for evaluation concerning COVID- 19

https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25798

Journal: Journal of Medical Virology *Published Online: March 30, 2020*
Authors from: USA

Ribavirin is a guanosine analog that **interferes with the replication of RNA and DNA viruses**. However, the antiviral activity of ribavirin is not limited to interfering with polymerases; it also interferes with RNA capping and inhibits natural guanosine generation. The wide availability and low cost of ribavirin underlie its potential to significantly impact the treatment of COVID-19. The challenges in the evaluation of ribavirin efficacy during the SARS and MERS outbreaks led to a summary evaluation of its **utility as controversial in the treatment of COVID-19 patients**. The large number of clinical studies and retrospective analyses that will come from the 2019-nCoV outbreak will put the controversy of ribavirin efficacy in a broader context. To further complicate the evaluation of high-dose ribavirin monotherapy in the SARS outbreak is the possibility that concomitantly used corticosteroids may have delayed viral clearance, prolonging infections while reducing the symptomatic inflammatory cytokines. Currently, these observations support the contraindication for the usage of corticosteroids for COVID-19. The original strain of SARS-CoV-2 was isolated from a patient from the Wuhan seafood Market and named WIV04. The earliest data of in vitro efficacy of five FDA-approved drugs with activity against WIV04 have been reported (ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine). In addition, two experimental drugs (remdesivir and favipiravir) have also shown activity against WIV04. **Treatment with ribavirin and chloroquine may permit some advantage due to immediate drug availability**. Adition of **ribavirin to lopinavir/ritonavir** is also considered.

COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection?

https://www.aging-us.com/article/103001/text

Journal: Aging *Published Online: March 20, 2020*

Authors from: UK

For some reason, COVID-19 shows a considerably higher mortality rate in patients with **advanced chronological age**. This begs the question as to whether there is a functional association between COVID-19 infection and the process of chronological aging. Two host receptors have been proposed for COVID-19, **CD26,** and **ACE-2**. Interestingly, both CD26 and the angiotensin system show associations with senescence. Similarly, two proposed therapeutics for the treatment of COVID-19 infection are **Azithromycin and Quercetin**, both with significant **senolytic activity**. Also, Chloroquine-related compounds inhibit the induction of the well-known senescence marker, Beta-galactosidase. Other anti-aging drugs should also be considered, such as **Rapamycin and Doxycycline**, as they behave as inhibitors of protein synthesis, blocking both SASP and viral replication. Therefore, we wish to speculate that the fight against COVID-19 disease should involve testing the hypothesis that **senolytics and other anti-aging drugs may have a prominent role in preventing the transmission of the virus,** as well as aid in its treatment. Thus, we propose that new clinical trials may be warranted, as several senolytic and anti-aging therapeutics are existing FDA-approved drugs, with excellent safety profiles, and would be readily available for drug repurposing efforts. As Azithromycin and Doxycycline are both commonly used antibiotics that inhibit viral replication and IL-6 production, we may want to consider this general class of antibiotics that functionally inhibits cellular protein synthesis as a side-effect, for the treatment and prevention of COVID-19 disease.

Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing

https://science.sciencemag.org/content/early/2020/03/30/science.abb6936

Journal: Science *Published Online: March 31, 2020*

Authors from: UK

The authors analyzed key parameters of epidemic spread to estimate the contribution of different transmission routes and determine requirements for case isolation and contact-tracing needed to stop the epidemic. They concluded that viral **spread is too fast to be contained by manual contact tracing**, but could be controlled if this process was faster, more efficient and happened at scale. A **contact-tracing App** which builds a memory of proximity contacts and immediately notifies contacts of positive cases can achieve epidemic control if used by enough people. By targeting recommendations to only those at risk, epidemics could be contained without the need for mass quarantines (‘lock-downs’) that are harmful to society. Further modeling is needed to compare the number of people disrupted under different scenarios consistent with sustained epidemic suppression. But a **sustained pandemic is not inevitable, nor is sustained national lockdown**. The authors recommend an urgent exploration of means for intelligent physical distancing via digital contact tracing. In the present article, they discuss the epidemiology, feasibility and the ethical requirements for an intervention of this kind.

Proposal for international standardization of the use of lung ultrasound for COVID- 19 patients; a simple, quantitative, reproducible method

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Journal: Journal of Ultrasound in Medicine *Published Online: March 30, 2020*

Authors from: Italy

Lung ultrasound (LUS) is able to detect interstitial lung disease, subpleural consolidations and ARDS from any etiological cause. Recent data is showing the usefulness of LUS for the management of patients with COVID-19 pneumonia, from diagnosis to monitoring and follow-up. According to the authors, this global emergency needs a global unified approach. For this reason, they propose a **standardization for the international use of LUS** for the management of COVID-19 patients. **14 areas** (three posterior, two lateral and two anterior) should be scanned per patient for 10 seconds along the lines indicated. Scans need to be intercostal, as to cover the widest surface possible with one scan. In case of performing LUS in critical care settings (such as patients on invasive ventilation) and for patients that are not able to maintain sitting position, the posterior areas might be difficult to be evaluated. In these cases, the operator should try to have a partial view of the posterior basal areas, currently considered a "hot-area" for COVID-19. Following **scoring system** is suggested by the authors:

Score 0: The pleura line is continuous, regular. Horizontal artifacts (A-line) are present. They are due to the high reflectivity of the normally aerated lung surface and characterize the visual representation of the multiple reflections happening between the ultrasound probe and the lung surface itself.

Score 1: The pleura line is indented. Below the indent, vertical areas of white are visible. These are due to local alterations in the acoustical properties of the lung, as for example the replacement of volumes previously occupied by air in favor of media which are acoustically much more similar to the intercostal tissue (water, blood, tissue). This phenomenon opens channels accessible to ultrasound, which can explain the appearance of the vertical artifacts

Score 2: The pleura line is broken. Below the breaking point, small to large consolidated areas (darker areas) appear with associated areas of white below the consolidated area (white lung). The darkening of the consolidated areas signals the loss of aeration and the transition of these areas towards acoustic properties similar to soft tissue over the entire area represented by the consolidation itself. Beyond the consolidations, the appearance of areas of withe lung signals the presence of areas not yet fully deaerated, where air inclusions are still present butembedded in tissue like material. This highly scattering environment can explain this peculiar pattern

Score 3: The scanned area shows dense and largely extended white lung with or without larger consolidations

Possibility of transmission through dogs being a contributing factor to the extreme Covid- 19 outbreak in North Italy

https://www.spandidos-publications.com/10.3892/mmr.2020.11037

Journal: Molecular Medicine Reports *Published Online: March 23, 2020*

Authors from: Greece

Owning a dog as a pet in Italy is extremely common. The available information refers to a ratio of 1 dog for every 6 individuals. To summarise, it is known that i) Globally, to date, only 4 dogs have been tested for COVID- 19. These dogs had come into contact with infected individuals; ii) **dogs have an ACE2** that functions as a SARS- CoV receptor; iii) **dog ACE2 is similar to human** ACE2; iv)the infection of animals from humans and vice versa is plausible; v) no data are available to confirm or exclude the possibility of such human- to- dog and dog- to- human infetion; and vi) precautionary measures for such cases have been proposed from all authorities; however, it is highly questionable whether these are followed by dogs owners. Although >2 weeks have already passed from the time when Italian authorities restricted citizen mobility, the exponential increase in the number of positive cases and deaths continues. To date, there is no satisfactory explanation for this phenomenon. Exception from the mobility restriction in all territories is the possibility of walking out dogs. In a number of cases, this **exception is over- used**. Therefore, further than the every- day contact between dogs and Italian families, there is a constant more- than- one, every- day contact between animals and other owners. All the above facts create the need to reconsider the possibility that dogs are intermediate hosts contributing to the extremely high Covid- 19 transmission in North Italy. Possible actions to this direction could include the biased testing of dogs living in houses with positive cases opposed to home quarantine, and non- experimental studies for the investigation of such transmission, using appropriate methodologies such as in silico docking to evaluate the binding of COVID- 19 with dogs ACE2 and sequence- based computational estimations of hosts susceptibility.