INFOLETTER 7 – COVID-19

15 April 2020

Content overview

Extracorporeal Membrane Oxygenation (ECMO): Does It Have a Role in the Treatment of Severe COVID-19? 3

Interim Guidance for Basic and Advanced Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With the Guidelines®-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration with the American Academy of Pediatrics, American Association for Respiratory Care, American College of Emergency Physicians, The Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists: Supporting Organizations: American Association of Critical Care Nurses and National EMS Physicians 4

Acute Stroke Management Pathway During Coronavirus-19 Pandemic 9

Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19 11

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study 12

The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society 12

Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy 13

Triage Considerations for Patients Referred for Structural Heart Disease Intervention During the Coronavirus Disease 2019 (COVID-19) Pandemic: An ACC /SCAI Consensus Statement 14

High-Sensitivity Cardiac Troponin Can Be An Ally in the Fight Against COVID-19 16

ANNALS EXPRESS: On the Clinical Utility of Cardiac Troponin Measurement in COVID-19 Infection 17

Integrated Radiologic Algorithm for COVID-19 Pandemic 18

Prevalence of Venous Thromboembolism in Patients With Severe Novel Coronavirus Pneumonia 19

ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19 20

Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome 20

CAPACITY-COVID: a European registry to determine the role of cardiovascular disease in the COVID-19 pandemic 21

Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series 21

Caring for patients with pain during the COVID-19 pandemic: Consensus recommendations from an international expert panel 22

Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients 23

Lung Transplantation as Therapeutic Option in Acute Respiratory Distress Syndrome for COVID-19-related Pulmonary Fibrosis 24

The Role of Cytokines Including Interleukin-6 in COVID-19 Induced Pneumonia and Macrophage Activation Syndrome-Like Disease 24

Inositol and Pulmonary Function. Could Myo-Inositol Treatment Downregulate Inflammation and Cytokine Release Syndrome in SARS-CoV-2? 26

Comparative Replication and Immune Activation Profiles of SARS-CoV-2 and SARS-CoV in Human Lungs: An Ex Vivo Study With Implications for the Pathogenesis of COVID-19 26

Single-Dose, Intranasal Immunization With Recombinant Parainfluenza Virus 5 Expressing Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Spike Protein Protects Mice From Fatal MERS-CoV Infection 27

The FDA-approved Drug Ivermectin Inhibits the Replication of SARS-CoV-2 in Vitro 27

Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019 28

Therapeutic Potential for Tetracyclines in the Treatment of COVID-19 28

High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019 29

Metronidazole; A Potential Novel Addition to the COVID-19 Treatment Regimen 29

Tocilizumab Treatment in COVID-19: A Single Center Experience 29

Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients 30

Transplantation of ACE2 - Mesenchymal Stem Cells Improves the Outcome of Patients With COVID-19 Pneumonia 30

Extracorporeal Membrane Oxygenation (ECMO): Does It Have a Role in the Treatment of Severe COVID-19?

https://pubmed.ncbi.nlm.nih.gov/32251794/?from_term=covid+19&from_sort=date&from_page=56&from_pos=3

Journal: International Journal of Infectious Diseases *Published Online: April 3, 2020*
Authors from: China

ECMO, which can provide effective respiratory or cardiac support, has already been regarded as rescue therapy for severe ARDS. ECMO therapy during the influenza A (H1N1) pandemic in 2009 appeared to provide benefit, with ECMO-treated patients with H1N1-related ARDS demonstrating mortality of 21% according to one study. Another cohort study of using the ECMO database of patients with H1N1-related ARDS showed that hospital mortality rate was 24.0% for ECMO-referred patients vs 46.7% in non-referred when propensity score matching was used. A clinical trial CESAR was also encouraging, however, **EOLIA** clinical trial showed that 60-day mortality of very severe ARDS patients was not significantly lower, but there was a 28% crossover to ECMO for the failure of conventional mechanical ventilation and a lack of another therapeutic option. In 2018, a retrospectively study on MERS patients with refractory respiratory failure indicated that **ECMO should be used as rescue therapy**, with lower mortality in an ECMO group compared with the conventional group (65 vs 100%, P = 0.02).

According to the **interim guidance formulated by the WHO**, ECMO should be considered as rescue therapy for COVID-19 with refractory hypoxemia despite lung-protective ventilation. However, there is little experience with using ECMO to support SARS-CoV-2-infected patients. Most of the studies, except for two, didn't report the clinical outcomes. In the retrospective study conducted by Yang et al., 52 critically ill adult patients with SARS-CoV-2 pneumonia were identified and admitted to the ICU, 31 patients had died during the 28 days period. **6 patients from the group received ECMO, 5 of them died and 1 patient was still on ECMO** at the time of reporting. Another retrospective study by Guqin et al. included 221 patients with laboratory-confirmed SARS-CoV-2 pneumonia, 48 of severe patients developed ARDS, and **10 of them received invasive mechanical ventilation and ECMO support. 2 patients had a clinical benefit and had been discharged and 3 of them were non-survivors. The rest 5 patients were still on ECMO** at the time of reporting.

A published randomized clinical trial evaluating the role of ECMO in COVID-19 is lacking, however, ongoing trials are being conducted in China (ChiCTR2000030744 and ChiCTR2000029804). **Indications for ECMO are based on EOLIA inclusion criteria**. ECMO should be considered when meeting one of the following despite optimization of mechanical ventilation for <7days **(FiO2≥0.80, tidal volume of 6 ml/kg predicted body weight, PEEP≥ 10cmH2O); PaO2: FiO2 < 50mmHg for > 3 hours; PaO2: FiO2 < 80 mmHg for > 6 hours; pH<7.25 with PaCO2≥60mmHg for > 6 hours with a respiratory rate increased to 35 breaths per minute, adjusted for plateau pressure≤32 cmH2O).** Alternatively, ECMO can be considered after lung-protective ventilation (tidal volume 6ml/kg, PEEP≥ 10cmH2O) was adopted and combined with lung recruitment maneuver, prone position ventilation and high-frequency oscillation ventilation with pure oxygen when meeting the following criteria: **(1) PaO2/FiO2<100mmHg; (2) P(A-a)O2>600mmHg; (3) pH<7.2 and plateau pressure**

>30cmH2O with a respiratory rate more than 35 breaths per minute; (4) Age<65 years old; (5) Mechanical ventilation<7d; (6) Absence of contraindications. For patients at risk of ventilator-induced lung injury, lower ventilation and volumes and pressures may lead to hypercapnic acidosis. In this situation, **extracorporeal carbon dioxide removal** (ECCO2R) can be an important tool by providing direct removal of CO2 from the blood. Indeed, many factors could affect the outcomes of ECMO treatment, including the duration of mechanical ventilation, the severity of the underlying disease, the experience of trained medical staff, and ECMO equipment. Early evaluation, rapid assembly, and timely cannulation are important. Regardless of the efficacy of ECMO, under the special situation of the SARS-CoV-2 outbreak, we should also pay more attention to the safety of medical staff since they get infected easily when manipulating with an ECMO. Some other procedures, such as intubation, ventilator venting, and sputum suction also pose a high risk of infection to medical staff. Therefore, all related staff should be supplied with sufficient protection. As the pandemic spreads, a shortage of ECMO consoles may be another problem due to a surge of critically ill patients worldwide.

Interim Guidance for Basic and Advanced Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With the Guidelines®-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration with the American Academy of Pediatrics, American Association for Respiratory Care, American College of Emergency Physicians, The Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists: Supporting Organizations: American Association of Critical Care Nurses and National EMS Physicians

https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047463
Journal: Circulation *Published Online: April 9, 2020*
Authors from: USA, Canada

Graphic summaries of the algorithms can be found in the full-text.

Reduce provider exposure to COVID-19

- **Rationale**: It is essential that providers protect themselves and their colleagues from unnecessary exposure. Exposed providers who contract COVID-19 further decrease the already strained workforce available to respond and have the potential to add additional strain if they become critically ill.
- **Strategies:**
    1. Before entering the scene, all rescuers should don PPE to guard against contact with both airborne and droplet particles. Consult individual health or emergency medical services (EMS) system standards as PPE recommendations may vary considerably on the basis of current epidemiologic data and availability.
    2. Limit personnel in the room or on the scene to only those essential for patient care.
    3. In settings with protocols and expertise in place for their use, consider replacing manual chest compressions with mechanical CPR devices to reduce the number of

rescuers required for adults and adolescents who meet the manufacturer's height and weight criteria.

4. Clearly communicate COVID-19 status to any new providers before their arrival on the scene or receipt of the patient when transferring to a second setting.

Prioritize oxygenation and ventilation strategies with lower aerosolization risk

- **Rationale:** While the procedure of intubation carries a high risk of aerosolization if the patient is intubated with a cuffed endotracheal tube and connected to a ventilator with a high-efficiency particulate air (HEPA) filter in the path of exhaled gas and an in-line suction catheter, the resulting closed-circuit carries a lower risk of aerosolization than any other form of positive-pressure ventilation.
- **Strategies:**
    5. Attach a HEPA filter securely, if available, to any manual or mechanical ventilation device in the path of exhaled gas before administering any breaths.
    6. After healthcare providers assess the rhythm and defibrillate any ventricular arrhythmias, patients in cardiac arrest should be intubated with a cuffed tube, at the earliest feasible opportunity. Connect the endotracheal tube to a ventilator with a HEPA filter, when available.
    7. Minimize the likelihood of failed intubation attempts by a) Assigning the provider and approach with the best chance of first-pass success to intubate b) Pausing chest compressions to intubate
    8. Video laryngoscopy may reduce intubator exposure to aerosolized particles and should be considered, if available.
    9. Before intubation, use a bag-mask device (or T-piece in neonates) with a HEPA filter and a tight seal, or, for adults, consider passive oxygenation with a nonrebreathing face mask (NRFM), covered by a surgical mask.
    10. If intubation is delayed, consider manual ventilation with a supraglottic airway or bag-mask device with a HEPA filter.
    11. Once on a closed circuit, minimize disconnections to reduce aerosolization.

Consider the appropriateness of starting and continuing resuscitation.

- **Rationale:** Cardiopulmonary resuscitation is a high-intensity team effort that diverts rescuer attention away from other patients. In the context of COVID-19, the risk to the clinical team is increased and resources can be profoundly more limited, particularly in regions that are experiencing a high burden of disease. While the outcomes for cardiac arrest in COVID19 are as of yet unknown, the mortality for critically ill COVID-19 patients is high and rises with increasing age and comorbidities, particularly cardiovascular disease. Therefore, it is reasonable to consider age, comorbidities, and severity of illness in determining the appropriateness of resuscitation and balance the likelihood of success against the risk to rescuers and patients from whom resources are being diverted.

• **Strategies:**

    12. Address goals of care with COVID-19 patients (or proxy) in anticipation of the potential need for increased levels of care.
    13. Healthcare systems and EMS agencies should institute policies to guide front-line providers in determining the appropriateness of starting and terminating CPR for

patients with COVID-19, taking into account patient risk factors to estimate the likelihood of survival. Risk stratification and policies should be communicated to patients (or proxy) during the goals of care discussions.

14. There is insufficient data to support extracorporeal cardiopulmonary resuscitation (ECPR) for COVID-19 patients.

Situation- and Setting-Specific Considerations

Out-of-Hospital Cardiac Arrest (OHCA)

Below are specific considerations for cardiac arrest in victims with suspected or confirmed COVID-19 occurring outside of the hospital. Depending on the local prevalence of disease and evidence of community spread, it may be reasonable to suspect COVID-19 in all OHCAs, by default.

- **Lay rescuers:** Bystander CPR has consistently been shown to improve the likelihood of survival from OHCA, which decreases with every minute that CPR and defibrillation are delayed. Rescuers in the community are unlikely to have access to adequate PPE and, therefore, are at increased risk of exposure to COVID-19 during CPR, compared to healthcare providers with adequate PPE. Rescuers with increasing age and the presence of comorbid conditions, such as heart disease, diabetes, hypertension, and chronic lung disease, are at increased risk of becoming critically ill if infected with SARS-CoV2. However, when the cardiac arrest occurs at home (as has been reported in 70% of OHCAs before the recent wide-spread shelter-at-home ordinances) lay rescuers are likely to already have been exposed to COVID-19.

  – Chest compressions

  o For adults: Lay rescuers should perform at least hands-only CPR after recognition of a cardiac arrest event, if willing and able, especially if they are household members who have been exposed to the victim at home. A face mask or cloth covering the mouth and nose of the rescuer and/or victim may reduce the risk of transmission to a non-household bystander.

  o For children: Lay rescuers should perform chest compressions and consider mouth-to-mouth ventilation, if willing and able, given the higher incidence of respiratory arrest in children, especially if they are household members who have been exposed to the victim at home. A face mask or cloth covering the mouth and nose of the rescuer and/or victim may reduce the risk of transmission to a non-household bystander if unable or unwilling to perform mouth-to-mouth ventilation.

  – Public access defibrillation: Because defibrillation is not expected to be a highly aerosolizing procedure, lay rescuers should use an automated external defibrillator, if available, to assess and treat victims of OHCA.

- **EMS**

– Telecommunication (Dispatch): Telecommunicators, consistent with local protocols, should screen all calls for COVID-19 symptoms (eg, fever, cough, shortness of breath) or known COVID-19 infection in the victim or any recent contacts, including any household members.

- For lay rescuers, telecommunicators should provide guidance about risk of exposure to COVID-19 for rescuers and instructions for compression-only CPR, as above.
- For EMS, telecommunicators should alert dispatched EMS teams to don PPE if there is any suspicion for COVID-19 infection

– Transport
  - Family members and other contacts of patients with suspected or confirmed COVID-19 should not ride in the transport vehicle.
  - If the return of spontaneous circulation (ROSC) has not been achieved after appropriate resuscitation efforts in the field, consider not transferring to hospital given the low likelihood of survival for the patient, balanced against the added risk of additional exposure to prehospital and hospital providers.

In-Hospital Cardiac Arrest (IHCA)

Below are specific considerations for patients with suspected or confirmed COVID-19 in the hospital setting. These interim guidelines do not apply to patients who are known to be COVID19 negative. Those patients should receive standard basic and advanced life support. However, it may be reasonable to reduce personnel in the room for all resuscitations during the pandemic for social distancing purposes.

- Prearrest
  - Address advanced care directives and goals of care with all suspected or confirmed COVID-19 patients (or proxy) on hospital arrival and with any significant change in clinical status, such as an increase in the level of care.
  - Closely monitor for signs and symptoms of clinical deterioration to minimize the need for emergent intubations that put patients and providers at higher risk.
  - If the patient is at risk for cardiac arrest, consider proactively moving the patient to a negative pressure room/unit, if available, to minimize the risk of exposure to rescuers during a resuscitation.
- Close the door, when possible, to prevent airborne contamination of adjacent indoor space.
- Intubated patients at the time of the cardiac arrest
  - Consider leaving the patient on a mechanical ventilator with HEPA filter to maintain a closed circuit and reduce aerosolization.
  - Adjust the ventilator settings to allow for asynchronous ventilation (time chest compressions with ventilation in newborns). Consider the following suggestions:
    ○ Increase the FIO2 to 1.0.
    ○ Change the mode to Pressure Control Ventilation (Assist Control) and limit pressure as needed to generate adequate chest rise (6 mL/kg ideal body weight is often targeted, 4-6 mL/kg for neonates).
    ○ Adjust the trigger to Off to prevent the ventilator from auto-triggering with chest compressions and possibly prevent hyperventilation and air trapping.
    ○ Adjust respiratory rate to 10/min for adults and pediatrics and 30/min for neonates.

        - ○ Assess the need to adjust the positive end-expiratory pressure level to balance lung volumes and venous return.
        - ○ Adjust alarms to prevent alarm fatigue.
        - ○ Ensure endotracheal tube/tracheostomy and ventilator circuit security to prevent unplanned extubation.
    - If the return of spontaneous circulation is achieved, set ventilator settings as appropriate to patients' clinical conditions.
- Proned patients at the time of the arrest
    - For suspected or confirmed COVID-19 patients who are in a prone position without an advanced airway, attempt to place in the supine position for continued resuscitation.
    - While the effectiveness of CPR in the prone position is not completely known, for those patients who are in the prone position with an advanced airway, avoid turning the patient to the supine position unless able to do so without risk of equipment disconnections and aerosolization. Instead, consider placing defibrillator pads in the anterior-posterior position and provide CPR with the patient remaining prone with hands in the standard position over the T7/10 vertebral bodies.
- Post-arrest patients
    - Consult local infection control practices regarding transport after resuscitation.

Neonatal resuscitation: Every newly born baby should have a skilled attendant prepared to resuscitate irrespective of COVID-19 status. Although it remains unclear if newly born babies are infected or likely to be infectious when mothers have suspected or confirmed COVID-19, providers should don appropriate PPE. The mother is a potential source of aerosolization for the neonatal team.

- Initial steps: Routine neonatal care and the initial steps of neonatal resuscitation are unlikely to be aerosol-generating; they include drying, tactile stimulation, placement into a plastic bag or wrap, assessment of heart rate, placement of pulse oximetry and electrocardiograph leads.
- Suction: Suction of the airway after delivery should not be performed routinely for clear or meconium-stained amniotic fluid. Suctioning is an aerosol-generating procedure and is not indicated for uncomplicated deliveries.
- Endotracheal medications: Endotracheal instillation of medications, such as surfactant or epinephrine, are aerosol-generating procedures, especially via an uncuffed tube. Intravenous delivery of epinephrine via a low-lying umbilical venous catheter is the preferred route of administration during neonatal resuscitation.
- Closed incubators: Closed incubator transfer and care (with appropriate distancing) should be used for neonatal intensive care patients when possible but do not protect from aerosolization of the virus.

Maternal cardiac arrest: The tenets of maternal cardiac arrest are unchanged for women with suspected or confirmed COVID-19.

- The cardiopulmonary physiological changes of pregnancy may increase the risk of acute decompensation in critically ill pregnant patients with COVID-19.
- Preparation for perimortem delivery, to occur after 4 minutes of resuscitation, should be initiated early in the resuscitation algorithm to allow the assembly of obstetrical and neonatal teams with PPE even if ROSC is achieved and perimortem delivery is not required.

Acute Stroke Management Pathway During Coronavirus-19 Pandemic

https://link.springer.com/article/10.1007%2Fs10072-020-04375-9

Journal: Neurological Sciences *Published Online: April 9, 2020*
Authors from: Italy

Since the outbreak of the COVID-19 epidemic in Northern Italy, the authors had a constant aim of keeping the Stroke Unit COVID-free. For this reason, in addition to creating a dedicated hot-spot as a pre-triage just outside the Emergency Department, they **obtained a mobile CT unit that could be used by COVID-positive or COVID-suspected patients**. Furthermore, thanks to the collaboration with colleagues from different specialties (Infectious Disease, Internal Medicine, Intensive Care, Emergency Medicine), dedicated areas for COVID patients were activated. This led to a substantial change in the acute stroke management pathway for COVID positive patients. Patients deemed **eligible for intravenous thrombolysis follow the standard protocol.** If the ischemic stroke is not caused by a large vessel occlusion, the patient is transferred to a special unit of the Infectious Disease ward or to a dedicated medical ward where he is clinically monitored by the stroke team and by the internist. Conversely, if the ischemic stroke is determined by a **large vessel occlusion**, the patient is transferred to the Angio suite of the Neuroradiology Unit for **endovascular treatment, and the personnel is pre-alerted for adopting adequate PPEs**. At the end of the procedure, according to the type of anesthesia (i.e., conscious sedation or general anesthesia), the patient is transferred to the Infectious Disease ward or to a special Intensive Care Unit (ICU) dedicated to COVID-19 patients. In all cases, the stroke team is responsible for the stroke care of the patient.
The authors have also observed **a decreased number of patients with minor strokes and TIAs, longer onset-to-door and door-to-treatment times for major strokes, and a reduced number of transfers from strokes.** They strongly believe that the general population and family doctors are rightly focused on COVID, however, to remain at home with stroke symptoms does not mean to "stay safe at home".


Acute stroke patient
Emergency Department - Triage
COVID-19 positive pt
COVID-19 suspected pt
Not COVID-19 suspected pt
Hot-spot
Hot-spot
Standard acute stroke pathway
Fast-track nasopharyngeal swab
Mobile CT unit: cerebral CT, CTA and CTP
Mobile CT unit: cerebral CT, CTA and CTP
Large vessel occlusion
Large vessel occlusion
YES
NO
YES
NO
Angio-suite of the Neuroradiology Unit for endovascular treatment
Angio-suite of the Neuroradiology Unit for endovascular treatment
Dedicated area for suspected COVID-19 pts
COVID-19 screening
Positive, conscious
Negative, conscious
General Anestesia
NO
YES
Dedicated COVID-19 medical ward
Positive, intubated
Negative, intubated
Stroke Unit
Special ICU dedicated to COVID-19 patients
Neurointensive care unit

Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19

https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0736LE
Journal: American Journal of Respiratory and Critical Care Medicine
Published Online: April 8, 2020
Authors from: China

This study enrolled **344 ICU patients** with COVID-19 from Tongji hospital. Non-survivors were generally older than survivors, with a higher proportion aged over 60 years, and every ten-year increase in age was associated with a 58% additional risk. Dyspnea was more common in non-survivors, accompanied by a significantly higher respiratory rate and lower SpO2/FiO2 (S/F) ratio; **S/F was negatively correlated with the incidence of ARDS**, and every ten-unit increase in S/F correlated with a 10% decrease in a fatality. 88.3% of the patients who developed ARDS died during the 28-day period. Non-survivors were more likely to bear original comorbidities. **Lymphocytopenia was more common in non-survivors** (91.6% vs 55.7%, P<0.001); higher lymphocyte count was significantly associated with decreasing mortality (HR: 0.1, 95% CI: 0.06-0.18, P<0.001). 82.3% of the patients received antiviral and 77.3% antibacterial agents. Other supportive treatments included gamma globulin (in 45.3%), muscle relaxant (in 11.0%), and glucocorticoids (in 65.4%) respectively. Two (0.6%) patients were treated with ECMO and nine (2.6%) with continuous renal replacement therapy. 10.2% of the patients were treated with HFNC, of whom 65.7% also received invasive ventilation. Of the 12 patients who received HFNC only, 7 died. 40.6% of the patients were treated with mechanical ventilation (either non-invasive or invasive), of whom 34 received treatment of non-invasive ventilation only (27 died), while invasive ventilation was given to 100 patients (97 died); **median duration from admission to invasive ventilation was 5 days**, and the median duration of invasive ventilation was 4 days. Of the 145 patients who developed ARDS, 100 were treated with invasive ventilation. 38.7% of the patients died during the 28 days period with a median survival of 25 days. **The median duration from admission to death was 10 days** for non-survivors. Of the 211 survivors, 185 were discharged. The median duration from onset of symptoms to laboratory confirmation of infection by RT-PCR was 8 days. In survivors, the median duration **from positive RT-PCR result to negative was 12 days** while in non-survivors **median duration from infection confirmation to death was 15 days**

S/F may be a useful and non-invasive predictive marker, which was defined by the Kigali modification of the Berlin definition and had a good correlation with the diagnosis of ARDS. Given a large patient flow during epidemic conditions, this indicator **could be flexibly used for screening and monitoring**. Lymphcytopenia occurred in almost 70% and was predominant in non-survivors. Lymphocytopenia is a prominent feature of critically ill patients with SARS and MERS, which is the result of apoptosis of lymphocytes, thus **lymphocyte depletion could be harmful and lymphocyte count might serve as another prognostic factor** for SARS-CoV2. Unexpectedly, **non-survivors showed a higher level of IL-2R**. Highly expressed IL-2R initiates autoreactive cytotoxic CD8+ T cell-mediated autoimmunity. Meanwhile, IL-2 stimulates the proliferation of natural killer cells that highly express IL-2R, promoting the release of cytokines, further inducing the lethal "**cytokine storm**"

The high mortality rate of patients who received mechanical ventilation, which may be partly due to the centralized admission of a large number of intensive care patients in February and the fact that patients were sometimes transferred late to the hospital, made the authors question the **effectiveness of non-invasive ventilation treatment or HFNC in the first line**, and whether the early use of invasive ventilation would improve prognosis may be worth further study in a larger cohort.

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study

https://link.springer.com/article/10.1007%2Fs00405-020-05965-1
Journal: European Archives of Oto-Rhino-Laryngology Published Online: April 6, 2020
Authors from: Belgium, France, Spain

Patients with laboratory-confirmed COVID-19 infection were recruited from 12 European hospitals. Patients **completed olfactory and gustatory questionnaires** based on the smell and taste component of the National Health and Nutrition Examination Survey, and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS). A total of **417 mild-to-moderate COVID-19 patients** completed the study (263 females). The most prevalent general symptoms consisted of cough, myalgia, and loss of appetite. Face pain and nasal obstruction were the most disease-related otolaryngological symptoms. **85.6% and 88.0% of the patients reported olfactory and gustatory dysfunctions**, respectively. There was a significant association between both disorders ($p < 0.001$). Olfactory dysfunction (OD) appeared before the other symptoms in 11.8% of cases. The sQO-NS scores were significantly lower in patients with anosmia compared with normosmic or hyposmic individuals ($p = 0.001$). Among the 18.2% of patients **without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic**. The early olfactory recovery rate was 44.0%. Females were significantly more affected by olfactory and gustatory dysfunctions than males ($p = 0.001$). Olfactory and gustatory disorders are prevalent symptoms in European COVID-19 patients, who may not have nasal symptoms. The sudden anosmia or ageusia needs to be recognized by the international scientific community as important symptoms of the COVID-19 infection.

The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society

https://pubs.rsna.org/doi/10.1148/radiol.2020201365
Journal: Radiology *Published Online: April 7, 2020*
Authors from: USA, Canada, UK, Germany, France, Japan…

Thoracic imaging with chest radiography (CXR) and computed tomography (CT) are key tools for pulmonary disease diagnosis and management, but their role in the management of COVID-19 **has not been considered within the multivariable context** of the severity of the respiratory disease, pre-test probability, risk factors for disease progression, and critical resource constraints. To

address this deficit, a **multidisciplinary panel composed principally of radiologists and pulmonologists** from 10 countries with experience managing COVID-19 patients across a spectrum of healthcare environments evaluated the utility of imaging within three scenarios representing varying risk factors, community conditions, and resource constraints. **Fourteen key questions**, corresponding to 11 decision points within the three scenarios and three additional clinical situations, were rated by the panel based upon the anticipated value of the information that thoracic imaging would be expected to provide. The results were aggregated, resulting in **five main and three additional recommendations** intended to guide medical practitioners in the use of CXR and CT in the management of COVID-19.

Table 2. Summary of Recommendations for Imaging

Summary of Recommendations for Imaging
Main Recommendations
☐ Imaging is not routinely indicated as a screening test for COVID-19 in asymptomatic individuals
☐ Imaging is not indicated for patients with mild features of COVID-19 unless they are at risk for disease progression (Scenario 1)
☐ Imaging is indicated for patients with moderate to severe features of COVID-19 regardless of COVID-19 test results (Scenarios 2 and 3)
☐ Imaging is indicated for patients with COVID-19 and evidence of worsening respiratory status (Scenarios 1, 2, and 3)
☐ In a resource constrained environment where access to CT is limited, CXR may be preferred for patients with COVID-19 unless features of respiratory worsening warrant the use of CT (Scenarios 2 and 3)
Additional Recommendations
☐ Daily chest radiographs are NOT indicated in stable intubated patients with COVID-19
☐ CT is indicated in patients with functional impairment and/or hypoxemia after recovery from COVID-19
☐ COVID-19 testing is indicated in patients incidentally found to have findings suggestive of COVID-19 on a CT scan

Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy

https://jamanetwork.com/journals/jama/fullarticle/2764365
Journal: JAMA *Published Online: April 6, 2020*
Authors from: Italy

A **retrospective case series of 1591 consecutive patients** with laboratory-confirmed COVID-19 referred for ICU admission to the coordinator center (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy) of the COVID-19 Lombardy ICU Network and **treated at one of**

the ICUs of the 72 hospitals in this network between February 20 and March 18, 2020. The date of the final follow-up was March 25, 2020. Data were recorded by the coordinator center on an electronic worksheet during telephone calls by the staff of the COVID-19 Lombardy ICU Network. The median (IQR) age was 63 (56-70) years and 82% were male. Of the 1043 patients with available data, **68% had at least 1 comorbidity and 49% had hypertension**. Among 1300 patients with available respiratory support data, 99% needed respiratory support, including **88% who received mechanical ventilation** and **11% who received noninvasive ventilation**. The median positive end-expiratory pressure (PEEP) was 14 (IQR, 12-16) cm H2O, and Fio2 was greater than 50% in 89% of patients. The median Pao2/Fio2 was 160 (IQR, 114-220). The median PEEP level was not different between younger patients (n = 503 aged ≤63 years) and older patients (n = 514 aged ≥64 years). Median Fio2 was lower in younger patients: 60% vs 70%, and median Pao2/Fio2 was higher in younger patients: 163.5 vs 156. Patients with hypertension were older than those without hypertension and had lower Pao2/Fio2 (median 146 vs 173). Among the 1581 patients with ICU disposition data available as of March 25, 58% were still in the ICU, 16% were discharged from the ICU, and 26% had died in the ICU. Older patients (n = 786; age ≥64 years) had higher mortality than younger patients (n = 795). In this case series of critically ill patients with laboratory-confirmed COVID-19 **admitted to ICUs in Lombardy, Italy, the majority were older men, a large proportion required mechanical ventilation and high levels of PEEP, and ICU mortality was 26%.**

Triage Considerations for Patients Referred for Structural Heart Disease Intervention During the Coronavirus Disease 2019 (COVID-19) Pandemic: An ACC /SCAI Consensus Statement

https://www.sciencedirect.com/science/article/abs/pii/S1936879820308670?via%3Dihub
Journal: JACC Cardiovascular Interventions *Published Online: April 3, 2020*
Authors from: USA

The COVID-19 pandemic has strained health care resources around the world causing many institutions to curtail or stop elective procedures. This has resulted in the **inability to care for patients with valvular and structural heart disease** (SHD) in a timely fashion potentially placing these patients at **increased risk for adverse cardiovascular complications including congestive heart failure and death**. The effective triage of these patients has become challenging in the current environment as clinicians have had to weigh the risk of bringing susceptible patients into the hospital environment during the COVID-19 pandemic versus the risk of delaying a needed procedure. In this document, the authors suggest guidelines as to how to triage patients in need of SHD interventions and provide a framework of how to decide **when it may be appropriate to proceed with intervention despite the ongoing pandemic**. In particular, they address the triage of patients in need of **trans-catheter aortic valve replacement** and **percutaneous mitral valve repair.**

Transcatheter Aortic Valve Replacement (TAVR)
This writing group proposes the following for the timing of TAVR for severe AS during the COVID-19 pandemic:

1. **Symptomatic severe aortic stenosis** For the inpatients with severe symptomatic AS associated with a reduction in EF thought secondary to AS, presence of class III-IV

congestive heart failure (CHF), or syncope secondary to AS, TAVR should be considered to decrease the risk of clinical deterioration, prolonged hospital stay, or repeat hospitalization. It would be reasonable to schedule TAVR for outpatients with severe to critical aortic stenosis and class III-IV CHF symptoms.

2. **Minimally symptomatic severe to critical AS** For patients with class I-II NYHA CHF symptoms and quantitative measures of valve severity that indicate a critically tight valve, it is reasonable to consider either urgent TAVR or close outpatient virtual monitoring by the valve coordinator. Data to date are not robust enough to give firm recommendations but features that warrant consideration of TAVR include particularly high peak or mean gradient, very small calculated aortic valve area, or very low dimensionless index.
3. **Asymptomatic severe to critical AS** For truly asymptomatic patients, it is reasonable to postpone consideration of TAVR for three months or until after hospital operations resume elective procedures. Close outpatient monitoring, possibly via telehealth, should continue for all patients with severe AS.

Percutaneous Mitral Valve Repair

The majority of percutaneous mitral valve repair (edge-to-edge repair) can be safely deferred. The following groups of patients **should be considered for treatment with edge-to-edge repair during the COVID-19 pandemic**:

1. The inpatients with severe functional mitral regurgitation (FMR) (3+/4+) who cannot be safely discharged despite optimized guideline-directed medical therapy (GDMT) by a heart failure specialist.
2. Outpatients with severe FMR (3+/4+) with hospitalization for CHF within thirty days despite optimized GDMT by a heart failure specialist.
3. The inpatients with CHF and severe DMR (3+/4+) due to acute valvular dysfunction (i.e. secondary to a ruptured chord or papillary muscle rupture after myocardial infarction) who are high risk for surgical mitral valve repair/replacement.
4. Outpatients with severe DMR (3+/4+) with hospitalization within thirty days despite optimized medical therapy who are at high risk for surgical mitral valve repair/replacement.
5. Patients with either severe DMR or FMR who are in low-output, decompensated heart failure requiring ICU-level care where edge-to-edge device implantation might improve hemodynamics for extubation and/or transfer out of ICU setting.

It is the responsibility of the procedural team to keep in contact with the patients who are deferred on a weekly basis to ensure that there has been no decompensation requiring earlier intervention.

Transcatheter Mitral Valve-in-Valve Replacement (ViV TMVR) ViV TMVR is the only other transcatheter mitral valve intervention hat is currently the United States FDA approved. Since these procedures are resource-intensive, they should be deferred until after the COVID-19 pandemic has adequately resolved to provide such mitral valve patients can be sufficiently managed on medical therapy in the interim. ViV TMVR during the COVID-19 pandemic should be considered for patients with severe bioprosthetic mitral stenosis/regurgitation who are inpatients with CHF or outpatients who have had a hospitalization for CHF within 30 days despite optimized GDMT. Transcatheter mitral valve-in-ring (ViR TMVR) and valve-in-mitral annular calcification (ViMAC TMVR) are off-label

procedures and are at a much higher risk for complications that may prolong hospitalization. These latter procedures should be generally avoided during the COVID-19 pandemic.

Paravalvular Leak (PVL) Closure PVL closure (particularly mitral) is generally a lengthy procedure and requires general anesthesia and transesophageal echocardiography (TEE). Patients who have significant PVL but with symptoms that can be managed medically should be deferred until after the moratorium on nonessential procedures has been removed. Patients who should be considered for PVL closure during the COVID-19 pandemic are inpatients with CHF and/or hemolysis.

Other SHD Interventions Other commonly performed SHD interventions include patent foramen ovale (PFO) closure, atrial septal defect (ASD) closure, left atrial appendage (LAAO) occlusion and alcohol septal ablation for hypertrophic cardiomyopathy. These procedures treat conditions that rarely result in hospitalization or death without the procedure over the short-term. For these reasons, these procedures should be deferred until it is deemed safe to resume performing non-emergent procedures in the procedural suites.

High-Sensitivity Cardiac Troponin Can Be An Ally in the Fight Against COVID-19

https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047008

Journal: Circulation *Published Online: April 6, 2020*

Authors from: UK

The American College of Cardiology recently published a short review of the role of biomarker testing in patients with COVID-19. It states 'clinicians are advised to **only measure troponin if the diagnosis of acute myocardial infarction is being considered** on clinical grounds'. This approach was recommended on the basis that troponin elevation in patients with COVID-19 is likely to be multifactorial, and less likely to be due to atherothrombotic coronary occlusion. Circulating cardiac troponin is a **marker of myocardial injury, including but not limited to myocardial infarction or myocarditis** and the clinical relevance of this distinction has never been so clear. It is important to better understand the utility of this essential biomarker and to educate clinicians on its interpretation and implications for prognosis and clinical decision making. With COVID-19 infection, mortality rates are highest in those who are older and in those with a history of underlying cardiovascular disease. In a cohort of 191 patients with confirmed COVID-19, the univariable odds ratio for death when hs-cTnI concentrations were above the 99th percentile upper reference limit was 80.1. This was **higher than the odds ratios observed for all other biomarkers tested**, including D-Dimer and lymphocyte count. A further study of 416 hospitalized patients with COVID-19 reported that cardiac troponin concentrations were elevated in 1 in 5 patients on presentation. These patients were more likely to require invasive or noninvasive ventilation (22% versus 4%, and 46% versus 4%), and to develop acute respiratory distress syndrome (59% versus 15%l). The observed rate of mortality was 10-fold higher in those with myocardial injury on presentation (51% versus 5%, adjusted hazard ratio 3.41 (95% CI 1.62-7.16). Early recognition of this risk could facilitate appropriate triage to high intensity or critical care area, improve the understanding of the

systemic consequences of COVID-19, and inform the use of inotropes, vasopressors, and diuretics in those with significant cardiac dysfunction.

Furthermore, testing may identify patients with a **clearly defined cardiac phenotype with therapeutic implications**. For example, it has been suggested that patients with COVID-19 associated myocarditis may benefit from other therapies such as a combination of i**mmunoglobulin and corticosteroid therapy.** Cardiac troponin testing could also prompt the early initiation of measures to improve tissue oxygenation and perfusion.

Clinicians must recognize that **troponin is not a test for myocardial infarction, and it never was**. No biomarker has ever had the ability to detect acute atherothrombotic occlusion in a coronary artery. This myth has been perpetuated in clinical practice and it is limiting our ability to evaluate and triage care in critically unwell patients. We need, more rather than less, information to guide the international response to the COVID-19 pandemic. **Taken together with clinical assessment and the electrocardiogram, elevations of cardiac troponin can inform the diagnosis of a number of cardiac conditions related to COVID-19.** We must take advantage of all available prognostic markers to identify patients with important systemic consequences of COVID-19 and determine those at the highest risk of adverse outcomes as early as possible. Troponin should be considered an ally and a crucial diagnostic and prognostic aid in what will become even more challenging times for healthcare provision worldwide.

ANNALS EXPRESS: On the Clinical Utility of Cardiac Troponin Measurement in COVID-19 Infection

https://journals.sagepub.com/doi/pdf/10.1177/0004563220921888
Journal: Annals of Clinical Biochemistry *Published Online: April 7, 2020*
Authors from: UK

Cardiac complications of COVID-19 include the development of **incident heart failure, acute coronary syndrome (ACS) and arrhythmia** all of which are associated with an elevation in cTn and confer a poor prognosis. Evidence of COVID-19-associated increases in circulating cardiac troponin T (cTnT) and cardiac troponin I (cTnI) above the 99th percentile reference limit are emerging in the literature. Detectable cTnI has been observed in most COVID-19 patients. In a retrospective cohort analysis, **cTnI was significantly elevated in 54 subjects who died** compared to 137 survivors (median cTnI 22 vs 3 ng/L). The mechanism of cTn elevation in COVID-19 infection is not fully understood. Elevations are **likely to reflect non-coronary disease** rather than acute coronary disease such as myocardial infarction. The underlying pathophysiology is suggestive of a **cardioinflammatory response** as many critically ill COVID-19 patients demonstrate concomitant elevations in acute phase reactants such as CRP and the natriuretic peptides. This may present clinically as **fulminant myocarditis**. In one case report, a thirty-seven-year-old male presented with a three-day history of chest pain and dyspnoea. Electrocardiographic changes suggested an ST-segment elevation acute myocardial infarction and cTnT was substantially elevated at >10,000 ng/L, with concomitant elevations in CK and b-type natriuretic peptide. The initial working

diagnosis was ACS. Subsequent CT coronary angiography revealed no evidence of coronary stenosis. The working diagnosis changed to **coronavirus fulminant myocarditis with cardiogenic shock and pulmonary infection**. The patient was successfully treated with **glucocorticoid and human Ig** and cTnT decreased to 220 ng/L by one week and 21 ng/L by three weeks. A further mechanism for consideration involves angiotensin-converting enzyme 2 (ACE2) which is expressed in myocardial tissue. SARS-CoV-2 binds cells expressing ACE2. Binding of the virus can **down-regulate ACE2 intracellular pathways and mediate inflammation and edema**, contributing to respiratory failure. In theory, this could have a potential impact on patients taking ACE inhibitors (ACEi), resulting in a greater risk of acquiring COVID-19 infection and increased severity of the disease. However, at present, the European Society of Cardiology has highlighted a **lack of scientific evidence regarding COVID-19 infection in patients on ACEi or angiotensin receptor blockers** and supports the continuation of antihypertensive therapy in patients with confirmed infection.

Integrated Radiologic Algorithm for COVID-19 Pandemic

https://journals.lww.com/thoracicimaging/Citation/publishahead/Integrated_Radiologic_Algorithm_for_COVID_19.99424.aspx

Journal: Journal of Thoracic Imaging *Published Online: April 7, 2020*

Authors from: Italy

When COVID-19 was notified in Northern Italy, the regional parliament issued COVID-19 guidelines to organize first-level dedicated triage for respiratory symptoms, integrated with **second-level triage including radiography and computed tomography (CT)**. The first impression on this political decision raised some skepticism: no thoracic radiologist would ever propose radiology for the management of a respiratory virus, because of limited accuracy in the etiological definition of diffuse alveolar damage (DAD) and/or organizing pneumonia. Nonetheless, the authors were somehow induced to use imaging and witnessed it as a practical approach in this unique contingency where **pretest probability of one specific etiology is substantially higher** than any other hypothesis. First, the authors decided to use both radiography and CT, notably to use mainly radiography and offer supplementary CT in more severe cases or cases in whom radiography was difficult to interpret. This strategy quite overlaps the current ACR recommendation. But practical experience soon showed dilated times for swab analysis (>24 h) and the need to switch from radiography to CT with the purpose of increasing “both sides” of accuracy in a clinically integrated quick workflow. CT allows some confidence in the definition of alternative diagnosis for severe acute respiratory symptoms and **discharging the suspect of COVID-19 in favor of other diagnoses** (eg, lobar pneumonia, bronchiolitis, heart failure, etc.), but CT also allows to **detect subtle diffuse ground-glass opacities** that are variably detected by radiography. However, an early negative CT can be interpreted as the absence of pneumonia but does not tell anything about the presence of infection from SARS-CoV-2. Furthermore, subjects with normal CT may develop severe COVID-related pneumonia shortly (eg, in 2 days). On the basis of scientific data, knowledge in thoracic radiology, and Institutional intensive experience with the COVID-19 epidemic, the authors drew and adapted an **integrated radiologic algorithm** based on the first 702 cases of patients who referred

to dedicated COVID-19 radiology protocol after first-level clinical triage in a dedicated emergency unit.

Category 1 – Negative for COVID-19 includes both normal CT and CT signs certainly attributable to a specific disease, with the aim of ruling out from the dedicated COVID-19 protocol. This category was meant and assigned with absolute caution, to minimize false negatives. The authors observed 16% (111/702) cases with normal CT despite decent clinical symptoms and blood gas abnormality. Further, 13% (90/702) cases were highly consistent with other disorders. Overall, category 1 **allowed to exclude 29% of referrals**. Among those with completely negative CT, the authors report 5% (6/111) later onset of CT findings of COVID-19 (within 1 wk, CT performed for further clinical worsening), which is an important limitation of the different clinical-radiologic phases of this disease.

Category 2 – Indeterminate for COVID-19 included differential diagnosis between COVID-19 OR other disease and potential overlap of COVID-19 AND other disease. This category includes any CT finding that does not safely suggest an exclusive alternative diagnosis. We observed 10% (72/702) patients with differential diagnosis and 9% (66/ 702) patients with potential overlap. Overall, category 2 was assigned in 19% of cases. A comparison with prior CT will be very helpful in this setting.

Category 3 – Typical Pattern of COVID-19 includes a number of typical patterns of COVID-19 with a range of disease phases and severity. Category 3 was assigned in 52% (363/702) of cases. The authors observed classical peripheral ground-glass opacity and crazy paving pattern, also recognizing the spectrum of the DAD-related initial phases at CT, essentially exudative, or organizing. Furthermore, in keeping with previous findings, they observed multiple ground-glass nodules (of variable size) randomly distributed in the lungs.

Prevalence of Venous Thromboembolism in Patients With Severe Novel Coronavirus Pneumonia

https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14830

Journal: Journal of Thrombosis and Haemostasis *Published Online: April 9, 2020*
Authors from: China

Severe **novel coronavirus pneumonia** (NCP) patients have abnormal blood coagulation function, but their venous thromboembolism (VTE) prevalence is still rarely mentioned. In this study, **81 severe NCP patients in the ICU** in Wuhan were enrolled. The results of conventional coagulation parameters and **lower limb vein ultrasonography** of these patients were retrospectively collected and analyzed. **The incidence of VTE in these patients was 25%** and 8 patients with VTE events had died. VTE group was different from non-VTE group in age, lymphocytes counts, activated partial thromboplastin time (APTT) and D-dimer. If **1.5 μg/mL was used as the D-dimer cut-off** value to predict VTE, the **sensitivity was 85.0%, the specificity was 88.5% and the negative predictive value (NPV) was 94.7%.** Therefore, the significant increase of D-dimer in severe NCP patients is a good index for identifying high-risk groups of VTE.

ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19

https://erj.ersjournals.com/content/early/2020/03/26/13993003.00688-2020
Journal: European Respiratory Journal *Published Online: April 8, 2020*
Authors from: Canada

According to the results of this study, **smokers and individuals with COPD have increased airway expression of ACE-2**, which is the entry receptor for the COVID-19 virus. This may explain the increased risk of severe COVID-19 in these subpopulations and highlight the importance of smoking cessation. Patients undergoing bronchoscopy for clinical purposes were enrolled. Patients with COPD were defined as those having a clinical diagnosis of COPD made by a board-certified respiratory physician and either a forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <70% or clear evidence of emphysema on computed tomographic (CT) imaging on visual inspection. Cytologic brushings were obtained in subsegmental airways that were unaffected by the patient's underlying clinical indication for a bronchoscopy. Total RNA was extracted from cytologic brushings and transcriptomic sequencing was performed. The average age of the main cohort was 64.8±12.0 years; 55% were females and 24% were current smokers. Compared to control subjects (N=21), those with COPD (N=21) had lower FEV1% (72.0±15.6 versus 85.9±17.9% predicted; p=0.011) and FEV1/FVC (64.1±7.9 versus 76.3±5.9%; 2.621×10−6). Most (79%) underwent bronchoscopy for investigation of lung nodules, followed by chronic cough (7%) and lymphadenopathy (7%). **ACE-2 expression in the epithelial cells was significantly increased in COPD versus non-COPD subjects** and there was a significant inverse relationship between ACE-2 gene expression and FEV1% of predicted. Interestingly, **smoking status was also significantly related to ACE-2 gene expression levels in airways** of these participants with current smokers having a significantly higher gene expression than never smokers. Former smokers had gene expression levels in-between that.

Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome

https://onlinelibrary.wiley.com/doi/abs/10.1002/acr2.11135
Journal: ACR Open Rheumatology *Published Online: April 8, 2020*
Authors from: USA

The authors evaluated intravenous continuous **recombinant human interleukin-1 receptor antagonist anakinra** infusions in treating severely ill adult patients with **secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome** (sHLH/MAS). A retrospective chart review of five patients treated at Regions Hospital from 2016-2019. Demographic, clinical, laboratory characteristics and outcomes were recorded. Continuous IV anakinra infusions up to 2400 mg/day resulted in **rapid serologic, then a clinical response in 4/5 severely ill patients** who were refractory to all other therapies including subcutaneous anakinra. Subsequently, **3/5 have been maintained on anakinra or canakinumab with no recurrence of MAS.** Continuous infusion of IV anakinra may result in rapid serologic and subsequent clinical

improvement in adult patients with MAS. This method for **treating cytokine storm** should be **considered in the current COVID-19 pandemic** in the subgroup of patients with severe disease that have a cytokine storm presentation.

CAPACITY-COVID: a European registry to determine the role of cardiovascular disease in the COVID-19 pandemic

https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa280/5817734
Journal: European Heart Journal *Published Online: April 8, 2020*
Authors from: the Netherlands

The cardiovascular disease appears to play a prominent role in the COVID-19 pandemic on multiple levels: 1. patients with cardiovascular risk factors and pre-existent cardiovascular disease seem to have an **increased risk** of a poor outcome; 2. patients with COVID-19 have been, also in the absence of underlying cardiovascular disease, reported to **develop cardiovascular complications**; 3. therapeutics currently prescribed in an experimental setting such as antimalarial and antiviral drugs have **known cardiovascular side effects;** 4. There are concerns regarding the **safety of ACEIs and ARBs** in relation to COVID-19. Insufficient evidence is currently available to guide clinicians in the management of these patients.
To accelerate knowledge on the role of cardiovascular disease in the COVID-19 pandemic, standardized and coordinated data collection on a large scale is of pivotal importance.
For this reason, the authors **launched the CAPACITY-COVID (**https://capacity-covid.eu/**) registry.** All patients with a highly suspected or proven infection with SARS-CoV-2 are eligible for inclusion in CAPACITY-COVID. The authors strongly encourage the international community to participate. The study protocol, patient information form, and standard operating procedures are all freely available.

Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series

https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14828
Journal: Journal of Thrombosis and Haemostasis *Published Online: April 8, 2020*
Authors from: USA

A hallmark of severe COVID-19 is coagulopathy, with 71.4% of patients who die of COVID-19 meeting ISTH criteria for **disseminated intravascular coagulation** (DIC) while only 0.6% of patients who survive meet these criteria. Additionally, it has become clear that this is not a bleeding diathesis but rather a **predominantly pro-thrombotic DIC** with high venous thromboembolism rates, elevated D-dimer levels, high fibrinogen levels in concert with low anti-thrombin levels, and pulmonary congestion with microvascular thrombosis and occlusion on pathology. In addition, there is a mounting experience with **high rates of central line thrombosis** and **vascular occlusive events** (e.g. ischemic limbs, strokes, etc.) observed by those who care for critically ill COVID-19

patients. There is evidence in both animals and humans that **fibrinolytic therapy** in Acute Lung Injury and ARDS improves survival, which also points to fibrin deposition in the pulmonary microvasculature as a contributory cause of ARDS and would be expected to be seen in patients with ARDS and concomitant diagnoses of DIC on their laboratory values such as what is observed in more than 70% of those who die of COVID-19. In the present case series, the authors present 3 clinical cases treated with off-label intravenous administration of tPA (Alteplase). In all 3 cases, the patients demonstrated an **initial improvement in their P/F ratio**, with improvements ranging from a 38% improvement to a ~100% improvement. The observed improvements were transient and **lost over time in all 3 patients after completion of their tPA infusion**.

There is a precedent for using larger bolus doses of tPA in the already existing literature and doing so while patients remain on a therapeutic heparin drip, such as in sub-massive pulmonary embolism where the use of a 100mg bolus of tPA (Alteplase) while on a therapeutic heparin drip has been shown to be highly effective in reducing mortality and only increases bleeding risk by 1.2%. Such an approach using **larger bolus-dose tPA** (50mg or 100mg bolus) **without holding anticoagulation** in order to prevent recurrence of the suspected pulmonary microvascular thrombosis underlying COVID-19 ARDS is worthy of further consideration and study, and while the mortality in COVID-19 ARDS is exceptionally high **the risks of tPA must still be carefully considered given the ~1% risk of catastrophic bleeding** from tPA in non-stroke patients Formal studies are needed to evaluate the matter further.

Caring for patients with pain during the COVID-19 pandemic: Consensus recommendations from an international expert panel

https://onlinelibrary.wiley.com/doi/abs/10.1111/anae.15076
Journal: Anaesthesia *Published Online: April 7, 2020*
Authors from: Canada, USA, Portugal, UK, the Netherlands

All elective surgeries, procedures, and patient visits, **including pain management services**, have been postponed or canceled. This has impacted the care of **chronic pain patients**. Most are elderly with multiple comorbidities, which puts them at risk of COVID-19 infection. Important considerations that need to be recognized during this pandemic for chronic pain patients include: **ensuring continuity of care and pain medications, especially opioids; the use of telemedicine; maintaining biopsychosocial management; the use of anti-inflammatory drugs; use of steroids; and prioritizing necessary procedural visits.** There are no guidelines to inform physicians and healthcare providers engaged in caring for patients with pain during this period of crisis. The authors assembled an expert panel of pain physicians, psychologists and researchers from North America and Europe to formulate recommendations to guide practice. As the COVID-19 situation continues to evolve rapidly, these recommendations are based on the best available evidence and expert opinion at this present time and may need adapting to local workplace policies.

Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa394/5816960
Journal: Clinical Infectious Diseases *Published Online: April 7, 2020*
Authors from: France

Hydroxychloroquine (HCQ) appears to be a promising treatment for COVID-19. However, all ongoing clinical trials with HCQ use different dosing regimens. This **prospective cohort pharmacokinetic (PK) study included 13 consecutive ICU patients** with COVID-19, who received 200 mg of oral HCQ, three times daily. Blood samples for determination of drug levels were drawn as part of routine care, with the decision to perform therapeutic drug monitoring based on medical guidance. **HCQ trough levels >1 mg/L and <2 mg/L were considered to be therapeutic**. The medical team received all results in real-time to allow for dose adjustments, as necessary. The median age of patients was 68 years, most were male (85%) and 46% were considered to be obese. Median renal function estimated by the CKD-EPI formula was 79.6 mL.min-1; 30.7% of subjects presented moderate or severe renal failure. Twelve patients were mechanically ventilated. One patient was treated by ECMO and another patient was treated by renal replacement therapy. A total of 161 blood levels were recorded and used for the analysis and 6 samples were below the limit of quantification of the assay. Only **8/13 patients achieved the supposed minimum therapeutic level** and **2/13 patients exceeded** a concentration of 2 mg/L. The mean time to reach the minimum therapeutic level was 2.7 days. Four patients underwent dose de-escalation and subsequently received 200 mg of HCQ twice daily. HCQ was withdrawn in two patients: due to QT interval prolongation (381 to 510 ms and 432 to 550 ms) on days 2 and 3 with HCQ blood levels of 0.03 mg/L and 1.74 mg/L, respectively.

It is known from the existing literature that HCQ presents marked PK variability with a very long half-life (5 to 40 days), particularly due to large distribution into blood and tissues. **Steady-state concentrations are therefore achieved within weeks** and vary from individual to individual with the same dosing regimen. However, ICU patients present certain characteristics that can affect the PK of drugs. For example, the presence of ECMO may affect the already altered PK of ICU patients by further increasing the volume of distribution, causing changes in clearance, and causing adsorption or absorption into the circuit. In the one patient treated by ECMO in this study, HCQ blood levels increased more slowly than in the other patients. The therapeutic level of HCQ in COVID-19 patients has not yet been established. Some in vitro and in silico studies have reported a virustatic effect of chloroquine and HCQ and estimated the therapeutic blood level from EC50, ranging from 0.3 to 2.1 mg/L. The toxic HCQ concentration has not been established, although a number of arguments suggest that a **concentration of 2 mg/L should not be exceeded to avoid ocular toxicity**. However, the most dreaded adverse effect for COVID-19 patients is cardiac toxicity. The relationship between cardiac toxicity and HCQ blood levels has not been determined, but it can be assumed that excessive HCQ exposure is likely to be harmful. In this study, two patients experienced cardiac toxicity at variable HCQ blood concentrations. All of the 9 clinical trials concerning the therapeutic use of HCQ in COVID-19 registered in clinicaltrials.gov (on March 26) are using **different dosing regimens**. Based on the simulations in the present study, some of these dosing regimens will fail to reach therapeutic levels, while others will probably induce levels higher

than 2 mg/L. **Therapeutic drug monitoring** should be used to personalize the optimal dosing regimen.

Lung Transplantation as Therapeutic Option in Acute Respiratory Distress Syndrome for COVID-19-related Pulmonary Fibrosis

https://journals.lww.com/cmj/Abstract/publishahead/Lung_transplantation_as_therapeutic_option_in.99314.aspx
Journal: Chinese Medical Journal *Published Online: April 1, 2020*
Authors from: China

Critical patients with COVID-19, even those whose nucleic acid test results had turned negative and those receiving maximal medical support, have been noted to progress to irreversible fatal respiratory failure. **Lung transplantation** (LT) as the sole therapy for **end-stage pulmonary fibrosis** related to acute respiratory distress syndrome has been considered as the ultimate rescue therapy for these patients. From February 10 to March 10, 2020, three male patients were urgently assessed and listed for transplantation. After conducting a full ethical review and after obtaining assent from the family of the patients, the authors **performed three LT procedures for COVID-19 patients with illness durations of >1 month** and extremely high sequential organ failure assessment (SOFA) scores. **Two of the three recipients survived** post-LT and started participating in a rehabilitation program. The pathological results of the explanted lungs were concordant with the critical clinical manifestation and provided insight towards a better understanding of the disease. Government health affairs systems, virology detection tools, and modern communication technology all play key roles in the survival of the patients and their rehabilitation. Lung transplantation can be performed in end-stage patients with respiratory failure due to COVID-19-related pulmonary fibrosis. If confirmed **positive-turned-negative virology status without organ dysfunction**, LT provided the final option for these patients to avoid certain death.

The Role of Cytokines Including Interleukin-6 in COVID-19 Induced Pneumonia and Macrophage Activation Syndrome-Like Disease

https://www.sciencedirect.com/science/article/pii/S1568997220300926?via%3Dihub
Journal: Autoimmunity Reviews *Published Online: April 3, 2020*
Authors from: UK, Israel, Ireland

Severe COVID-19 associated pneumonia patients may exhibit features of systemic hyper-inflammation designated under the umbrella term of **macrophage activation syndrome** (MAS) or **cytokine storm**, also known as **secondary haemophagocytic lymphohistocytosis** (sHLH). This is distinct from HLH associated with immunodeficiency states termed primary HLH -with radically different therapeutic strategies in both situations. COVID-19 infection with MAS typically occurs in subjects with adult respiratory distress syndrome (ARDS) and historically, **non-survival in ARDS was linked to sustained IL-6 and IL-1** elevation. The authors provide a model for the classification

of MAS to stratify the MAS-like presentation in COVID-19 pneumonia and explore the complexities of discerning ARDS from MAS. They discuss the potential impact of timing of anti-cytokine therapy on viral clearance and the impact of such therapy on intra-pulmonary macrophage activation and emergent pulmonary vascular disease.

COVID-19 pneumonia may represent a **novel viral MAS-like immunopathology**, where hyper-inflammation may be key to virus control in the face of disabled type-1 interferon responses. Furthermore, the recognition of MAS/sHLH is problematic in COVID-19 pneumonia cases with the severe inflammation emanating from the pulmonary compartment mimicking MAS, but the lack of other classical systemic clinical features making MAS presentation atypical and diagnosis more difficult. Consequently, many cases receiving anti-IL-6R or other cytokine inhibitors therapy may have **a severe infection related ARDS without superimposed MAS**. Although inflammation is more lung centered, than multi-organ, the argument for IL-6 involvement in COVID-19 related MAS comes from biochemical parameters changes including ferritin and the preliminary open reports of anti-IL6R efficacy. We appear to be dealing with a **pulmonary pathology distinct from MAS with DIC with both the macrophage activation and associated coagulopathy** being more **centered on the lung and not systemic.**

Early use of anti-retroviral therapy strategies to reduce viral load appears crucial to preventing the relative immunosuppression that might be contributing to the MAS like picture development. It is presently unclear if elevated IL-6 levels are detrimental or beneficial in COVID-19 pneumonia. In experimental model systems, IL-6 can either suppress or facilitate viral replication, so studies on COVID-9 are urgently needed. The timing of **anti-IL-6R**, if too early might **adversely affect viral clearance which needs to be assessed in trials**. If it emerges that blocking IL-6R early in the course of COVID pneumonia MAS-like disease has a detrimental impact on type-2 pneumocyte anti-viral immunity, then local augmentation of IL-6 could be considered.

If a MAS-like state exists and excessive IL-6 levels are detrimental - **why shouldn't corticosteroids be first-line therapy as these will vigorously suppress IL-6 and a raft of other cytokines?** Although the recent open-label study from Wu and colleagues showed a benefit for corticosteroids, the consensus is that these should not be used based on clinical experience in SARS-CoV, MER-CoV and other infections including influenza and respiratory syncytial virus infection, where collectively there is evidence for delayed viral clearance. The MAS-like state in COVID-19 exhibits features of both primary and secondary HLH with **death being linked to respiratory viral persistence** in the aforementioned Wu et al. study, indicating that, analogous to primary HLH, **the ongoing infection may be a driver.** The role of IL-6 and other cytokines in what could be a distinct MAS-like lung inflammation with associated inflammation-driven pulmonary vascular disease awaits clarification.

Inositol and Pulmonary Function. Could Myo-Inositol Treatment Downregulate Inflammation and Cytokine Release Syndrome in SARS-CoV-2?

https://www.europeanreview.org/article/20715
Journal: European Review for Medical and Pharmacological Sciences
Published Online: March, 2020
Authors from: Italy

ARDS is the leading cause of death in COVID-19. Preliminary data point out that **a dramatic increase in IL-6 and subsequent cytokine release syndrome** may account for the development of fatal interstitial pneumonia. Inhibition of IL-6 by blocking its specific receptor with monoclonal antibodies has been advocated as a promising attempt. In this review, the authors assess the potential utility of **myo-Inositol**, a polyol already in use **for treating the newborn Respiratory Distress Syndrome**, in downregulating the inflammatory response upon Sars-CoV-2 infection. Myo-Inositol proved to reduce IL-6 levels in a number of conditions and to mitigate the inflammatory cascade while being devoid of any significant side effects. It is tempting to speculate that inositol could be beneficial in managing the most dreadful effects of Sars-CoV-2 infection.

Comparative Replication and Immune Activation Profiles of SARS-CoV-2 and SARS-CoV in Human Lungs: An Ex Vivo Study With Implications for the Pathogenesis of COVID-19

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa410/5818134
Journal: Clinical Infectious Diseases *Published Online: April 9, 2020*
Authors from: China (Hong Kong)

Although SARS-CoV-2 and SARS-CoV share a number of common clinical manifestations, **SARS-CoV-2 appears to be highly efficient in person-to-person transmission** and frequently causes asymptomatic infections. However, the underlying mechanism that confers these viral characteristics on high transmissibility and asymptomatic infection remains incompletely understood. The authors comprehensively investigated the replication, cell tropism, and immune activation profile of SARS-CoV-2 infection in human lung tissues with SARS-CoV included as a comparison. SARS-CoV-2 infected and replicated in human lung tissues more efficiently than that of SARS-CoV. **Within the 48-hour interval, SARS-CoV-2 generated 3.20 folds more infectious virus particles than that of SARS-CoV from the infected lung tissues** ($P<0.024$). SARS-CoV-2 and SARS-CoV were similar in cell tropism, with both targeting types I and II pneumocytes, and alveolar macrophages. Importantly, despite the more efficient virus replication, **SARS-CoV-2 did not significantly induce types I, II, or III interferons** in the infected human lung tissues. In addition, while SARS-CoV infection upregulated the expression of 11 out of 13 (84.62%) representative pro-inflammatory cytokines/chemokines, SARS-CoV-2 infection only **upregulated 5 of these 13 (38.46%) key inflammatory mediators despite replicating more efficiently.** The study provided the first quantitative data on the comparative replication capacity and immune activation profile of SARS-CoV-2 and SARS-CoV infection in human lung tissues. The results provided important insights on the pathogenesis, high transmissibility, and asymptomatic infection of SARS-CoV-2.

Single-Dose, Intranasal Immunization With Recombinant Parainfluenza Virus 5 Expressing Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Spike Protein Protects Mice From Fatal MERS-CoV Infection

https://doi.org/10.1128/mbio.00554-20
Journal: mBio *Published Online: April 7, 2020*
Authors from: USA

MERS-CoV can cause severe and fatal acute respiratory disease in humans and remains endemic in the Middle East since first being identified in 2012. There are currently no approved vaccines or therapies available for MERS-CoV. In this study, the authors evaluated **the parainfluenza virus 5-based vaccine expressing the MERS-CoV envelope spike protein (PIV5/MERS-S)** in a human DPP4 knockin C57BL/6 congenic **mouse model** (hDPP4 KI). Following a **single-dose intranasal immunization**, PIV5-MERS-S **induced neutralizing antibody and robust T cell responses** in hDPP4 KI mice. A single intranasal administration of 104 PFU PIV5-MERS-S provided complete protection against a lethal challenge with mouse-adapted MERS-CoV (MERSMA6.1.2) and improved virus clearance in the lung. In comparison, single-dose intramuscular immunization with 106 PFU UV-inactivated MERSMA6.1.2 mixed with Imject alum provided protection to only 25% of immunized mice. Intriguingly, an influx of eosinophils was observed only in the lungs of mice immunized with inactivated MERS-CoV, suggestive of a hypersensitivity-type response. Overall, the study indicated that PIV5-MERS-S is a promising effective vaccine candidate against MERS-CoV infection. Furthermore, the success of the PIV5-based MERS vaccine **can be employed to develop a vaccine for emerging CoVs such as SARS-CoV-2, which causes COVID-19.**

The FDA-approved Drug Ivermectin Inhibits the Replication of SARS-CoV-2 in Vitro

https://www.sciencedirect.com/science/article/pii/S0166354220302011?via%3Dihub
Journal: Antiviral Research *Published Online: April 3, 2020*
Authors from: Australia

The authors report here that **Ivermectin, an FDA-approved anti-parasitic** previously shown to have broad-spectrum antiviral activity in vitro, is an inhibitor of the causative virus, with a single addition to Vero-hSLAM cells 2 hours post-infection with SARS-CoV-2 able to effect ~the 5000-fold reduction in viral RNA at 48 h. Ivermectin, therefore, warrants further investigation for possible benefits in humans. This early data need to be confirmed by further preclinical and eventually clinical testing.

Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019

https://www.europeanreview.org/article/20706
Journal: European Review for Medical and Pharmacological Sciences
Published Online: March, 2020
Authors from: China

The **non-randomized study** aimed to investigate whether **lopinavir/ritonavir (LPV/r)** in combination with other pneumonia-associated adjuvant drugs has a better therapeutic effect on COVID-19 then adjuvant drugs alone. **47 patients with COVID-19** were divided into the test group and the control group **according to whether they had been treated with LPV/r or not during hospitalization**. Patients in the test group were treated with LPV/r combined with adjuvant medicine, while those in the control group were just treated with adjuvant medicine. Both groups achieved a good therapeutic effect with the body temperature of patients decreased gradually from admission to the 10th day of treatment. But the **body temperature of patients in the test group decreased faster** than that of the control group. Blood routine indexes showed that compared with the control group, the **abnormal proportion of white blood cells, lymphocytes and C-reactive protein of the test group could be reduced to some extent.** Blood biochemical indexes exhibited that the proportion of patients with abnormal alanine aminotransferase and aspartate aminotransferase in the test group were lower than the control group. The number of days for **nCoV-RNA turning negative after treatment was significantly decreased in the test group** than that in the control group. Compared with the treatment of pneumonia-associated adjuvant drugs alone, the combination treatment with LPV/r and adjuvant drugs has a more evident therapeutic effect in lowering the body temperature and restoring normal physiological mechanisms with no evident toxic and side effects. In view of these conclusions, the authors suggest that the use of LPV/r combined with pneumonia-associated adjuvant drugs in the clinical treatment for patients with COVID-19 should be promoted.

Therapeutic Potential for Tetracyclines in the Treatment of COVID-19

https://accpjournals.onlinelibrary.wiley.com/doi/abs/10.1002/phar.2395
Journal: Pharmacotherapy *Published Online: April 8, 2020*
Authors from: Canada

Based on the available evidence the authors believe that **tetracyclines may be effective** agents in the treatment of COVID-19. Tetracyclines (e.g. tetracycline, doxycycline, and minocycline) are highly lipophilic antibiotics that are known to **chelate zinc compounds on matrix metalloproteinases** (MMPs). Coronaviruses are also known to heavily rely on host MMPs for survival, cell infiltration, cell to cell adhesion, and replication, many of which have zinc as part of their MMP complex. It is possible that the **zinc chelating properties of tetracyclines may also aid in inhibiting COVID-19 infection in humans**, limiting the viral ability to replicate within the host.

High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019

https://academic.oup.com/ofid/article/7/3/ofaa102/5810740
Journal: Open Forum Infectious Diseases *Published Online: March 21, 2020*
Authors from: China

The authors reported the **cases of 3 patients with severe COVID-19 who received high-dose intravenous immunoglobulin (IVIg) with satisfactory recovery.** The timing of IVIg administration is critical in practice. Patients might not receive much benefit when systemic damage has already taken place. Based on these observations, randomized studies of high-dose IVIg should be considered in deteriorating patients infected with COVID-19. Currently, a **randomized controlled trial evaluating the efficiency of high-dose IVIg therapy in severe COVID-19 has been initiated** (NCT 04261426).

Metronidazole; A Potential Novel Addition to the COVID-19 Treatment Regimen

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7114714/
Journal: Archives of Academic Emergency Medicine *Published Online: March 30, 2020*
Authors from: Iran

Previous studies have found **higher initial plasma levels of most pro-inflammatory cytokines** during the course of the infection. In this context, both in vitro and in vivo studies have revealed that **metronidazole could decrease the levels of several cytokines**, which are known to increase during the COVID-19 infection, including interleukin (IL)8, IL6, IL1B, tumor necrosis factor (TNF)α, IL12, IL1α, and interferon (IFN)γ, as well as the levels of CRP and neutrophil count. Furthermore, the drug could decrease neutrophil-generated reactive oxygen species during inflammation. Metronidazole could counteract the majority of the immunopathological manifestations of the COVID-19 infection. Therefore, **studies with a large sample size are required** to determine the efficacy of metronidazole in the treatment of COVID-19 infection.

Tocilizumab Treatment in COVID-19: A Single Center Experience

https://pubmed.ncbi.nlm.nih.gov/32253759/?from_term=covid+19&from_sort=date&from_page=50&from_pos=4
Journal: Journal of Medical Virology *Published Online: April 6, 2020*
Authors from: China

Tocilizumab (TCZ), a **monoclonal antibody against IL-6**, emerged as an alternative treatment for COVID-19 patients with a risk of cytokine storms. In the present study, the authors aimed to **retrospectively** assess the treatment response of TCZ therapy in fifteen COVID-19 infected patients. Two of the patients were moderately ill, six seriously and seven critically ill. TCZ was used in combination with methylprednisolone (MP) in eight patients. Five patients received the TCZ administration twice or more. Although TCZ treatment initially ameliorated the increased CRP in

all patients rapidly, three out of the four critically ill patients who **received only a single dose of TCZ** died and the remaining patient experienced disease aggravation. Serum IL-6 level tended to further spike first but decreased after TCZ therapy in 10 patients. A persistent and dramatic increase of IL-6 was observed in these 4 patients who failed treatment. TCZ appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms. For these **critically ill patients with elevated IL-6, a repeated dose of the TCZ is recommended**.

Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients

https://pubmed.ncbi.nlm.nih.gov/32253318/?from_term=covid+19&from_sort=date&from_page=51&from_pos=5
Journal: Proceedings of the National Academy of Sciences of the USA
Published Online: April 6, 2020
Authors from: China

In this **prospective** study, **10 severe patients with COVID-19** confirmed by real-time viral RNA test were enrolled. **One dose of 200 mL of convalescent plasma** (CP) derived from recently recovered donors **with the neutralizing antibody titers above 1:640** was transfused to the patients as an addition to maximal supportive care and antiviral agents. The primary endpoint was the safety of CP transfusion. The secondary endpoints were the improvement of clinical symptoms and laboratory parameters within 3 days after CP transfusion. The median time from onset of illness to CP transfusion was 16.5 days. After CP transfusion, **the level of neutralizing antibody increased rapidly up to 1:640 in five cases**, while that of the other four cases maintained at a high level (1:640). The **clinical symptoms were significantly improved** along with the increase of oxyhemoglobin saturation within 3 days. Several parameters tended to improve as compared to pretransfusion, including increased lymphocyte counts (0.65 × 109/L vs. 0.76 × 109/L) and decreased CRP (55.98 mg/L vs. 18.13 mg/L). Radiological examinations showed varying degrees of absorption of lung lesions within 7 days. **The viral load was undetectable after transfusion in seven patients who had the previous viremia**. No severe adverse effects were observed. This study showed CP therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases. The optimal dose and time point, as well as the clinical benefit of CP therapy, needs further investigation in larger well-controlled trials.

Transplantation of ACE2 - Mesenchymal Stem Cells Improves the Outcome of Patients With COVID-19 Pneumonia

http://www.aginganddisease.org/EN/10.14336/AD.2020.0228
Journal: Aging and Disease *Published Online: March 9, 2020*
Authors from: China

Preventing and **reversing the cytokine storm** may be the key to save the patients with severe COVID-19 pneumonia. **Mesenchymal stem cells** (MSCs) have been shown to possess a comprehensive powerful immunomodulatory function. This study aims to investigate whether

MSC transplantation improves the outcome of **7 enrolled patients with COVID-19 pneumonia.** The clinical outcomes, as well as changes of inflammatory and immune function levels and adverse effects, were **assessed for 14 days after MSC injection**. MSCs could cure or significantly improve the functional outcomes of seven patients without observed adverse effects. The **pulmonary function and symptoms of these seven patients were significantly improved in 2 days a**fter MSC transplantation. Among them, two common and one severe patient recovered and were discharged 10 days after treatment. After treatment, the peripheral lymphocytes increased, the CRP level decreased, and the overactivated cytokine-secreting immune cells CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells disappeared in 3-6 days. In addition, a group of CD14+CD11c+CD11bmid regulatory DC cell population dramatically increased. Meanwhile, the level of TNF-α decreased significantly, while IL-10 increased in the MSC treatment group compared to the placebo control group. Furthermore, the gene expression profile showed MSCs were ACE2- and TMPRSS2- which indicated MSCs are free from COVID-19 infection. Thus, the **intravenous transplantation of MSCs was safe and effective** for treatment in patients with COVID-19 pneumonia, especially for the patients in critically severe conditions.