INFOLETTER 8 – COVID-19

24 April 2020

Content Overview

Compassionate Use of Remdesivir for Patients With Severe Covid-19

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Journal: NEJM *Published Online: April 10, 2020*
Authors from: Canada, USA, Spain, Italy, France, Japan…

Remdesivir, a **nucleotide analog prodrug that inhibits viral RNA polymerases**, has shown in vitro activity against SARS-CoV-2. The authors provided remdesivir on a compassionate-use basis to patients hospitalized with COVID-19. Eligible patients had an oxygen saturation of **94% or less** while they were breathing ambient air or needed oxygen support. Patients received a **10-day course of remdesivir**, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the **53 patients whose data were analyzed**, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients **(57%) were receiving mechanical ventilation** and 4 **(8%) were receiving extracorporeal membrane oxygenation**.

During a median follow-up of 18 days, 36 patients **(68%) had an improvement in oxygen-support class**, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients **(47%) were discharged**, and 7 patients **(13%) died**; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation. In this cohort of patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy.

Delayed Initiation of Remdesivir in a COVID-19 Positive Patient

https://accpjournals.onlinelibrary.wiley.com/doi/abs/10.1002/phar.2403
Journal: Pharmacotherapy *Published Online: April 13, 2020*
Authors from: USA

The authors present a case of **late initiation of remdesivir** antiviral therapy in the successful treatment of a patient with SARS-CoV-2 in a mixed medical ICU of a community teaching hospital. A **previously healthy 40-year-old male** was admitted to the hospital three days after the onset of COVID-19 symptoms, including dry cough, fever, and shortness of breath progressing to i**ntubation and increased mechanical ventilator support**. A request for compassionate use remdesivir was submitted on the same hospital day as the positive COVID-19 PCR result. Supportive measures, in addition to a 5-day course of **hydroxychloroquine**, were maintained until **remdesivir could be supplied on day 9** of hospitalization, **13 days after symptom onset**. Sixty hours after initiating remdesivir, the patient was **successfully extubated** and was able to **transition to room air within 24 hours** of extubation. **Late initiation of remdesivir may be effective** in treating SARS-CoV-2, unlike antivirals utilized for different disease states, such as oseltamivir, which are most effective when started as soon as possible following symptom onset. Urgent action is needed by regulatory

agencies to work with drug manufacturers to expedite the study and approval of investigational agents targeting SARS-CoV-2 as well as to meet manufacturing demands.

Myocardial localization of coronavirus in COVID-19 cardiogenic shock

https://onlinelibrary.wiley.com/doi/full/10.1002/ejhf.1828
Journal: European Journal of Heart Failure *Published Online: April 10, 2020*
Authors from: Italy

A case of a 69-year-old man with an acute cardiac injury directly linked to myocardial localization of SARS-CoV-2 is reported. The patient with flu-like symptoms rapidly progressed to **respiratory distress, hypotension, and cardiogenic shock**. He was **successfully treated** with mechanical ventilation and **veno-arterial ECMO** implantation as a bridge to recovery. Cardiac function fully recovered in 5 days and ECMO was removed. Endomyocardial biopsy demonstrated low-grade myocardial inflammation and viral particles in the myocardium suggesting either a viraemic phase or infected macrophage migration from the lung.

Acute myocardial involvement in COVID-19 is currently described as 'acute cardiac injury', defined as blood levels of hs-TnI above the 99th-percentile upper reference limit. It is described in more than 20% of patients and seems to be related to increased mortality. The identification of the cause, either myocardial inflammation (**myocarditis or myopericarditis**), or **necrosis**, is clinically relevant for the correct diagnostic and therapeutic management of patients, especially those with severe infections admitted to the intensive care unit (ICU).

ISTH interim guidance on recognition and management of coagulopathy in COVID-19

https://onlinelibrary.wiley.com/doi/10.1111/jth.14810
Journal: Journal of Thrombosis and Haemostasis *Published Online: March 25, 2020*
Authors from: UK, China, Italy, Japan

One of the most significant poor prognostic features in COVID-19 patients is the development of coagulopathy. The interim guidelines of the **International Society of Thrombosis and Haemostasis** (ISTH) are summed up below. This guidance document aims to provide a risk stratification at admission and to describe the management of coagulopathy.

Coagulation markers at admission: In observational studies, COVID-19 patients requiring hospitalisation had elevated D-dimers and elevated D-dimers were one of the predictors of mortality. In patients, who have markedly raised D-dimers (which may be arbitrarily defined as three-four fold increase), **admission to hospital should be considered** even in the absence of other severity symptoms since this clearly signifies increased thrombin generation. **PT** was also prolonged in the non-survivors at admission but only rather modestly. Of note, likely, such subtle changes will not be picked up if the prothrombin time is reported as INR. **Thrombocytopenia** is

often considered an indicator of sepsis mortality. Interestingly, this is not the case at admission in many of the COVID-19 patients. However, a meta-analysis of nine studies including COVID-19 patients with nearly 400 with severe disease identified that the platelet count was significantly lower in patients with more severe COVID-19 and a subgroup analysis of non-survivors noted that a lower platelet count correlated with mortality. Thrombocytopenia was also associated with over fivefold increased risk of severe COVID-19 illness. This suggests thrombocytopenia at presentation may be a prognosticator, but is not very consistent. Based on the currently available literature, **we would recommend measuring D-dimers, prothrombin time and platelet count** (decreasing order of importance) in all patients who present with COVID-19 infection. This may help in stratifying patients who may need admission and close monitoring. Any underlying condition (e.g.; liver disease) or medication (e.g.; anticoagulants) which may alter the parameters should be accounted for while using the algorithm.

Monitoring coagulation markers: Tang et al. noted the development of DIC on day 4 in the 71.4% of patients who didn't survive compared to just one patient (0.6%) who survived. The researchers also noted a statistically significant increase in D-dimer levels, and PT, and decrease in fibrinogen levels in non-survivors at days 10 and 14. This establishes the huge importance of regular laboratory monitoring in these patients. Based on this study and the experience, **monitoring PT, D-dimer, platelet count and fibrinogen can be helpful** in determining prognosis in COVID-19 patients requiring hospital admission. If there is worsening of these parameters, more aggressive critical care support is warranted and consideration should be given for more 'experimental' therapies and blood product support as appropriate. If these makers are stable or improving, it gives the added confidence for stepdown of treatment if corroborating with the clinical condition.

Management of COVID-19 coagulopathy: This section is based on the currently available evidence that markedly increased D-dimer is associated with high mortality in COVID-19 patients and that multi-organ failure is more likely in patients with sepsis if they develop coagulopathy and inhibiting thrombin generation may have benefit in reducing mortality. The only widely available treatment in this respect is **a prophylactic dose low molecular weight heparin (LMWH) which should be considered in ALL patients (including non-critically ill) who require hospital admission for COVID-19**, in the absence of any contraindications (active bleeding and a platelet count less than 25 x 109/L; monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication). LMWH will also protect critically ill patients **against venous thromboembolism**. Besides, LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID infection where proinflammatory cytokines are markedly raised. Bleeding is rare in the setting of COVID-19. If bleeding does develop, similar principles to septic coagulopathy as per the harmonised ISTH guidelines with respect to blood transfusions may be followed. There are several other therapies for COVID-19 which can only be considered experimental at the moment including antithrombin supplementation, recombinant thrombomodulin and hydroxychloroquine based on mitigating the excess thrombin generation hypothesis and immunosuppressive agents including inhalational therapies which may put a check on 'immunothrombosis' model (bidirectional relationship between inflammation and thrombosis).

Hypercoagulability of COVID-19 patients in Intensive Care Unit. A Report of Thromboelastography Findings and other Parameters of Hemostasis

https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14850
Journal: Journal of Thrombosis and Haemostasis *Published Online: April 17, 2020*
Authors from: Italy

The severe inflammatory state secondary to Covid-19 leads to a severe derangement of hemostasis that has been recently described as a **state of disseminated intravascular coagulation** (DIC) and **consumption coagulopathy**, defined as decreased platelet count, increased fibrin(ogen) degradation products such as D-dimer as well as low fibrinogen. Whole blood from **24 patients** admitted at the ICU because of Covid-19 was collected and evaluated with **thromboelastography** by the TEG point-of-care device on a single occasion and six underwent repeated measurements on two consecutive days for a total of 30 observations. Plasma was evaluated for the other parameters of hemostasis. TEG parameters are **consistent with a state of hypercoagulability** as shown by decreased R and K values, and increased values of K angle and MA. Platelet count was normal or increased, prothrombin time and activated partial thromboplastin time were near normal. Fibrinogen was increased and D-dimer was dramatically increased. C-reactive protein was increased. Factor VIII and von Willebrand factor (n=11) were increased. Antithrombin (n=11) was marginally decreased and protein C (n=11) was increased. The results of this cohort of patients with Covid-19 are **not consistent with acute DIC**, rather they support **hypercoagulability together with a severe inflammatory** state. These findings may explain the events of venous thromboembolism observed in some of these patients and support antithrombotic prophylaxis/treatment. Clinical trials are urgently needed to establish the type of drug, dosage and optimal duration of prophylaxis.

Potential of Heparin and Nafamostat Combination Therapy for COVID-19

https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14858
Journal: Journal of Thrombosis and Haemostasis *Published Online: April 17, 2020*
Authors from: Japan

Tang et al. recently reported that **heparin anticoagulant therapy lowers the mortality** rate in patients who present with markedly elevated concentrations of D-dimer. The article did not describe to what extent heparin improves the abnormal coagulation and further studies by this group are anticipated. Abnormal coagulation seen in non-survivors of COVID-19 clearly differs from the abnormal coagulation typically seen in other severe infectious diseases. Specifically, **markedly decreased fibrinogen** levels and **markedly elevated fibrin degradation product** (FDP) levels have been observed in COVID-19 non-survivors. These observations carry the characteristics of **disseminated intravascular coagulation (DIC) with enhanced fibrinolysis** rather than the DIC with suppressed fibrinolysis that is caused by infectious diseases (where FDP and D-dimer levels are mildly elevated and fibrinogen is not decreased). Regarding this point, we state that a **rapid and progressive decrease in fibrinogen levels should be noted with caution** in COVID-19. Most reports concerning COVID-19 non-survivors have shown that D-dimer levels are significantly increased in

these patients, and that prognosis can be predicted based on D-dimer elevations. Since FDP increases more sensitively than D-dimer in DIC with enhanced fibrinolysis, **evaluation of FDP rather than D-dimer may be an option** to assess the prognosis of COVID-19.

In Japan, anticoagulants used for DIC include heparin, as well as antithrombin, concentrates, recombinant human soluble thrombomodulin and **nafamostat mesylate** (NM). NM is a drug that has been used for over 30 years in Japan for pancreatitis and DIC treatment, as well as dialysis (for preventing coagulation of perfused blood). NM is a **serine protease inhibitor that potently inhibits proteolytic enzymes such as thrombin, plasmin, and trypsin**. NM, unlike heparin, does **not result in hemorrhagic side effects** even at the doses used for DIC, representing a major advantage. NM is a drug used for the treatment of DIC, but possesses potent **antifibrinolytic actions** and is, therefore, a compatible drug to treat DIC with enhanced fibrinolysis. An increasing amount of data in Japan shows that NM is extremely effective against DIC, even in patients with DIC and enhanced fibrinolysis associated with primary diseases such as an aortic aneurysm or malignant tumor that do not improve. NM has been globally featured recently in the media for its suppressive actions against coronaviruses such as SARS-CoV-2. Inoue et al. noted that NM may **effectively block the requisite viral entry process** the new coronavirus uses to spread and cause disease. In other words, NM may be effective against COVID-19 from **both "anti-viral" and "anti-DIC with enhanced fibrinolysis" perspectives**. The disadvantage of NM is that it has weaker anticoagulation actions compared with its antifibrinolytic actions. **A combination with heparin** may compensate for this weakness and further augment the positive effects. Future investigations are needed.

Incidence of Thrombotic Complications in Critically Ill ICU Patients With COVID-19

https://www.thrombosisresearch.com/article/S0049-3848(20)30120-1/pdf
Journal: Thrombotic Research *Published Online: April 10, 2020*
Authors from: the Netherlands

COVID-19 may predispose to **both venous (VTE) and arterial thromboembolism** due to excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation. Reports on the incidence of thrombotic complications are, however, not available. The authors evaluated the incidence of the **composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism** in all COVID-19 patients admitted to the ICU of 3 Dutch hospitals. 184 ICU patients with proven COVID-19 pneumonia were included of whom 23 died (13%), 22 were discharged alive (12%) and 139 (76%) were still in the ICU at the time of reporting. All patients received **at least standard doses of thromboprophylaxis**. The cumulative **incidence of the composite outcome was 31%**, of which CTPA and/or ultrasonography confirmed VTE was present in 27% and arterial thrombotic events in 3.7%. **PE was the most frequent thrombotic complication** (in 25, 81%). **Age** (adjusted hazard ratio (aHR) 1.05/per year) and **coagulopathy**, defined as spontaneous prolongation of the prothrombin time > 3 s or activated partial thromboplastin time > 5 s (aHR 4.1), were **independent predictors of thrombotic complications**. The 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high. The findings reinforce the recommendation

to strictly apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU and are strongly suggestive of increasing the prophylaxis towards **high-prophylactic doses**, even in the absence of randomized evidence.

Antiplatelet Therapy Following Percutaneous Coronary Intervention in Patients Complicated by COVID-19: Implications from Clinical Features to Pathological Findings

https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.046988
Journal: Circulation *Published Online: April 16, 2020*
Authors from: China

Approximately 5 million **percutaneous coronary interventions** (PCIs) are performed annually worldwide. There are concerns regarding **dual antiplatelet therapy** (DAPT) and life-threatening bleeding complications among SARS-CoV-2 infected patients, especially the risk of **diffuse alveolar hemorrhage** (DAH). COVID-19 is associated with disseminated intravascular coagulation (DIC) and DAH was reported as a common finding in COVID-19 autopsies. The term DAH refers to a distinct form of life-threatening pulmonary hemorrhage that originates **from pulmonary microcirculation** and should be distinguished from other causes of pulmonary hemorrhage. In addition to thrombosis and hemostasis, emerging evidence supports a putative role of **platelets in host defense against infections**, which add a greater layer of complexity in evaluating the role of antiplatelet therapy in the setting of viral pneumonia.

The following issues should be considered when interpreting the impact of antiplatelet therapy on disease progression. First, the **timing of administration**: In the early phase of infection, platelet inhibition may reduce intravascular fibrin and thrombus formation, thereby preventing the ensuing consequences. Supportively, pre-hospital aspirin use, but not post-admission use, was associated with a lower risk for developing ARDS and mortality in patients with community-acquired pneumonia.

Second, the **choice of oral P2Y12 inhibitors**: despite the fact that all P2Y12 inhibitors reduce platelet-leukocyte aggregates and platelet-derived pro-inflammatory cytokines from α-granules, **ticagrelor is unique** in having the only well-documented additional target of inhibition, the **equilibrative nucleoside transporter 1** (ENT1), contributing to inhibition of cellular adenosine uptake. Therefore, ticagrelor confers **more potent anti-inflammatory properties** via dual inhibition of platelet P2Y12 receptor and ENT1. Encouragingly, the XANTHIPPE trial, as well as post-hoc analyses of PLATO study and basic research, provides evidence demonstrating the clinical **benefit of ticagrelor in the management of pneumonia** by preventing the complications of sepsis and reducing lung injury.

Third, **the circulating platelet counts**: both primary (immune thrombocytopenia) and secondary (enhanced consumption) thrombocytopenia are associated with increased risk for infection (including pneumonia) and worsened clinical outcomes associated with ARDS. Individuals that are thrombocytopenic would lose the ability to deposit fibrinogen and fail to seal the damaged

pulmonary vasculature. With regards to clinical significance, current expert consensus warrants proactive measures or even stopping all antiplatelet therapy in patients with a platelet count < 100,000/μL and < 50,000/μL, respectively.

On the contrary, emerging evidence suggests DAPT is an important aggravating factor for DAH. Notably, the clinical features of DAH in these case studies could be initially mistaken as pneumonia, due to similarities in clinical manifestations, i.e., coughing, radiographic evidence of mild infiltrations and fever. **Given the high bleeding risk in patients following PCI complicated by COVID-19, shorter-duration DAPT may be beneficial in this population**. To counterbalance an increased bleeding risk associated with DAPT, emerging findings from large randomized controlled trials provide evidence supports a net benefit of **aspirin-free strategies** after PCI for patients at low, intermediate and high risk for both ischemia and bleeding, which is mainly driven by the reduction in bleeding events. This strategy r**educes the duration of aspirin (1 to 3 months) while allowing for more prolonged use of potent P2Y12 inhibitors**.

Among patients currently on DAPT, maintaining P2Y12 inhibitor monotherapy (preferably ticagrelor) **may be scientifically reasonable for patients with PCI performed ≥ 3 months.** Due to the lack of convening evidence, **for those with PCI performed < 3 months, DAPT should not be discontinued.** Notably, considering the recent experience from China demonstrating the effectiveness of low molecular weight heparin (LMWH) in reversing DIC in COVID-19, the routine practice of the International Society of Thrombosis and Hemostasis DIC scoring system and platelet counting should be warranted daily or more frequently to identify patients who would **benefit either from early LMWH administration or from discontinuation of P2Y12 antagonist** due to clinically meaningful thrombocytopenia. The situation of a trade-off between ischemia and bleeding may be challenging when patients on oral P2Y12 inhibitor concomitantly with an indication for LMWH prophylaxis. An alternative approach in this setting would involve **utilizing an intravenous P2Y12 inhibitor such as cangrelor as a bridge therapy.**

Plasminogen Improves Lung Lesions and Hypoxemia in Patients With COVID-19

https://academic.oup.com/qjmed/article/doi/10.1093/qjmed/hcaa121/5818885
Journal: QJM *Published Online: April 10, 2020*
Authors from: China

Lungs of patients with COVID-19 have shown typical signs of ARDS, the formation of hyaline membrane mainly composed of fibrin, and 'ground-glass' opacity. The authors have already previously shown that plasminogen itself is a key regulator in fibrin degradation, wound healing and infection. In the present study, they evaluated whether plasminogen can improve lung lesions and hypoxemia of COVID-19. **Thirteen clinically moderate, severe or critical COVID-19 patients were treated with atomization inhalation of freeze-dried plasminogen**. Levels of their lung lesions, oxygen saturation, and heart rates were compared before and after treatment by CT scanning images and patient monitor. After plasminogen inhalation, **lung lesions in 5 clinically moderate patients have quickly improved**, shown as the decreased range and density of 'ground-glass'

opacity. **Improvements in oxygen saturation were observed in 6 clinically severe patients**. In the 2 critical patients, the **oxygen levels have significantly increased from 79-82% to 91% in just about 1 hour** after the first inhalation. In 8 of 13 patients, the heart rates had slowed down. For the 5 clinically moderate patients, the difference is even statistically significant. Furthermore, a general relief of chest tightness was observed. This study suggests that additional plasminogen may be effective and efficient in treating lung lesions and hypoxemia during COVID-19 infections. **Further studies are needed**.

Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) – A Review

https://jamanetwork.com/journals/jama/fullarticle/2764727
Journal: JAMA *Published Online: April 13, 2020*
Authors from: USA

No proven effective therapies for this virus currently exist. The rapidly expanding knowledge regarding SARS-CoV-2 virology provides a significant number of potential drug targets. The **most promising therapy is remdesivir**. Remdesivir has potent in vitro activity against SARS-CoV-2, but it is not US FDA approved and currently is being tested in ongoing randomized trials. **Oseltamivir has not been shown to have efficacy**, and **corticosteroids are currently not recommended**. Current clinical evidence does not support stopping angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with COVID-19.

The search on ClinicalTrials.gov resulted in 351 related active trials, with **291 trials specific to COVID-19** as of April 2, 2020. Of these 291 trials, approximately 109 trials (including those not yet recruiting, recruiting, active, or completed) included pharmacological therapy for the treatment of COVID-19 in adult patients. Of these 109 trials, 82 are interventional studies, with 29 placebo-controlled trials. Per the description of the studies, there are 11 phase 4, 36 phase 3, 36 phase 2, and 4 phase 1 trials. Twenty-two trials were not categorized by phase or not applicable.
A detailed review of the available data is provided for the following **FDA approved agents**: chloroquine and hydroxychloroquine, lopinavir/ritonavir, ribavirin, and other antiretrovirals and antivirals. Additional information is listed for other miscellaneous drugs. Regarding **experimental agents**, remdesivir and favipavir are described in detail. As for **adjunctive therapies**, corticosteroids, anti-cytokine or immunomodulatory agents and immunoglobulin therapy are reviewed in the article full-text.

Guidance On Minimizing Risk of Drug-Induced Ventricular Arrhythmia During Treatment of COVID-19: A Statement from the Canadian Heart Rhythm Society

https://www.onlinecjc.ca/article/S0828-282X(20)30325-1/pdf
Journal: The Canadian Journal of Cardiology *Published Online: April 8, 2020*
Authors from: Canada

The use of medications with unproven benefits for treatment of COVID-19 should primarily focus on robust evaluation within a clinical trial whenever possible. The authors recommend that clinical trials include **an effort to mitigate the risk of treating patients with a known predictably high risk of torsade de pointes with drugs which may further prolong the QT interval**. If drugs with the potential to cause ventricular arrhythmia through prolongation of repolarization, including **azithromycin, chloroquine, hydroxychloroquine, lopinavir/ritonavir** are contemplated for treatment of COVID-19, the following precautions should be observed:

- Review medications and discontinue unnecessary medications which may prolong QT.
- For patients with known inherited long QT syndrome or a history of drug-induced torsade de Pointes, the use of these drugs should be undertaken only after consultation with a heart rhythm specialist. Potential mitigations could include use of cardiac monitoring, or repeated QTc interval checks. Risk and potential benefit should be individually assessed.
- For patients with no history of prolonged QT, unexplained syncope or family history of premature sudden cardiac death, who are not taking other medications which may prolong the QT interval, and for patients with a prior known normal QTc, it may be reasonable to proceed with antimicrobial drug administration without a baseline or follow-up ECG, if obtaining an ECG may increase population risk of infection.
- For hospitalized patients, or for those not fulfilling the above criteria obtain baseline assessment of **ECG to assess QTc** if not performed within the last 3 months and **electrolytes** (Ca++, Mg++, K+) if possible.
    - If QTc ≥ 500 ms, reassess after correction of electrolyte abnormalities or discontinuation of other QT-prolonging drugs.
    - If QTc remains ≥ 500 ms, recommend expert consultation and careful evaluation of benefits and risks.
    - If QTc is ≥470 ms (male) or QTc is ≥480 ms (female), but < 500 ms, initiate antimicrobial drugs and consider repeat ECG in 48 hours.
    - If patients have clinically severe disease or are taking multiple medications which may prolong QT, recheck QTc 48 hours after initiation of antimicrobial drugs.
    - If follow-up QTc increases by ≥ 60 ms OR is ≥ 500 ms, discontinue antimicrobial or seek expert consultation.

Precautions and Procedures for Coronary and Structural Cardiac Interventions during the COVID-19 Pandemic: Guidance from Canadian Association of Interventional Cardiology

https://www.onlinecjc.ca/article/S0828-282X(20)30300-7/fulltext

Journal: The Canadian Journal of Cardiology *Published Online: March 24, 2020*

Authors from: Canada

Table 1: CAIC-ACCI Guidance for the Management of Coronary and Structural Procedures as COVID-19 Escalates and Abates

Response Level	Level 1 Minor restriction in regular services	Level 2 Major restriction in regular services	Level 3 Complete inability to provide services due to staff/resource limitations
CORONARY			
STEMI	• Patients with **low** probability of COVID-19 – PPCI OR pharmacoinvasive as per current regional practice. • Patients with **moderate/High** probability or **COVID-19 +ve** - PPCI with Aerosol Level PPE and N95 mask OR pharmacoinvasive at discretion of the treating team. If pharmacoinvasive with successful fibrinolysis, consider emergent COVID-19 testing with planned PCI within 24hrs.	• Most patients now considered **Moderate/High** probability or **COVID-19 +ve** - pharmacoinvasive OR PPCI with Aerosol Level PPE and N95 mask at discretion of the treating team. If pharmacoinvasive with successful fibrinolysis, consider emergent COVID-19 testing with scheduled PCI within 24 hours.	Complete inability to provide PPCI. All patients will be treated with Thrombolysis as per regional protocols.
Cardiogenic Shock	• Patients with **low** probability of COVID-19 – Continue as per usual regional practice. • Patients with **moderate/High** probability or **COVID-19 +ve** - Consider an invasive approach with Aerosol Level PPE and N95 mask if age OR comorbidities do not preclude a reasonable likelihood of meaningful survival.	• Most patients now considered **Moderate/High** probability or **COVID-19 +ve** - Consider an invasive approach with Aerosol Level PPE and N95 mask if age OR comorbidities do not preclude a reasonable likelihood of meaningful survival.	Medical management of all cardiogenic shock cases.
Out of Hospital Cardiac Arrest (OHCA)	• Patients with **low** probability of COVID-19 – Continue as per usual regional practice. • Patients with **moderate/High** probability or **COVID-19 +ve** - Consider an invasive approach with Aerosol Level PPE and N95 mask if age OR comorbidities do not preclude a reasonable likelihood of meaningful survival.	• Most patients now considered **Moderate/High** probability or **COVID-19 +ve** - Consider an invasive approach with Aerosol Level PPE and N95 mask if age OR comorbidities do not preclude a reasonable likelihood of meaningful survival.	Medical management of all OHCA

NSTEMI (High Risk) (Refractory symptoms, hemodynamic instability, significant LV dysfunction, suspected LM or significant proximal epicardial disease, GRACE risk score >140)	• Patients with **low** probability of COVID-19 – Invasive approach as per current regional practice. • Patients with **moderate/High** probability of COVID-19 – Invasive approach with Aerosol Level PPE and N95 mask. • **COVID-19 +ve** – consider invasive strategy with Aerosol Level PPE and N95 mask	• Most patients now considered **Moderate/High** probability or **COVID-19 +ve** - Consider an invasive approach with Aerosol Level PPE and N95 mask.	Medical management of all ACS
Low/Medium Risk NSTEMI and UA	Invasive approach OR medical management for most patients. If medical management selected and failed, screen (symptom questionnaire AND swab) all patients for COVID-19 prior to invasive approach. If **COVID-19 +ve,** Aerosol Level PPE and N95 mask.	Medical management favored over an invasive approach for most patients. If medical management selected and failed, screen (symptom questionnaire AND swab) all patients for COVID-19 prior to invasive approach. If **COVID-19 +ve,** Aerosol Level PPE and N95 mask.	Medical management of all ACS
Type 2 MI (Consider COVID-19 myocarditis)	Investigations and treatment as per clinical judgement. Consider CT coronary angiography with Droplet Level PPE instead of an invasive approach.	Investigations and treatment as per clinical judgement. Consider CT coronary angiography with Droplet Level PPE instead of an invasive approach.	Medical management of all Type 2 MI
Outpatients	• Consider cardiac catheterization for outpatients who are clinically considered to be moderate to higher risk. • Screen (symptom questionnaire AND/OR swab) all patients for COVID-19. • All non-urgent/elective cases should be deferred for > 30 days.	• Consider cardiac catheterization for "urgent" outpatients only including those with symptoms AND non-invasive testing suggesting high risk for CV events in the short term. • Screen (symptom questionnaire AND/OR swab) all patients for COVID-19. • Others should be considered lower-risk and deferred for >30 days	Medical management for all Outpatients
CHIP	• Limited cases that would facilitate hospital discharge. • Screen (symptoms questionnaire AND swab) all patients for COVID-19.	Complete cessation of cases	Complete cessation of cases
CTO	Complete cessation of cases	Complete cessation of cases	Complete cessation of cases
STRUCTURAL HEART			
TAVI	High risk TAVI cases only with short expected LOS (low EF, valve-in-valve with severe AR, or recent hospitalization).	Limited inpatient cases that would facilitate hospital discharge	Complete cessation of cases
MitraClip	High risk cases with history of repeated HF hospitalizations or ER visits	Limited inpatient cases that would facilitate hospital discharge	Complete cessation of cases
Myocardial Biopsies	Limited cases in collaboration with Transplant Team	Limited cases in collaboration with Transplant Team	Complete cessation of cases
ASD/PFO	Complete cessation of cases	Complete cessation of cases	Complete cessation of cases
LAAC	Complete cessation of cases	Complete cessation of cases	Complete cessation of cases
Adult Congenital	Limited cases in collaboration with Adult Congenital Team	Complete cessation of cases	Complete cessation of cases
Pre-Solid Organ Transplant	Complete cessation of cases	Complete cessation of cases	Complete cessation of cases
Pulmonary HTN	Limited cases in collaboration with Pulmonary Hypertension Team	Complete cessation of cases	Complete cessation of cases

ESGE and ESGENA Position Statement on gastrointestinal endoscopy and the COVID-19 pandemic

https://www.thieme-connect.de/products/ejournals/abstract/10.1055/a-1155-6229
Journal: Endoscopy *Published Online: April 17, 2020*
Authors from: Italy, Germany, Belgium, UK, Poland, Croatia, Switzerland…

The **European Society of Gastrointestinal Endoscopy** (www.esge.com) and the **European Society of Gastroenterology and Endoscopy Nurses and Associates** (www.esgena.org) are joining forces to provide guidance during this pandemic to help assure the highest level of endoscopy care and protection against COVID-19 for both patients and endoscopy unit personnel. **Full recommendations are to be found on the link above.**

Timing of endoscopy during the COVID-19 pandemic according to medical indication

1. GI endoscopy units should strongly consider temporarily postponing elective, non-urgent endoscopy procedures, based upon availability of local human resources and local policies that may depend on regional/national pandemic rules/regulations.

2. The following list of GI endoscopy procedures should always be performed:
   - Acute upper/lower GI bleeding with hemodynamic instability
   - Capsule/enteroscopy for urgent/emergent bleeding
   - Anemia with hemodynamic instability
   - Foreign body in the esophagus and/or high-risk foreign body in the stomach
   - Obstructive jaundice
   - Acute ascending cholangitis

3. During the current COVID-19 pandemic, the following list of GI endoscopy procedures should be postponed with no need to reschedule before 12 weeks (low priority):
   - Surveillance for:
     - Barrett's Esophagus without dysplasia or Low-Grade Dysplasia or after endoscopic treatment
     - Gastric atrophy/Intestinal Metaplasia
     - Inflammatory Bowel Disease
     - Primary Sclerosing Cholangitis
   - Post-endoscopic resection (including immediate endoscopy after resection), surgical resection of cancer or post-polypectomy surveillance
   - Diagnosis/surveillance of Lynch syndrome and other hereditary syndromes
   - Diagnosis of Irritable Bowel Syndrome-like symptoms
   - Diagnosis of reflux disease, dyspepsia (no alarm symptoms)
   - Screening in high-risk patients for esophageal cancer, gastric cancer, colon cancer (primary screening endoscopy) or pancreatic cancer
   - Bariatric GI endoscopy procedures (e. g., intragastric balloons, endoscopic sleeve gastroplasty)

4. Each of the following GI endoscopy procedures warrants a case-by-case evaluation based on medical necessity. In general, therapeutic endoscopic procedures or those affecting prognosis (and whenever further therapies can be assured), namely those that are cancer-related or severely symptomatic, should be ranked as “high-priority” (either to be performed immediately or postponed within 12 weeks). All others “low priority” may be either performed immediately or postponed to beyond 12 weeks on a case-by-case assessment.

High-priority endoscopy procedures

- Endoscopic treatment of high-grade dysplasia (HGD) or early intra-mucosal cancer in the esophagus, stomach, or large colonic polyps at high-risk of submucosal invasion
- Malignant stricture stenting
- PEG/PEJ/NJ tube
- Upper GI fistula/leakage
- Dysphagia or dyspepsia with alarm symptoms present
- Upper GI bleeding without hemodynamic instability
- Rectal bleeding
- Colonoscopy for melena after negative upper-GI endoscopy
- Severe anemia with no hemodynamic instability
- Tissue acquisition needed for the initiation of systemic therapy/surgery
- Colonoscopy within organized FOBT + CRC screening program
- Foreign body in the stomach, low-risk
- Benign stricture requiring dilation/stenting
- Radiologic evidence of mass
- Lymph node EUS sampling
- Gallstone-related pancreatitis
- Pancreatic mass/stricture
- Biliary stricture dilation
- Pancreaticobiliary stent replacement for non-urgent indication
- Necrosectomy

Low-priority endoscopy procedures

- Endoscopic treatment of esophageal or gastric low-grade dysplasia (LGD)
- Duodenal polyp
- Ampullectomy
- Band ligation/non-emergency
- Iron deficiency anemia
- A pancreatic cyst (depending on risk features)
- Biliary stricture/no urgency (no cholangitis, no jaundice, etc.)
- Submucosal lesion EUS sampling
- Achalasia (POEM, balloon dilation)
- gFOBT/FIT + (outside of an organized regional/national screening program)

Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19

https://jitc.bmj.com/content/8/1/e000878

Journal: Journal for ImmunoTherapy of Cancer *Published Online: April 16, 2020*

Authors from: Italy, USA, the Netherlands, UK, Switzerland

It is becoming apparent that the 'ground-glass' infiltrative appearance seen on CT scans from patients with COVID-19 with pneumonitis is **reminiscent of imaging from patients with an immune checkpoint inhibitor (ICI)-induced pneumonitis**. Additionally, **elevated IL-6** is a hallmark inflammatory signature seen in the serum of patients with severe COVID-19 acute respiratory distress. Members of the **Society for Immunotherapy of Cancer (SITC)** have experience with the administration of immune-modulatory agents, which is why the cancer immunotherapy community is poised to contribute to the current fight against COVID-19. One possibility is to encourage the use of FDA approved IL-6 or IL-6R blocking antibodies like **tocilizumab**, **sarilumab, and siltuximab**. These agents could be used on easily and immediately available compassionate use protocols. **Tocilizumab also is already FDA approved to manage cytokine release syndrome (CRS)** in patients receiving chimeric antigen receptor T cell therapy. In addition, **tocilizumab has been shown to reduce toxicity in patients treated with ICIs** who were steroid-refractory and has been added to the ICI agents ipilimumab and nivolumab in an ongoing US phase II study to ameliorate immune-related toxicity. In **Castleman's disease**, a lymphoproliferative disorder caused by **Kaposi's Sarcoma Herpesvirus**, a pathogen that produces viral IL-6, **tocilizumab has been shown to reduce viral loads**. Tocilizumab is also being explored as a potential supportive care measure for the management of CRS in patients with cancer treated with a number of CD3-based bispecific molecules. Now, data from the frontlines of the pandemic indicates that the agent may offer lifesaving benefit for COVID-19 patients with respiratory distress. Emerging evidence suggests that high levels of CRP and IL-6 are observed in patients infected with COVID-19. Anecdotal experience on the use of tocilizumab at doses comparable to those used for the management of CRS from investigators in Italy and China has reported **rapid improvement in both intubated and non-intubated patients**. In these reports, the expeditious administration of anti-IL-6R therapy for patients in acute respiratory distress has been critical. A recent study protocol to evaluate the efficacy of tocilizumab in COVID-19-induced pneumonitis accrued over 300 patients worldwide in less than 24 hours. Additionally, Genentech will also provide 10 000 vials of tocilizumab to the US Strategic National Stockpile. Tocilizumab was also approved in China in March 2020, for the treatment of patients with COVID-19 with serious lung damage and elevated IL-6. In the USA, a trial of sarilumab in the COVID-19 setting is ongoing.

Anesthetic Management of Endovascular Treatment of Acute Ischemic Stroke During COVID-19 Pandemic: Consensus Statement from Society for Neuroscience in Anesthesiology & Critical Care (SNACC)_Endorsed by Society of Vascular & Interventional Neurology (SVIN), Society of NeuroInterventional Surgery (SNIS), Neurocritical Care Society (NCS), and European Society of Minimally Invasive Neurological Therapy (ESMINT)

https://journals.lww.com/jnsa/Abstract/9000/Anesthetic_Management_of_Endovascular_Treatment_of.99076.aspx

Journal: Neurosurgical Anesthesiology *Published Online: April 6, 2020*

Authors from: USA, Denmark, China, Canada

The pandemic of COVID-19 has unique implications for the anesthetic management of **endovascular therapy (EVT) for acute ischemic stroke (AIS)**. The Society for Neuroscience in Anesthesiology and Critical Care appointed a task force to provide timely, consensus-based expert recommendations using available evidence for its safe and effective anesthetic management. Recommendation on relevant general considerations, choice of anesthetic technique, anesthetic management of EVT in known or suspected COVID-19 positive patients (irrespective of anesthetic technique), general anesthesia (GA) / intubation, monitored anesthesia care (MAC), urgent conversion from MAC to GA, and within the hospital, transport could be found in the article full-text, as well as administrative recommendations, the anticipated impact of recommendations and their limitations.

Key Recommendations

General considerations

- Most patients presenting for EVT are expected to be “unknown” or “suspected” COVID-19 unless a rapid diagnostic test becomes available.
- Healthcare personnel should use airborne precautions for all EVT procedures, including N95 mask or PAPR, surgical cap, eye protection (goggles and face shield), full gown and double gloves.
- Delays in cerebral reperfusion should be minimized while ensuring essential COVID-19 precautions.
- Each institution should adapt these consensus recommendations to suit local workflow, while continuously monitoring AIS quality measures and patient outcomes.

Anesthetic technique

- The choice of anesthetic technique (GA versus MAC) should be individualized based on the patient’s neurological status and the risk of infection to healthcare personnel.
- In general, a lower threshold to use GA electively is recommended to avoid the need for urgent conversion from MAC to GA. However, GA is not recommended for all patients.
- The decision to intubate and use GA should be made early, based on multidisciplinary consensus accounting for local practices.
- The use of MAC is best suited for experienced centers with a low rate of conversion from MAC to GA.

- Irrespective of the anesthetic technique, hemodynamic stability, and oxygenation/ventilation should be optimized and maintained within the recommended range.

Intubation/extubation

- Intubation and extubation should ideally be performed in an airborne isolation room that has negative-pressure relative to the surrounding area.
- Intubation and extubation should be managed by the most experienced person available.

Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome

https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.047349
Journal: Circulation *Published Online: April 16, 2020*
Authors from: USA

A substantial minority of patients develop an **Acute COVID-19 Cardiovascular Syndrome (ACovCS)** that can manifest with a variety of clinical presentations, but often as an acute cardiac injury with **cardiomyopathy, ventricular arrhythmias and hemodynamic instability in the absence of obstructive coronary artery disease**. The etiology of this injury is uncertain but is suspected to be related to myocarditis, microvascular injury, systemic cytokine-mediated injury or stress-related cardiomyopathy. Although histologically unproven, SARS-CoV-2 has the potential to directly replicate within cardiomyocytes and pericytes leading to **viral myocarditis**. Systemically elevated cytokines are also known to be cardiotoxic and have the potential to result in profound myocardial injury. Prior experience with SARS-CoV has helped expedite the evaluation of several promising therapies including anti-viral agents, interleukin-6 inhibitors, and convalescent serum. Management of ACovCS should involve a **multidisciplinary team** including intensive care specialists, infectious disease specialists, and cardiologists. Priorities for managing ACovCS include balancing the goals of minimizing healthcare staff exposure for testing that will not change clinical management with early recognition of the syndrome at a time point where intervention may be most effective. A review of the available data on ACovCS **epidemiology, pathogenesis, diagnosis and treatment can be found in the article full-text.** Management summary is below:

There are no comprehensive expert recommendations and limited data from high-quality studies for the pharmacotherapy of ACovCS. Published experiences of COVID-19 associated myocardial injury is even more limited. Several experimental therapies attempting to l**imit SARS-CoV-2 replication** or the **immune response** have been proposed with multiple clinical trials currently underway. **Hydroxychloroquine** is a proposed treatment for COVID-19 on the basis of in vitro testing and a small open-label study with significant methodological limitations. The study authors concluded that hydroxychloroquine had a significant effect and led to rapid SARS-CoV-2 clearance. This conclusion appears overstated based upon the study design and results, and further studies of hydroxychloroquine, including its impact on ACovCS, are required. **Antiviral therapies** may have a role in the treatment of ACovCS. The use of **lopinavir/ritonavir** for severe COVID-19 was tested prospectively in 199 patients but unfortunately did not lead to a significant reduction in viral-load

or symptomatic improvement. **Remdesivir** has also been proposed. The subsequent investigation demonstrated a significant reduction of viral replication and symptoms in a mouse model and in vitro testing of a human cell line demonstrated markedly reduced SARS-CoV-2 activity. This led to compassionate use of remdesivir in COVID-19 patients, an effort which was eventually suspended with the initiation of currently **enrolling prospective clinical trials**. Both hydroxychloroquine and antiviral therapies may increase the risk for torsades de pointes via QTc prolongation. **Immunosuppression** for myocardial injury in ACovCS has been proposed as a treatment option; however, prior experiences with broad immunosuppression (corticosteroids and their combination with azathioprine or cyclosporine) for acute myocarditis historically have not been favorable. **Steroid use** in severe COVID-19 appears common in reports, and use is numerically higher in non-survivors, although that observation is likely confounded by indication for steroid initiation. Given the concern that steroids may prolong SARS-COV-2 viral persistence, **corticosteroid treatment should not be routine, but rather may be considered salvage therapy** with multidisciplinary input in select cases with hemodynamically unstable patients. As discussed above, cytokine activation appears to be a prominent feature of severe COVID-19 illness and ACovCS with marked elevations of IL-6 and other inflammatory markers. **Sarilumab, siltuximab, and tocilizumab** are IL-6 inhibitors that have potential utility in ACovCS and severe COVID-19. Tocilizumab is FDA-approved to manage cytokine release syndrome due to CAR-T cell therapy and is being investigated for pneumonitis induced by immune checkpoint inhibitors. Trials are underway, but in the interim, these agents can be considered for compassionate use on a case-by-case basis with multidisciplinary input.

Given the known association between myocarditis and auto-antibodies, **intravenous immunoglobulin (IVIG)** is theorized as a possible treatment for viral-associated myocarditis. However, in a well-conducted study in the pre-COVID era, IVIG did not improve LVEF or event-free survival at a 1-year follow-up. This study highlighted the lack of high-quality evidence for the routine use of IVIG to treat with idiopathic dilated cardiomyopathy or myocarditis, although the treatment appeared safe. Use of 1 g/kg IVIG daily for two days can be considered in select cases for hemodynamically unstable patients due to suspected fulminant myocarditis **as salvage therapy with multidisciplinary input**. However, it is important to note this is an extremely limited resource and should be reserved for patients with high clinical suspicion of cardiomyopathy due to myocarditis rather than cytokine storm or stress-induced cardiomyopathy. More focused antibody therapy using **convalescent plasma** from recovered COVID-19 patients has been approved recently by the FDA. A recent report described the treatment of 5 critically ill patients with convalescent plasma containing a SARS-CoV2– specific antibody (IgG) obtained from COVID-19 survivors. In this uncontrolled case series, they **reported an improved clinical status**, an observation that merits further clinical investigation.

If the myocardial injury is diagnosed clinically and the patient recovers from COVID-19, similar to historical expert opinion recommendations for non-COVID myocarditis, **abstinence from competitive sports or aerobic activity would be reasonable for a period of 3-6 months** until resolution of myocardial inflammation by cardiac MRI and/or normalization of troponin. The initiation of guideline-directed medical therapy (GDMT) may be considered for all patients with suspected myocarditis and reduced systolic function in accordance with the most recent

guidelines for the management of heart failure after a period of clinical stability and improvement such that individuals are preparing for discharge. The authors advise delaying GDMT until that later time point given that respiratory status can deteriorate rapidly earlier in the illness and require intubation leading to hypotension. Finally, in select cases with refractory shock or ventricular arrhythmias due to ACovCS, **mechanical support** can be considered. Case reports have described the successful rescue of patients with cardiogenic shock with the use of veno-arterial (VA), and veno-arterial-veno (V-A-V) ECMO. If cardiogenic shock is suspected secondary to myocarditis, expert consultation with an advanced heart failure team should be strongly considered.

The Imperfect Cytokine Storm: Severe COVID-19 With ARDS in Patient on Durable LVAD Support

https://pubmed.ncbi.nlm.nih.gov/32292915/?from_term=covid+19&from_sort=date&from_page=64&from_pos=1

Journal: JACC Case Reports *Published Online: April 8, 2020*
Authors from: USA

A 70-year-old male with a destination therapy **HeartMate 3** left ventricular assist device (LVAD) implanted in 2016 developed fever, flank pain, and hematuria. CT abdomen and pelvis incidentally found possible **atypical or viral pneumonia**. He was tested for COVID-19 but left against medical advice. In the ensuing days, he continued to have fevers, new-onset myalgias, diarrhea, and dyspnea. He returned to the ED and in acute hypoxic respiratory failure, requiring supplemental oxygen to maintain peripheral oxygen saturation ≥94%. His medical history includes **ischemic cardiomyopathy**, **stage 3 chronic kidney disease, and obesity**. His post-LVAD complications include gastrointestinal bleeding, ventricular tachycardia, and right ventricular (RV) dysfunction, but no infectious complications. RT-PCR for SAR-CoV-2 was positive at the initial ED visit. The patient was initiated on **hydroxychloroquine** for COVID-19 pneumonia while monitoring the QTc. He experienced ARDS necessitating **endotracheal intubation and ventilator support** with low tidal volume ARDSNet protocol. Despite aggressive supportive care, "**cytokine storm**" ensued with **MODS** as evidenced. Two successive doses of intravenous IL-6R receptor antagonist tocilizumab were administered. Though clinical improvement was observed after initial tocilizumab therapy, he developed worsening shock, refractory hypoxemia, and suffered PEA arrest with successful ROSC.

Patients with heart failure on LVAD support compose a unique population at risk for COVID-19. The authors present such a patient who developed COVID-19 complicated by "cytokine storm" with severe ARDS and myocardial injury and illustrates clinical considerations that arose during his clinical course. The host response to COVID-19 is often localized in the lung parenchyma, but a surge in pro-inflammatory cytokines can occur. Known as a "cytokine storm," this phenomenon is described in graft-versus-host disease and viral illnesses including influenza and COVID-19. The complication is MODS including ARDS and cardiac manifestation. Serial evaluation of inflammatory markers should be done to risk stratify the critically ill from patients with milder disease**. Inflammation and myocardial injury from COVID-19 must be differentiated from baseline inflammation often encountered during LVAD support**. In the above LVAD patient, several biomarkers including LDH, absolute lymphocyte count, brain natriuretic peptide (BNP) and troponin

have previously been obtained. Experience in China has shown that COVID-19 could adversely affect the cardiovascular system. The patient had **evidence of myocardial injury** as part of this COVID-19 presentation. The myocardial effect is likely a multifactorial process due to the "bystander effect" from MODS, viral myocarditis, and activation of adverse remodeling mechanisms. Furthermore, PEA arrest in the patient may be a sequela of such cardiac damage, and as such, **LVAD support may have been instrumental in his resuscitation.** In this context, the management of patients on LVAD support with COVID-19 is difficult as there is a complex interplay between volume status and biventricular dynamics. Such patients should be closely monitored for **RV failure and need for inotropic support** and **LVAD speed drops or suction events, low flow, or pulsatility index** (PI) events due to vasoplegia associated with infection. Patients on LVAD support are particularly vulnerable to **infectious complications** due to the inherent presence of hardware and driveline exposure as well as the fact that prolonged support has been associated with immune dysregulation. Finally, **prone ventilation** is beneficial in severe ARDS and may prevent the need to escalate to ECMO.

Nonetheless, it may be prohibitive in heart failure patients on LVAD support. Prone positioning could result in complications such as **compression of outflow graft and driveline, impaired venous return from increased thoracic pressure, hardware malpositioning, and worsening RV hemodynamics**. There may be additional anxiety for staff caring for COVID-19 patients, not otherwise familiar with LVAD management. Due to these considerations, prone ventilation was not performed in the aforementioned patient.

Prognostic Value of NT-proBNP in Patients With Severe COVID-19

https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-020-01352-w
Journal: Respiratory Research *Published Online: April 15, 2020*
Authors from: China

Cardiac injury is a common condition among hospitalized patients with COVID-19. However, whether NT-proBNP predicted the outcome of severe COVID-19 patients was unknown. 102 consecutive patients with severe COVID-19 were screened with **54 eligible patients included** in the analysis. The primary outcome was in-hospital death defined as the case fatality rate. The data were **obtained from medical records**. The best **cut-off value of NT-proBNP for predicting in-hospital death was 88.64 pg/mL with the sensitivity of 100% and the specificity of 66.67%**. Patients with high NT-proBNP values (> 88.64 pg/mL) had a significantly increased risk of death during the follow-up compared with those with low values (≤88.64 pg/mL). After adjustment for potential risk factors, NT-proBNP was independently correlated with in-hospital death.

Neprilysin inhibitor–angiotensin II receptor blocker combination (sacubitril/valsartan): rationale for adoption in SARS-CoV-2 patients

https://academic.oup.com/ehjcvp/article/doi/10.1093/ehjcvp/pvaa028/5819438
Journal: European Heart Journal - Cardiovascular Pharmacotherapy
Published Online: April 13, 2020
Authors from: Italy

The authors describe a possible, alternative approach for treating COVID-19. A recent hypothesis suggests that the **inhibition of the angiotensin 1 receptor (AT_1R)** may provide benefits to COVID-19 patients. This hypothesis is based on the observation that the SARS-CoV-2 virus uses angiotensin-converting enzyme 2 **(ACE2) as a receptor to bind the virus to the bronchial cell** membrane. The enzymes ACE and ACE2 belong to the same peptidase family but have two very different physiological functions. ACE cleaves angiotensin I to generate angiotensin II (Ang II), which binds to and activates AT_1R, and thus promotes vasoconstriction. ACE2 cleaves Ang II and generates angiotensin 1-7, a powerful vasodilator acting through Mas receptors. AT_1R antagonists are widely used in hypertensive patients but they increase the ACE2 cardiac expression in rats and the urinary concentration of ACE2.
It has been demonstrated that the **binding of virus to ACE2 leads to ACE2 down-regulation**, which increases the production of Ang II but reduces angiotensin 1-7. This contributes to increased **AT_1-mediated pulmonary vascular permeability**, thereby mediating increased lung pathology. Therefore, **higher ACE2 expression following chronic therapy with sartans may protect COVID-19 patients from acute lung injury rather than increasing the risk for SARS-CoV-2.** Two complementary mechanisms may explain such a hypothesis: sartans will continue to block excessive angiotensin-mediated AT_1R activation due to the viral infection, and, in parallel, they will up-regulate ACE2, thus increasing angiotensin 1-7 production.
In such a setting, the role of **neprilysin (NEP) and its inhibitor sacubitril** should also be revised. Recently, Zhang et al. demonstrated that sacubitril/valsartan **reduced the concentration of pro-inflammatory cytokines** and neutrophil count, while **increasing lymphocyte count more than valsartan alone or placebo.** This finding might be related to the increase in plasma levels of atrial/brain/C-type natriuretic peptide, Ang I/II, substance P, bradykikin, and endothelin secondary to neprilisin inibition by sacubitril. The authors have recently shown that **early sacubitril/valsartan administration reduces hsCRP and increases lymphocyte count in patients with acute heart failure**. These pieces of evidence support the biological plausibility of early administration of sacubitril/valsartan in COVID-19 patients, in order to maximize the anti-inflammatory effects of sacubitril and contain the effect of Ang I on the lungs.

Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19

https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.120.317134
Journal: Circulation Research *Published Online: April 17, 2020*
Authors from: China, USA, UK, Canada

The use of ACEIs and ARBs is a major concern for clinicians treating COVID-19 patients with hypertension. This **retrospective, multi-center** study included **1128 adult patients** with hypertension diagnosed with COVID-19 in China, including **188 taking ACEI/ARB** (median age 64; 53.2% men) and 940 without using ACEI/ARB (median age 64; 53.5% men). **The unadjusted mortality rate was lower in the ACEI/ARB group** (3.7% vs. 9.8%; P = 0.01). In the mixed-effect Cox model treating site as a random effect, after adjusting for age, gender, comorbidities, and in-hospital medications, the detected **risk for all-cause mortality was lower in the ACEI/ARB group** (adjusted HR, 0.42; 95% CI, 0.19-0.92; P =0.03). In a **propensity score-matched** analysis followed by adjusting imbalanced variables in mixed-effect Cox model, the results **consistently demonstrated a lower risk of COVID-19 mortality** in patients who received ACEI/ARB versus those who did not receive ACEI/ARB (adjusted HR, 0.37; 95% CI, 0.15-0.89; P = 0.03). Further subgroup propensity score-matched analysis indicated that, **compared to the use of other antihypertensive drugs, ACEI/ARB was also associated with decreased mortality** (adjusted HR, 0.30; 95%CI, 0.12-0.70; P = 0.01) in COVID-19 patients with hypertension. While study interpretation needs to consider the potential for residual confounders, it is unlikely that in-hospital use of ACEI/ARB was associated with increased mortality risk.

High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion

https://erj.ersjournals.com/content/early/2020/04/08/13993003.00892-2020
Journal: European Respiratory Journal *Published Online: April 16, 2020*
Authors from: USA

The primary strategy for COVID-19 patients is supportive care, including oxygen therapy for hypoxemic patients, in which **high-flow nasal cannula (HFNC)** was reported as effective in improving oxygenation. Among patients with acute hypoxemic respiratory failure, HFNC was proven to avoid intubation compared to conventional oxygen devices. However, there is an important **concern that HFNC may increase bio-aerosol dispersion in the environment** due to the high gas flow used. The increased dispersion might favor the transmission of infection. There appears to be uncertainty and a trend to avoid HFNC among COVID-19 patients in the western world, thus **increasing early intubation rates** and potentially associated harms such as sedation and prolonged intensive care unit stay but also intubation procedures per se which represent a high-risk situation for viral exposure. Early intubation increases the demand for ventilators, contributing to the critical shortage reported worldwide. Avoiding or delaying invasive mechanical ventilation could substantially reduce immediate demand for ventilators. Thus, the authors aimed

to discuss the **scientific evidence supporting the risk of HFNC induced bio-aerosol dispersion** in the COVID-19 context.

According to a **manikin model** by Hui et al. using smoke dispersion, it appears that when using HFNC, dispersion is greater at 60 L/min than at 10 L/min. Interestingly, using the same study method and similar breathing patterns, the exhaled smoke dispersion distance from the manikin with HFNC at 60 L/min was similar to the one observed with a simple oxygen mask at 15 L/min and was even smaller than with other oxygenation devices, particularly non-rebreathing and Venturi masks. However, the particle size of smoke (<1 μm), only represents a small fraction of the mass of bio-aerosol generated by patients naturally. Leung and colleagues reported a **randomized controlled trial** comparing the utilization of HFNC at 60 L/min with an oxygen mask at 8.6±2.2 L/min in 19 ICU patients with bacterial pneumonia on the environmental contamination. The patient's room air was sampled and settle plates were placed at 0.4 m and 1.5 m from patients. **No significant difference in bacterial counts was reported**. In-vitro and clinical studies demonstrated that **placing a simple surgical protection mask on patients significantly reduces dispersion distance** and virus-infected bio-aerosol 20 cm away from patients while coughing. Such a surgical mask **can be worn by a patient oxygenated through a nasal cannula (standard nasal cannula or HFNC)** but not when using simple, non-rebreathing or Venturi oxygen masks.
In conclusion, massive numbers of clinicians were infected during the COVID-19 outbreak, which raised concerns about implementing aerosol-generating procedures, consequently, there appears to be a trend to avoid HFNC. The scientific evidence of generation and dispersion of bio-aerosols via HFNC summarised above **show a similar risk to standard oxygen masks. HFNC with a surgical mask on a patient's face** above could thus be a reasonable practice that may benefit hypoxemic COVID-19 patients and avoid intubation. Clinicians should consider moving away from the dogma refraining the use of HFNC among COVID-19 patients.

Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19

https://www.journalofinfection.com/article/S0163-4453(20)30188-2/pdf
Journal: Journal of Infection *Published Online: April 10, 2020*
Authors from: China

In this study, the authors compared the antiviral effects and safety of **lopinavir/ritonavir** and **arbidol** in patients with COVID-19. **Fifty patients** with laboratory-confirmed COVID-19 were divided into two groups: the lopinavir/ritonavir group (n=34) and the arbidol group (n=16). Lopinavir/ritonavir group received 400 mg/100mg of Lopinavir/ritonavir, twice a day for a week, while the arbidol group was given 0.2 g arbidol, three times a day. Data from these patients were **retrospectively analyzed**. The cycle threshold values of open reading frame 1ab and nucleocapsid genes by RTPCR assay were monitored during antiviral therapy. None of the patients developed severe pneumonia or ARDS. There was no difference in fever duration between the two groups (P=0.61). **On day 14 after the admission, no viral load was detected in the arbidol group, but the viral load was found in 15 (44.1%) patients treated with lopinavir/ritonavir.** Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group

(P<0.01). Moreover, no apparent side effects were found in both groups. In conclusion, our data indicate that arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19. More data are needed.

Clinical and Microbiological Effect of a Combination of Hydroxychloroquine and Azithromycin in 80 COVID-19 Patients With at Least a Six-Day Follow Up: A Pilot Observational Study

https://www.sciencedirect.com/science/article/pii/S1477893920301319?via%3Dihub
Journal: Travel Medicine and Infectious Diseases *Published Online: April 11, 2020*
Authors from: France

The authors conducted an **uncontrolled, non-comparative, observational study** in a cohort of **80 inpatients** with COVID-19 with relatively **mild disease.** The subjects were treated with a combination of **hydroxychloroquine and azithromycin** over a period of at least three days, with three main objectives: clinical outcome, contagiousness as assessed by PCR and culture, and length of stay in infectious disease unit (IDU). All patients improved clinically except for one 86 year-old patient who died, and one 74-year-old patient who was still in intensive care in the time of reporting. A **rapid fall of nasopharyngeal viral load** was noted, with 83% negative on Day 7, and 93% at Day 8. Virus cultures from patient respiratory samples were negative in 97.5% of patients on Day 5. Consequently, patients were able to be rapidly discharged from IDU with a **mean length of stay of five days**. The authors believe there is an urgency to evaluate the effectiveness of this potentially-life saving therapeutic strategy at a larger scale, both to treat and cure patients **at an early stage before irreversible severe respiratory complications** take place and to decrease the duration of infectiousness in order to avoid the spread of the disease. Furthermore, the cost of the treatment is negligible.

Virological and Clinical Cure in Covid-19 Patients Treated With Hydroxychloroquine: A Systematic Review and Meta-Analysis

https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25898
Journal: Journal of Medical Virology *Published Online: April 16, 2020*
Authors from: India

Following the demonstration of the efficacy of hydroxychloroquine against SARS-CoV-2 in-vitro, many trials started to evaluate its efficacy in clinical settings. However, no systematic review and meta-analysis have addressed the issue of **the safety and efficacy of hydroxychloroquine** (HCQ) in COVID-19. The authors, therefore, conducted a systematic review and metaanalysis with the objectives of evaluation of safety and efficacy of HCQ alone or in combination in terms of "time to clinical cure", "virological cure", "death or clinical worsening of disease", "radiological progression" and safety. **Seven studies (n=1358)** were included in the systematic review. In terms of clinical cure, two studies reported possible benefit in "time to body temperature normalization" and one study reported less "cough days" in the HCQ arm. Treatment with HCQ resulted in a lower number

of cases showing the radiological progression of lung disease (OR 0.31, 0.11-0.9). No difference was observed in virological cure (OR 2.37, 0.13-44.53), death or clinical worsening of disease (OR 1.37, 1.37-21.97) and safety (OR 2.19, 0.59-8.18), when compared to the control/conventional treatment. Five studies reported either the safety or efficacy of HCQ + Azithromycin. Although the drug seems safe and effective, more data is required for a definitive conclusion. **HCQ seems to be promising in terms of a lower number of cases with radiological progression with a comparable safety profile to control/conventional treatment.**

Systematic Review of the Efficacy and Safety of Antiretroviral Drugs Against SARS, MERS or COVID-19: Initial Assessment

https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25489
Journal: Journal of International AIDS Society *Published Online: April, 2020*
Authors from: Switzerland

The authors systematically reviewed the clinical outcomes of using **antiretroviral drugs** for the prevention and treatment of coronaviruses, as well as planned clinical trials. From an initial screen of 433 titles, **two randomized trials and 24 observational studies** provided clinical outcome data on the use of antiretroviral drugs; most studies reported outcomes using **lopinavir/ritonavir (LPV/r)** as treatment. Of the 21 observational studies reporting treatment outcomes, there were three studies on SARS, six studies on MERS and **12 studies on COVID-19**. In one **randomized trial**, 99 patients with severe COVID-19 illness were randomized to receive LPV/r (400/100 mg twice a day) and 100 patients to the standard of care for 14 days: **LPV/r was not associated with a statistically significant difference in time to clinical improvement**, although LPV/r given within 12 days of symptoms was associated with shorter time to clinical improvement; 28-day mortality was numerically lower in the LPV/r group (14/99) compared to the control group (25/100), but this difference was not statistically significant. The **second trial found no benefit**. The certainty of the evidence for the randomized trials was low. In the observational studies**, 3 out of 361 patients who received LPV/r died**; the certainty of the evidence was very low. Three studies reported a possible protective effect of LPV/r as post-exposure prophylaxis. Again, the certainty of the evidence was very low due to uncertainty due to the limited sample size. On the basis of the available evidence**, it is uncertain whether LPV/r and other antiretrovirals improve clinical outcomes or prevent infection among patients at high risk of acquiring COVID-19.**

The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients

https://ashpublications.org/blood/article/doi/10.1182/blood.2020006288/454437/The-BTKinhibitor-ibrutinib-may-protect-against

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Authors from: USA

The BTK-inhibitor ibrutinib is used to treat indolent B-cell malignancies and chronic graft versus host disease. The potential for ibrutinib to abrogate pulmonary inflammatory cytokines, lung injury and death was previously demonstrated in a highly relevant, lethal flu animal model. The authors care for approximately 300 Waldenstrom's Macroglobulinemia (WM) patients per year who are on a BTK-inhibitor. They **identified 6 patients receiving ibrutinib who were diagnosed with COVID-19**. Their median age was 66 years and median time on ibrutinib was 52 months. Their median time with COVID-19 related symptoms prior to diagnostic testing was 5 days. All 6 patients experienced cough and fever as prodromal symptoms. **The 5 patients on ibrutinib at 420 mg/day experienced no dyspnea and required no hospitalization**. Their course was marked by steady improvement, and resolution or near resolution of COVID-19 related symptoms in all five of these patients during the follow-up period. **The patient on reduced dose ibrutinib (140 mg/day due to arthralgias) experienced progressive dyspnea and hypoxia** prompting hospitalization. Chest CT showed bilateral ground-glass opacities and pleural effusion on admission prompting a hold on ibrutinib during which his hypoxia acutely worsened necessitating supplemental oxygen use. Hydroxychloroquine (HCQ) and azithromycin were administered but stopped due to wide QRS complex tachyarrhythmia. Hypoxia worsened and fever persisted. **Ibrutinib was restarted at 140 mg/day and tocilizumab 400 mg was co-administered on hospital day 5 with improved oxygenation and decreased CRP levels (83 to 9 mg/L).** Intravenous immunoglobulin was also given on hospital days 6-10. On day 10 of hospitalization, the patient experienced worsening hypoxia accompanied by increased CRP (28 mg/L) and required mechanical ventilation. Given the lack of hypoxia in the other COVID-19 infected WM patients on full dose ibrutinib, **ibrutinib was increased to 420 mg/day** on days 11 and day 12. A **rapid improvement in oxygenation followed**, and the patient was successfully extubated late on day 12 and maintained oxygen saturation of 94-96% on 3 liters/min supplemental oxygen by nasal cannula. On day 14, oxygen saturation was 95% on room air, repeat CRP level was 6 mg/L, and he was discharged home off supplemental oxygen on 420 mg/day of ibrutinib. Seven days later he continues to do well, without fever, cough or dyspnea at rest. **He remains on ibrutinib at 420 mg/day and tolerating therapy well**.

Based on previous literature, the rationale exists that an **exaggerated cytokine release syndrome** triggered by ATII cells in the lungs and resident macrophages by SARS-CoV-2 may underlie pulmonary injury associated with COVID-19. Ibrutinib and possibly other BTK-inhibitors may provide protection against lung injury, and even improve pulmonary function in hypoxic patients with COVID-19 as the authors observed in this series of WM patients on ibrutinib. These findings should be considered **hypothesis-generating and preliminary in nature**. Patients on ibrutinib, and possibly other BTK-inhibitors may well benefit from a continuation of their therapy despite the diagnosis of COVID-19. It will be important to further validate these findings in other patient populations on BTK-inhibitors, including CLL patients. Clinical trials examining the benefit of BTK-inhibitors are being initiated by the authors and others in COVID-19 patients in pulmonary distress,

and the outcome of these prospective, randomized studies will be needed to confirm these preliminary observations.

The role of afferent pulmonary innervation in ARDS associated with COVID-19 and potential use of resiniferatoxin to improve prognosis of patients in advanced disease state: A review

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The authors hypothesize that the morbidity, severity of the disease, and underlying physiological events leading to mortality are **closely linked to the TRPV1 expressing neuronal system (afferent/efferent neurons) in the lungs**. TRPV1 expressing cells are responsible for pain transmission, inflammation and immunomodulation throughout the entire pulmonary system and are modulating the processes associated with localized cytokine release (storm) and overall rapid disease progression. They suggest that therapeutic approaches targeting TRPV1 containing nerve fibers in the lungs will modulate the inflammatory and immune signal activity, leading to reduced mortality and better overall outcomes. They also propose to further explore the use of **resiniferatoxin (RTX), an ultra-potent TRPV1 agonist** currently in clinical trials for cancer and osteoarthritis pain, as a possible ablating agent of TRPV1 positive pulmonary pathways in patients with advanced COVID-19 disease.

Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19

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Authors from: China

Intravenous immunoglobulin (IVIG) has been clinically used as an adjunctive drug in the treatment of severe pneumonia caused by influenza, but its use in COVID-19 pneumonia is controversial. In this **retrospective study**, the authors reviewed **58 cases** of severe or critical COVID-19 in Wuhan. All patients received oxygen therapy and **Arbidol antiviral** treatment and were empirically treated with the first line moxifloxacin and LMWH if indicated. All patients received IVIG, which was initiated **when the absolute lymphocyte count fell to < 0.5× 109/L**. If the absolute number of lymphocytes was still low five days later, the authors used Thymosin to boost immune function. Patients in the critical condition received intravenous administration of small doses of glucocorticoids (1-2 mg/kg) for 5-7 days depending on their condition. Patients were **divided according to the use of intravenous immunoglobulin within 48 h after admission or later.**
The cumulative dose of IVIG over 28 days was significantly higher in the >48 h group. After admission, patients in the >48 h group had an average delay of 1 day in using IVIG for the first time than patients in the ≤48 h group. Of all enrolled patients, 18.96% required mechanical ventilation

and 3.45% HFNO. **A total of 23 of the 58 patients died within 28 days** of admission, 7 in the ≤48 h group and 16 in the > 48 h group. **There was a statistically significant difference in 28-day mortality** between the two groups (p=0.009). The length of stay in the hospital of the ≤48 h group was significantly shorter than in the > 48 h group (11.50 ±1.030 vs 16.96 ±1.620 days, p=0.0055), and so was the length of stay in the ICU. Patients in the early initiation group **required mechanical ventilation less often** (6.67% vs 32.14%, p=0.016. The results will need confirmation in a large randomized clinical trial.

The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis

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Although corticosteroids were widely used during outbreaks of SARS and MERS, their efficacy remained highly controversial. The authors aimed to further evaluate the influence of corticosteroids on patients with COVID-19. A total of **5270 patients from 15 studies were included in this meta-analysis.** The result indicated that critical patients were more likely to require corticosteroids therapy (risk ratio [RR] = 1.56, 95% confidence interval [CI] = 1.28-1.90, P<0.001). However, corticosteroid treatment was associated with higher mortality (RR = 2.11, 95%CI = 1.13-3.94, P = 0.019), longer length of stay (weighted mean difference [WMD] = 6.31, 95%CI = 5.26–7.37, P<0.001), a higher rate of bacterial infection (RR = 2.08, 95%CI = 1.54–2.81, P<0.001), and hypokalemia (RR = 2.21, 95%CI = 1.07–4.55, P = 0.032) but not hyperglycemia (RR = 1.37, 95%CI=0.68–2.76, P = 0.376) or hypocalcemia (RR = 1.35, 95%CI = 0.77–2.37, P = 0.302). Patients with severe conditions were more likely to require corticosteroids. Corticosteroids could lead to higher mortality, longer LOS, a higher rate of bacterial infection and hypokalemia. Therefore, **the corticosteroid should be used with caution** in the treatment of COVID-19 patients: corticosteroids are not recommended for patients with mild conditions, and moderate corticosteroids can be used in patients with severe conditions to suppress the immune response and reduce symptoms. Nevertheless, **more multicenter clinical trials are needed** to further verify this conclusion.