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EVMS CRITICAL CARE
COVID-19 MANAGEMENT PROTOCOL

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URGENT! Please circulate as widely as possible. It is crucial that every pulmonologist, every critical care doctor and nurse, every hospital administrator, every public health official receive this information immediately.

This is our recommended approach to COVID-19 based on the best (and most recent) available literature including the Shanghai Management Guideline for COVID and recent information from Italy. We should not re-invent the wheel, but learn from the experience of others around the world. It is important to recognize that COVID-19 does not cause "typical ARDS"... this disease must be treated differently and it is likely that mechanical ventilation may be exacerbating this situation by causing ventilator induced lung injury (i.e. the ventilator may cause the disease we think we are treating). Patients suffer from oxygenation failure and not lung failure. Furthermore, this is predominantly an immune and clotting disorder and not a lung disease.

This is a very dynamic situation; therefore, we will be updating the guideline as new information emerges. Please check on the EVMS website for updated versions of this protocol.

EVMS COVID website: https://www.evms.edu/covid-19/medical_information_resources/
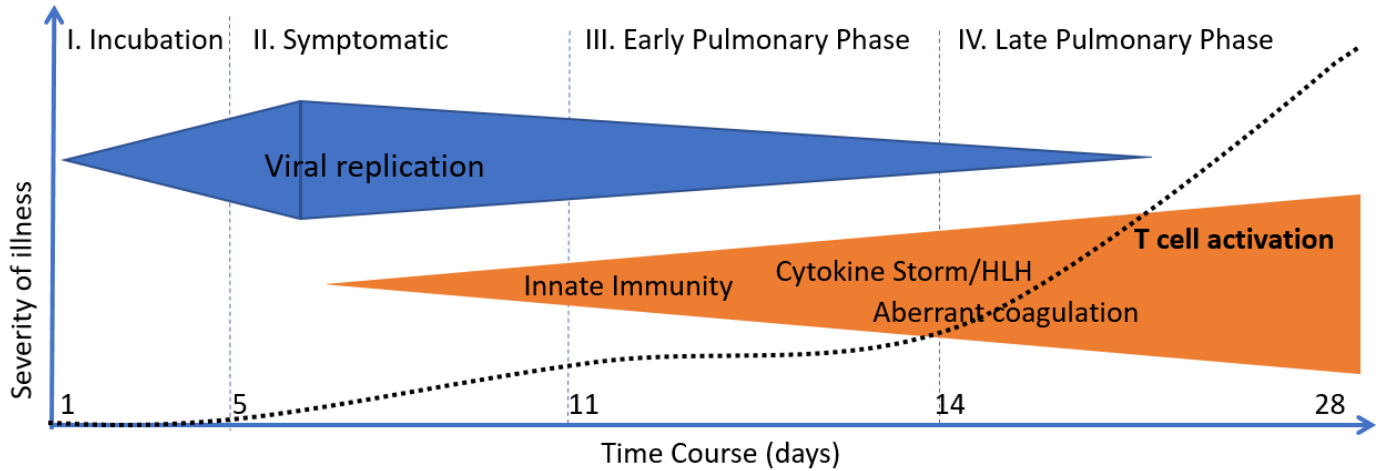Short url: evms.edu/covidcare

"If what you are doing ain't working, change what you are doing"

Dr AB (NYC).

"We have zero success for patients who were intubated. Our thinking is changing to postpone intubation to as long as possible, to prevent mechanical injury from the ventilator. These patients tolerate arterial hypoxia surprisingly well. Natural course seems to be the best."

The course of COVID-19 and General Approach to treatment is illustrated below.

Ground-glass infiltrates	+		++	+++	++++
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea		SOB – Mild hypoxia ≤4 L/min N/C & aSat < 95%	Progressive hypoxia	
Treatment approach	Antiviral Rx		Anti-inflammatory: Immune Suppressive Rx		
Potential therapies			MP 40mg/day	Methylprednisolone 80mg/day	
			Enoxaparin 40-60 mg/day	Enoxaparin 1mg/kg s/c q 12	
	? Hydroxychloroquine 400/200 5 days				
	Vitamin C 500mg PO BID			Vitamin C 3g Iv q 6	

Prophylaxis

While there is very limited data (and none specific for COVID-19), the following "cocktail" may have a role in the prevention/mitigation of COVID-19 disease. While there is no high level evidence that this cocktail is effective; it is cheap, safe and widely available.

- Vitamin C 500 mg BID and Quercetin 250-500 mg BID
- Zinc 75-100 mg/day (acetate, gluconate or picolinate). Zinc lozenges are preferred. After 1-2 months, reduce the dose to 30-50 mg/day.
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 1-2 mg at night
- Vitamin D3 1000-4000 u/day (optimal dose unknown).

Mildly Symptomatic patients (at home):

- Vitamin C 500mg BID and Quercetin 250-500 mg BID (if available)
- Zinc 75-100 mg/day
- Melatonin 6-12 mg at night (the optimal dose is unknown)
- Vitamin D3 1000-4000 u/day
- *Optional:* Hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days

Mildly Symptomatic patients (on floor):

- Vitamin C 500mg BID and Quercetin 250-500 mg BID (if available)
- Zinc 75-100 mg/day
- Melatonin 6-12 mg at night (the optimal dose is unknown)
- Vitamin D3 1000-4000 u/day
- Methylprednisolone 40 mg daily
- Enoxaparin 40-60 mg daily
- *Optional:* Hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days
- N/C 2L /min if required (max 4 L/min; consider early t/f to ICU for escalation of care).
- Avoid Nebulization and Respiratory treatments. Use "Spinhaler" or MDI and spacer if required.
- Avoid non-invasive ventilation
- T/f EARLY to the ICU for increasing respiratory signs/symptoms.

Respiratory symptoms (SOB; hypoxia- requiring N/C ≥ 4 L min: admit to ICU):

Essential Treatment (dampening the STORM)

1. Methylprednisolone 80 mg loading dose then 40mg q 12 hourly for at least 7 days and until transferred out of ICU. Alterative approach: Hydrocortisone 50 mg q 6 hourly.
2. Ascorbic acid (Vitamin C) 3g IV q 6 hourly for at least 7 days and/or until transferred out of ICU. Note caution with POC glucose testing (see below).
3. Full anticoagulation: Unless contraindicated we suggest FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e 1 mg kg s/c q 12 hourly (dose adjust with Cr Cl < 30mls/min). Heparin is suggested with CrCl < 15 ml/min. Alternative approach: Half-dose rTPA: 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation. On transfer to floor, consider reducing enoxaparin to 40-60 mg /day.

    Note: Early termination of ascorbic acid and corticosteroids will likely result in a rebound effect (see graphic below).

Additional Treatment Components (the Full Monty)

4. Melatonin 6-12 mg at night (the optimal dose is unknown).
5. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.4 mmol/l. Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc).
6. *Optional:* Azithromycin 500 mg day 1 then 250 mg for 4 days (has immunomodulating properties including downregulating IL-6; in addition Rx of concomitant bacterial pneumonia).
7. *Optional:* Atorvastatin 40-80 mg/day. Of theoretical but unproven benefit. Statins have been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial and antiviral effects. In addition, statins decrease expression of PAI-1
8. Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture (no bronchoscopy).
    Co-infection with other viruses appears to be uncommon, however a full respiratory viral panel is still recommended. Superadded bacterial infection is reported to be uncommon (however, this may not be correct).
9. Maintain *EUVOLEMIA* (this is not non-cardiogenic pulmonary edema). Due to the prolonged "symptomatic phase" with flu-like symptoms (6-8 days) patients may be volume depleted. Cautious rehydration with 500 ml boluses of Lactate Ringers may be warranted, ideally guided by non-invasive hemodynamic monitoring. Diuretics should be avoided unless the patient has obvious intravascular volume overload.
10. Early norepinephrine for hypotension. While the angiotenin II agonist Giapreza ™ has a limited role in septic shock, this drug may uniquely be beneficial in patients with COVID-19 (downregulates ACE-2).

11. Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible***

- Accept "permissive hypoxemia" (keep O2 Saturation > 84%)
- N/C 1-6 L/min
- High Flow Nasal canula (HFNC) up to 60-80 L/min
- Trial of inhaled Flolan (epoprostenol)
- Attempt proning (cooperative repositioning-proning; see Figure)
- Intubation … by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
- Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cmH$_2$O.
- Moderate sedation to prevent self-extubation
- Trial of inhaled Flolan (epoprostenol)
- Prone positioning
- ?? ECMO < 60 yrs. and no severe commodities/organ failure.

There is widespread concern that using HFNC could increase the risk of viral transmission. There is however, no evidence to support this fear. HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

A group of patients with COVID-19 deteriorates very rapidly (see graphic below). Intubation and mechanical ventilation may be required in these patients.

12. **Treatment of secondary HLH** (increasing Ferritin, CRP and transaminases)

- "High dose corticosteroids." Methylprednisolone 120 mg q 8 hourly for at least 3 days, then wean accruing to CRP, IL-6, Ferritin etc.
- Tocilizumab (IL-6 inhibitor) as per dosing guideline.
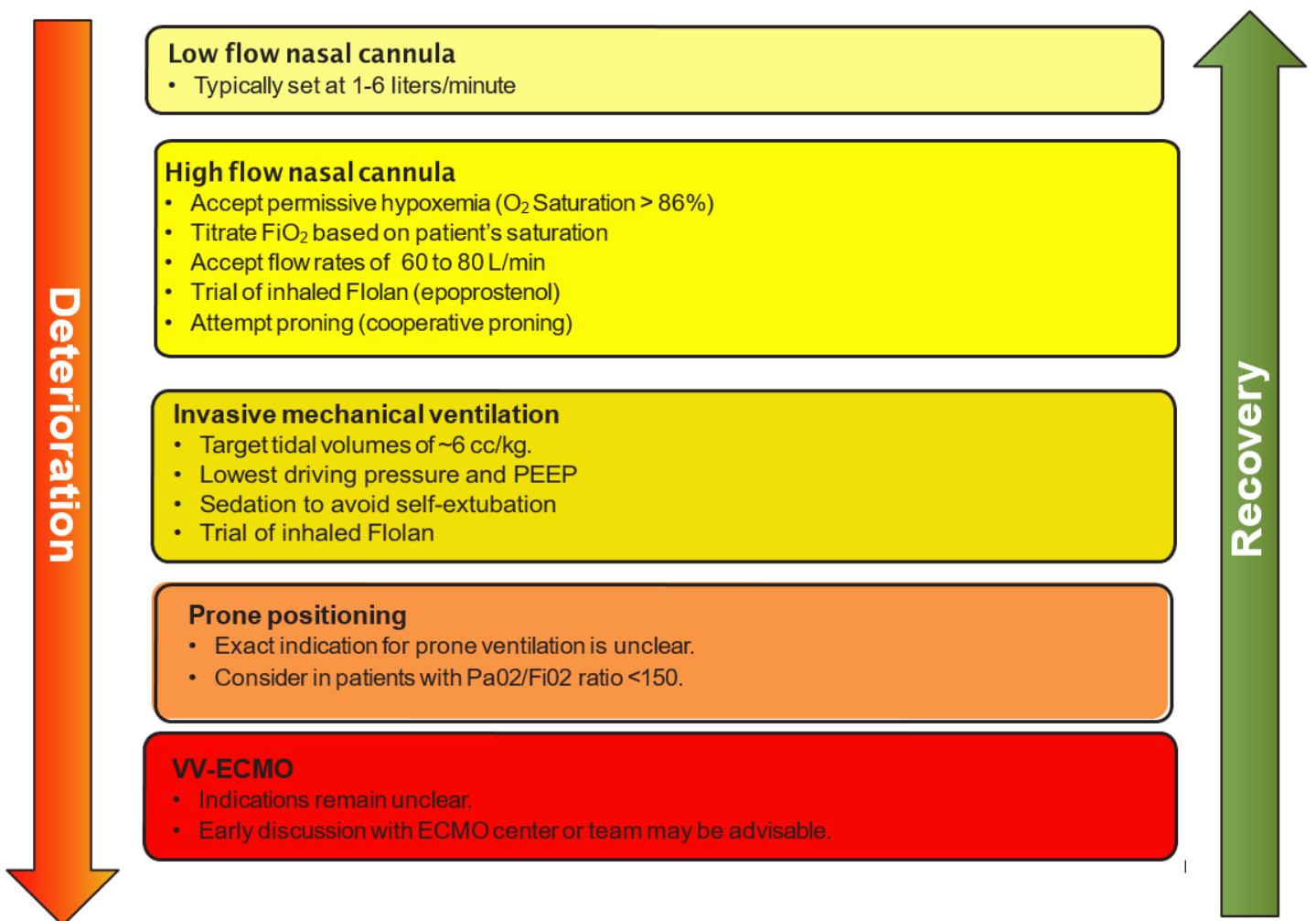- Consider plasma exchange

13. Monitoring
- Daily: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer, Mg, CRP and Ferritin are good biomarkers and track disease severity. Thromboelastogram (TEG) on admission and repeated as indicated.
- In patients receiving IV vitamin C, the Accu-Chek™ POC glucose monitor will result in spuriously high blood glucose values. Therefore, a laboratory glucose is recommended to confirm the blood glucose levels.
- Monitor QTc interval if using chloroquine/hydrochloroquine and azithromycin and monitor Mg++ (torsades is uncommon in monitored ICU patients)
- No routine CT scans, follow CXR and chest ultrasound.
- Follow ECHO closely; Pts develop a severe cardiomyopathy.

14. **Post ICU management**
    a. Enoxaparin 40-60 mg s/c daily
    b. Methylprednisone 40 mg day, the wean slowly
    c. Vitamin C 500 mg PO BID
    d. Melatonin 3-6 mg at night
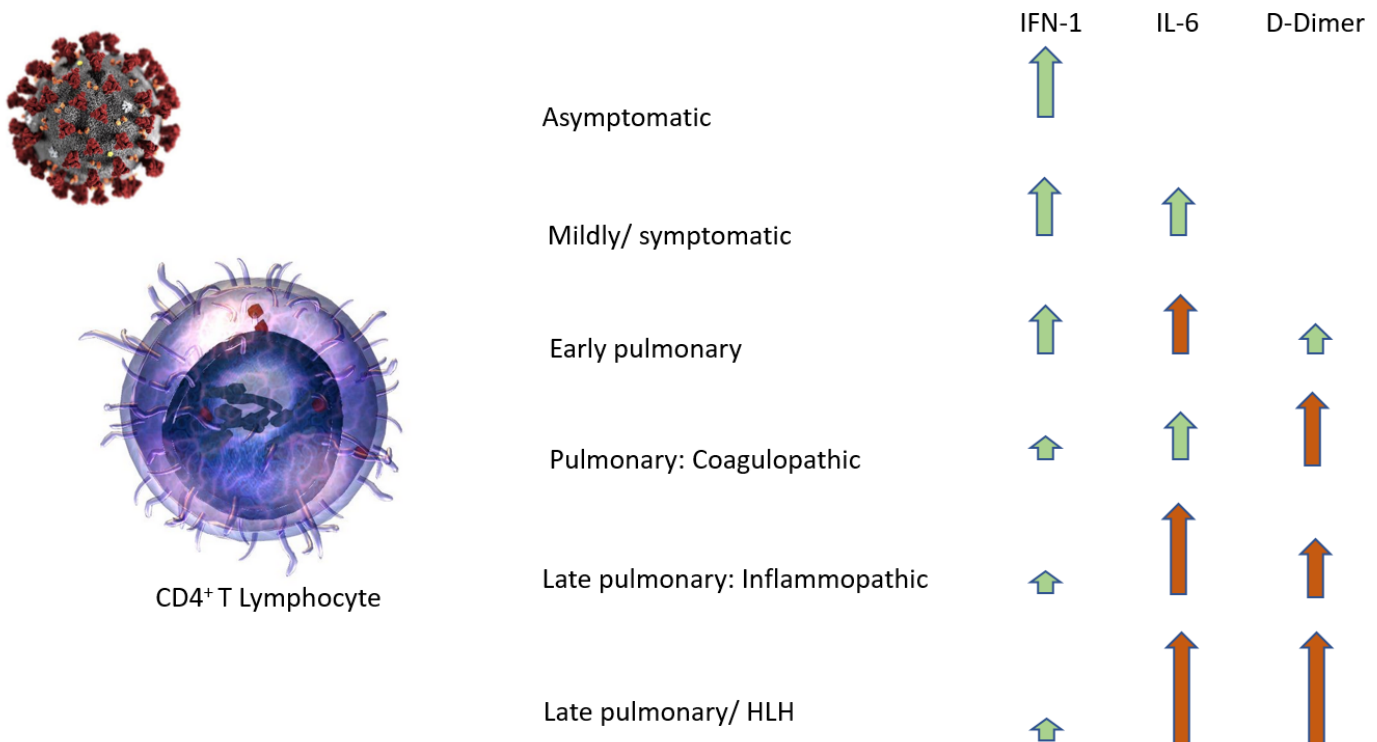
General schema for respiratory support in patients with COVID-19
Try to avoid intubation if possible

Low flow nasal cannula
- Typically set at 1-6 liters/minute

High flow nasal cannula
- Accept permissive hypoxemia (O_2 Saturation > 86%)
- Titrate FiO_2 based on patient's saturation
- Accept flow rates of 60 to 80 L/min
- Trial of inhaled Flolan (epoprostenol)
- Attempt proning (cooperative proning)

Invasive mechanical ventilation
- Target tidal volumes of ~6 cc/kg.
- Lowest driving pressure and PEEP
- Sedation to avoid self-extubation
- Trial of inhaled Flolan

Prone positioning
- Exact indication for prone ventilation is unclear.
- Consider in patients with Pa02/Fi02 ratio <150.

VV-ECMO
- Indications remain unclear.
- Early discussion with ECMO center or team may be advisable.

Deterioration

Recovery

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Heparin anticoagulation and high-dose vitamin C treatment are recommended [9,10]. Low-molecular-weight heparin 1 to 2 mg/kg per day, continued until the patient's D-dimer level returned to normal. Once fibrinogen degradation product (FDP) ≥10 μg / mL and / or D-dimer ≥5 μg / mL, switch to unfractionated heparin. Vitamin C is administered at a dose of 50 to 100 mg / kg per day, and continued until significant improvement in the oxygenation index.

COVID-19: Subtypes of Infection

|	IFN-1	IL-6	D-Dimer
Asymptomatic	⬆		
Mildly/ symptomatic	⬆	⬆	
Early pulmonary	⬆	⬆	⬆
Pulmonary: Coagulopathic	⬆	⬆	⬆
Late pulmonary: Inflammopathic	⬆	⬆	⬆
Late pulmonary/ HLH	⬆	⬆	⬆

CD4+ T Lymphocyte

A few General thoughts:

1. Severe COVID-19 disease results in a dysregulated immune response with aberrant CD4+ T cell activation. Patients have significantly elevated levels of IL-6, IL-10 and TNFα. Downregulating the **cytokine storm** is an essential component of the treatment of severe COVID-19 disease.

2. COVID-19 patients developed a severe hypercoagulable state (see Figures). This likely results in pulmonary micro- and macrovascular disease which may lead to hypoxia/pulmonary shunting. These patients have a markedly increased risk of pulmonary and cerebral emboli (see Figure).

3. This is not your "typical" ARDS… but something else. Chest CT shows bilateral, discreet, irregular, multilobar "ground-glass" infiltrates and not the typical dependent air-space consolidation ("sponge lung/baby lung") characteristic of "typical" ARDS. Physiologically "COVID-19 ARDS" is different; our data suggests that lung water (EVLWI) is normal or only marginally increased (therefore by definition this is NOT ARDS). Furthermore, lung compliance is quite good yet there is severe hypoxia (due to shunting). This suggest microvascular disease and pulmonary vasoplegic resulting in marked V/Q mismatching (shunt). In addition, pulmonary embolism appears to be very common in these patients and may be the cause of sudden death (see Figure). The typical ARDS that develops over time (see Figures) is due mechanical ventilator induced lung injury and/or superadded bacterial pneumonia.

4. It is important to stress that there is no known drug/treatment that has been proven unequivocally to improve the outcome of COVID-19. This, however, does not mean we should adopt a nihilist approach and limit treatment to "supportive care". Furthermore, it is likely that there will not be a single "magic bullet" to cure COVID-19. Rather, we should be using multiple drugs/interventions that have synergistic and overlapping biological effects that are safe, cheap and "readily" available. The impact of COVID-19 on middle- and low-income countries will be enormous; these countries will not be able to afford expensive designer molecules.

5. Randomized controlled rials are not the answer to this catastrophic pandemic. It will likely take many months before these studies are completed and the results are available; many tens of thousands of patients will die from COVID-19 related complications in the intervening time. Furthermore, treating patients with placebo wold appear to be ethically unsound.

6. Good medical practice and the best interests of the patient require that physicians use legally available drugs according to their best knowledge and judgement. If physicians use a product for an indication not currently approved, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

7. Zinc (Zn^{++}) inhibits viral RNA dependent RNA polymerase (replicase).

8. Chloroquine and hydroxychloroquine have broad antiviral properties. In addition, these drugs are potent Zn ionophores and have favorable immunomodulating properties including inhibition of PAI-1 expression. These drugs may have a role in the EARLY viral replicative phase.

9. Ascorbic acid has numerous proven biological properties (anti-inflammatory, anti-oxidant, immune enhancing, antiviral) that are likely to be of benefit in patients with COVID-19 disease. Furthermore, it is important to stress that ascorbic acid has proven synergistic effects when combined with corticosteroids.

10. Recent data suggests that in addition to being a potent anti-oxidant, melatonin may have direct antiviral effects against COVID-19. In healthy people, melatonin levels plummet after the age of 40 years. This may partly explain the increased risk of death in patients with COVID-19 who are over the age of 40. Melatonin may therefore have a role in both the prevention and treatment of COVID-19.

11. Vitamin D has important immune-enhancing effects. Much of the population, especially the elderly have sub-optimal vitamin D levels, particularly during the winter months. Low vitamin D levels have been shown to increase the risk of developing viral upper respiratory tract infections. Therefore, prophylactic vitamin D should be considered especially in the elderly.
12. Quercetin is a plant phytochemical. Experimental and early clinical data suggests that this compound has broad antiviral properties (including against coronavirus) and acting at various steps in the viral life cycle. Quercetin is a potent inhibitor of heat shock proteins (HSP 40 and 70) which are required for viral assembly. This readily available and cheap plant-derived compound may play a role in the prophylaxis of COVID-19 in high-risk populations.
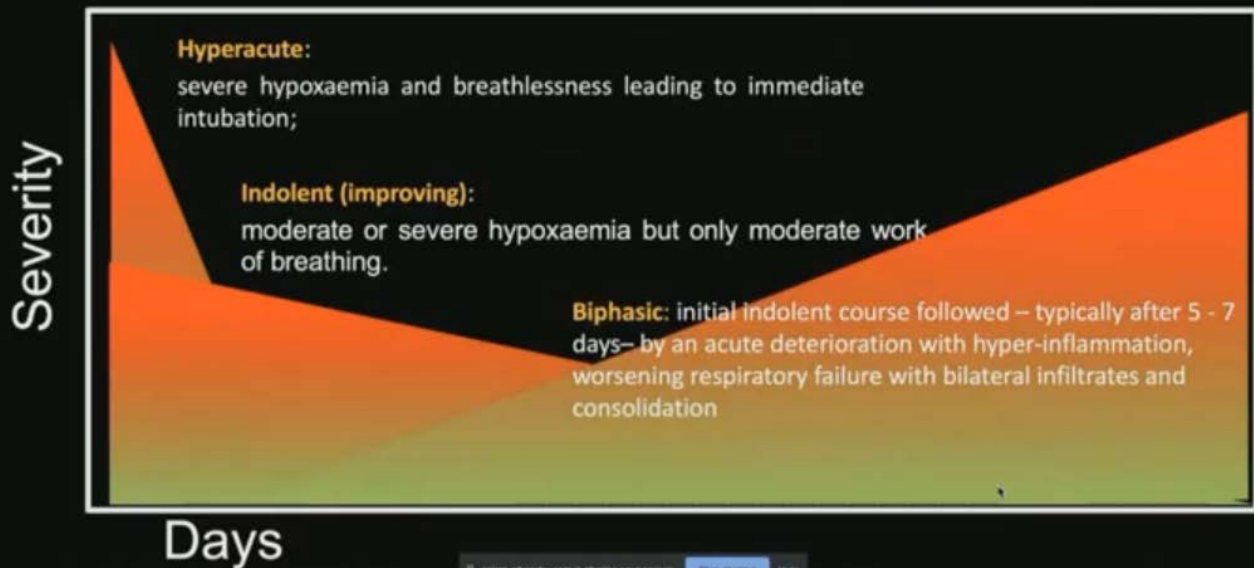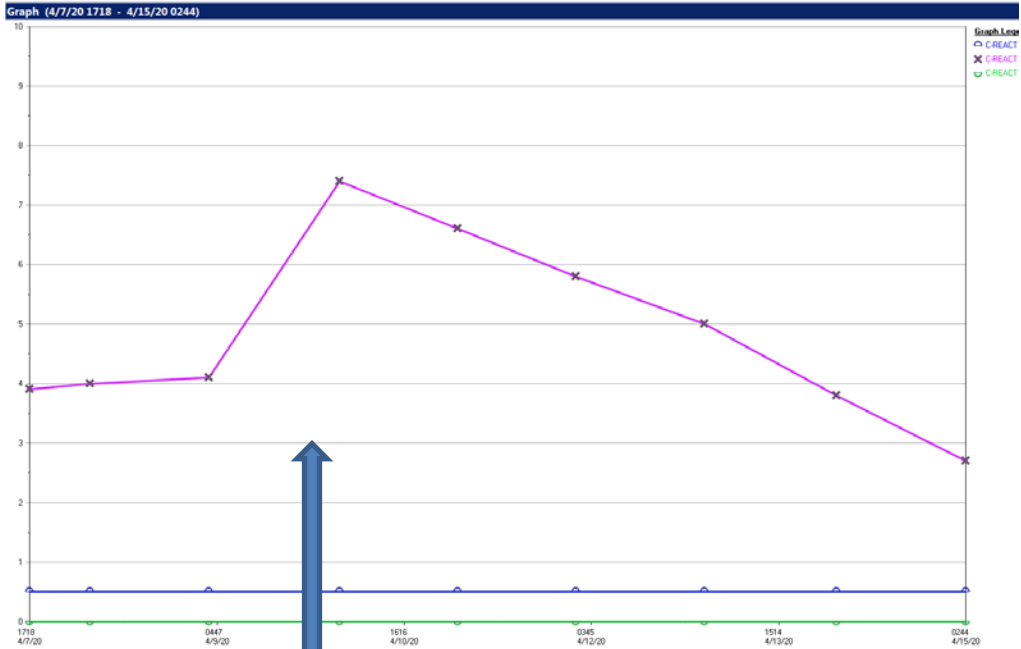
Premature discontinuation of Corticosteroids and Vitamin C (after 4 days), and the effect of reinitiation of this Vital Combination on CRP. Clinical course followed CRP profile.
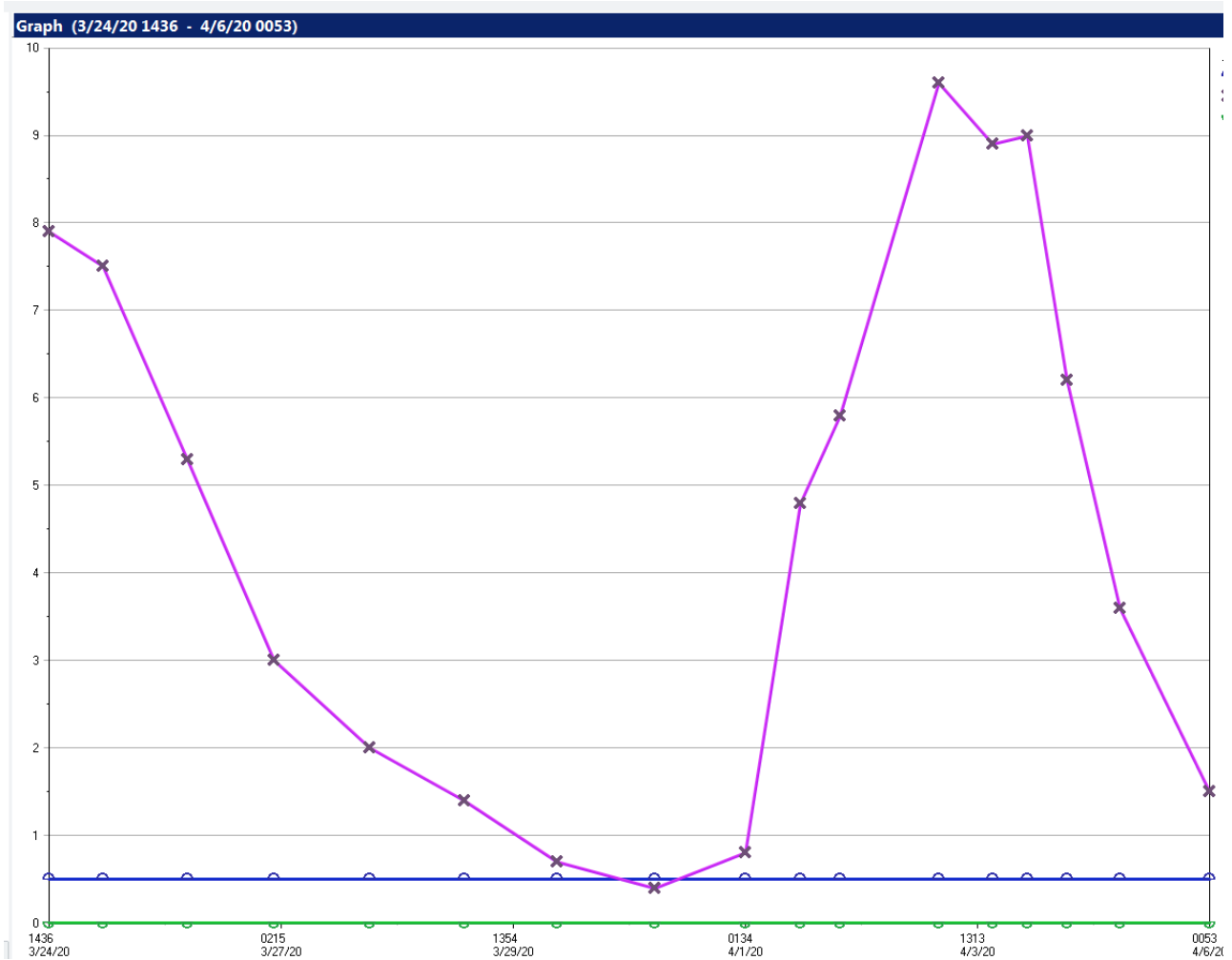
Secondary HLH Rx with Vitamin C 3g IV q 6 and increased methylprednisolone
(125 mg q 8 hourly)

CRP

125 mg Methylprednisolone q 8

AST

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Heparin anticoagulation and high-dose vitamin C treatment are recommended [9,10]. Low-molecular-weight heparin 1 to 2 mg/kg per day, continued until the patient's D-dimer level returned to normal. Once fibrinogen degradation product (FDP) ≥10 μg / mL and / or D-dimer ≥5 μg / mL, switch to unfractionated heparin. Vitamin C is administered at a dose of 50 to 100 mg / kg per day, and continued until significant improvement in the oxygenation index.
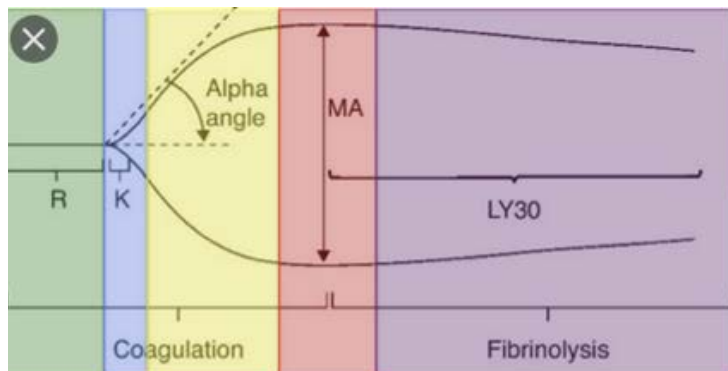
CT scan of Typical COVID-19 Patient
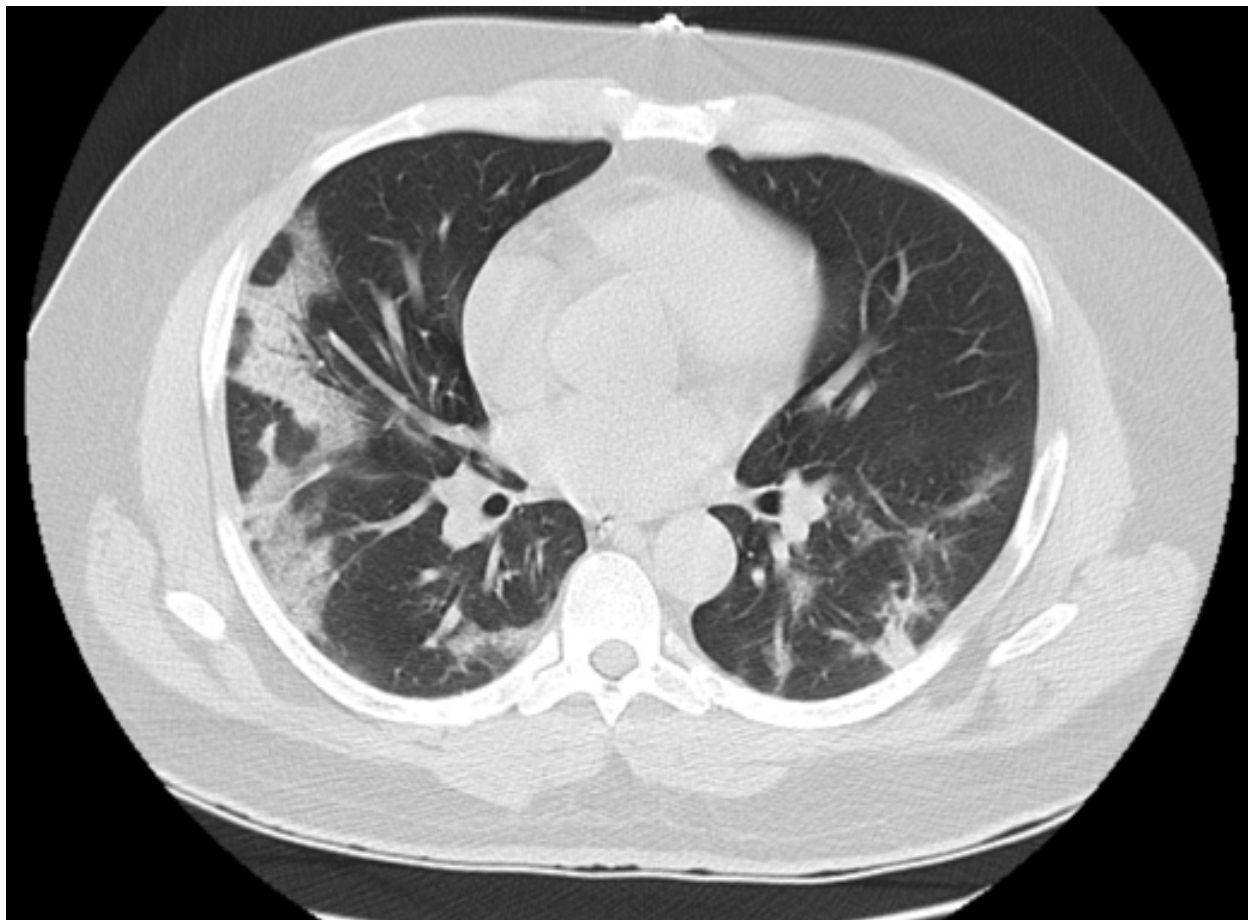
CTPA of 44 yr. old COVID + patient (with no risk factor for DVT/PE) presenting with severe tachycardia

"Cooperative" proning-repositioning of non-intubated patient

Thromboelastogram (TEG) of COVID-19 patient on admission to ICU
Demonstrating marked hypercoagulable state

R (min)	K (min)	ANGLE (deg)	MA (mm)	LY30 (%)
3.3	0.8	80.0	74.0	0.3

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Thromboelastogram (TEG)

Components	Definition	Normal Values	Problem with...	Treatment
R Time	Time to start forming clot	5 – 10 minutes	Coagulation Factors	FFP
K Time	Time until clot reaches a fixed strength	1 – 3 minutes	Fibrinogen	Cryoprecipitate
Alpha angle	Speed of fibrin accumulation	53 – 72 degrees	Fibrinogen	Cryoprecipitate
Maximum Amplitude (MA)	Highest vertical amplitude of the TEG	50 – 70 mm	Platelets	Platelets and/or DDAVP
Lysis at 30 Minutes (LY30)	Percentage of amplitude reduction 30 minutes after maximum amplitude	0 – 8%	Excess Fibrinolysis	Tranexemic Acid and/or Aminocaproic Acid

Covid-19 shedding

No. of samples positive for SARS-CoV-2 by RT-PCR/ total no. of samples in aggregated studies (%)

Nasopharyngeal swabs: 31/35 (88.6%)
Zou L et al, NEJM, 2020
Kujawski et al, medRxiv, 2020
Chan JF et al, Lancet

Conjunctival swabs: 2/188 (1.1%)
Xu L et al, medRxiv, 2020
Zhang X et al, medRxiv, 2020
Sun X et al, medRxiv, 2020

Sputum: 48/49 (97.9%)
Pan Y et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Chen L et al, Am J Gastroenterol, 2020
Lin C et al, medRxiv, 2020
Chan JF et al, Lancet, 2020

Throat swabs: 45/75 (60%)
Post. throat saliva: 31/35 (88.6%)
Oral swabs: 7/15 (46.7%)
Pan Y et al, Lancet Infect Dis, 2020
Zou L et al, NEJM, 2020
Kujawski et al, medRxiv, 2020
Chen L et al, Am J Gastroenterol, 2020
Lin C et al, medRxiv, 2020
To KKW et al, Lancet Infect Dis, 2020
To KKW et al, Clin Infect Dis, 2020
Chan JF et al, Lancet, 2020

Stool: 34/48 (70.8%)
Anal swabs: 16/78 (20.5%)
Rectal swabs: 4/23 (17.4%)
Cui P et al, medRxiv, 2020
Chen W et al, Emerg Microbes Infect
Pan Y et al, Lancet Infect Dis, 2020
To KKW et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Xie C et al, IJID, 2020
Young BE et al, JAMA, 2020
Zhang L et al, IMV, 2020

Urine: 0/76 (0%)
Pan Y et al, Lancet Infect Dis, 2020
To KKW et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Xie C et al, IJID, 2020
Young BE et al, JAMA, 2020
Wolfel R et al, medRxiv, 2020

Blood: 20/162 (12.3%)
Chen W et al, Emerg Microbes Infect, 2020
To KKW et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Xie C et al, IJID, 2020
Young BE et al, JAMA, 2020
Chan JF et al, Lancet, 2020
Wolfel R et al, medRxiv, 2020

Vaginal swabs: 0/35 (0%)
Cui P et al, medRxiv, 2020

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