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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. We should not re-invent the wheel, but learn from others' experience. This is a very fluid situation; therefore, I 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

A few General thoughts:

1. We are all inhabitants of the same planet and we are all in this together. The medical community needs to get off their "high pedestal" and act decisively and immediately; there is no time to lose.
2. It is likely that 40-80% of the population across the world will become infected with this virus. It is therefore unrealistic for us to expect this will just go away. Our goal, therefore, should be to reduce the mortality in those who are at greatest risk of dying. This requires those at risk to "socially" isolate themselves. Once they become infected, we should treat aggressively to prevent disease progression.
3. The course of the disease is quite predictable. Acute respiratory failure occurs on day 6-8 (due to cytokine storm). In those patients requiring supplemental oxygen, we need to be very aggressive to prevent progression to ARDS. Once ARDS develops, the mortality is high.
4. This is not your "typical" ARDS. Chest CT shows bilateral, discreet, irregular, multilobar infiltrates and not the typical dependent air-space consolidation ("sponge lung") characteristic of the usual ARDS. Physiologically "COVID-19 ARDS" is different; our preliminary data suggests that lung water (EVLWI) is only marginally increased. Furthermore, lung compliance is quite good yet there is severe hypoxia (due to shunting). Cause unclear?? Microvascular thrombosis.
5. It is important to stress that there is no known drug/treatment that has been proven to improve the outcome of COVID. This, however, does not mean we should adopt a nihilist approach. 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 could be made readily available. The impact on middle- and low-income countries will be enormous; these countries will not be able to afford expensive designer molecules.

6. Preliminary data suggests that chloroquine and hydroxychloroquine decrease the duration of viral shedding. These agents (if available) could be used to mitigate/curtail the spread of this virus. They may be used in elderly patients with comorbidities at risk of progression and death.
7. Zinc (Zn^{++}) inhibits viral RNA dependent RNA polymerase (replicase). Chloroquine and hydroxychloroquine are potent Zn ionophores that increase intracellular Zn concentrations.
8. 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. Therefore, steroids are recommended in patients with COVID-19 and moderate to severe ARDS (see corticosteroids below). The benefit of ascorbic acid (without corticosteroids) in patients with severe ARDS appears to be limited. While the optimal dose of ascorbic acid is unknown, we suggest 3 g IV q 6 hourly. It should be noted that in the presence of free iron (released from ferritin) ascorbic acid may potentially have pro-oxidant effects. Therefore, the trends in CRP and ferritin need to be closely monitored; in those patients who ferritin AND CRP are increasing, reducing the dose to 1.5g q 6 hourly should be considered.
9. Very 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.
10. 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.
11. 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.

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, especially amongst the most vulnerable citizens in our community; i.e. those over the age of 60 years and those with medical comorbidities. While there is no high level evidence that this cocktail is effective; it is cheap, safe and should be readily available. So what is there to lose?

- Vitamin C 500 mg BID
- Zinc 75-100 mg/day (acetate or gluconate)
- Quercetin 500-1000 mg/day
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 1-2 mg at night
- Vitamin D3 5000 u/day

Mildly Symptomatic patients (on floor):

- Vitamin C 500mg BID
- Zinc 75-100 mg/day
- Quercetin 500-1000 mg/day
- Melatonin 6-12 mg at night(the optimal dose is unknown)
- Vitamin D 5000u/day
- Observe closely.
- N/C 2L /min if required (max 6L/min; however, consider early t/f to ICU for escalation of care).
- Avoid Nebulization and Respiratory treatments. Use MDI if required.
- **NO Bagging.**
- **Avoid non-invasive ventilation**
- T/f EARLY to the ICU for increasing respiratory signs/symptoms.

Respiratory symptoms (SOB; hypoxia: admit to ICU):

1. Chloroquine 500mg PO BID for 7-10 days or hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days.
2. Ascorbic acid (Vitamin C) 3g IV q 6 hourly until extubated and for at least 4 days up to 10 days (see dosage adjustment below and caution with POC glucose testing).
3. Thiamine 200mg q 12 (PO or IV).
4. Azithromycin 500mg day 1 then 250mg for 4 days.
5. Melatonin 6-12 mg at night (the optimal dose is unknown).
6. Zinc 75-100 mg daily.
7. Atorvastatin 40-80 mg/day. Of theoretical but unproven benefit. Statins have been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype (which is similar to COVID-19).
8. 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).
9. Broad-spectrum antibiotics only 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).

10. Fluid restrictive strategy.
11. 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).
12. DVT prophylaxis with enoxaparin 40mg/daily (heparin in AKI/CRF); additional role of ASA unknown (see hypercoagulable state)
13. *Optional:* Tocilizumab (if available) may have a role in cytokine storm (specific IL-6 inhibitor).
14. *Optional:* Consider full anticoagulation with heparin in patients with rapidly increasing D-dimer and/or those with severe "refractory" hypoxic respiratory failure (? due to pulmonary microvascular thrombosis). The use of half-dose rTPA has also been suggested: 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.
15. Escalation of respiratory support (steps)
    - N/C 1-6 l/min
    - High Flow up to 30 L/min
    - Intubation … by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
    - Volume protective ventilation following ARDSnet table
    - APRV
    - Prone positioning
    - ?? ECMO < 60yrs and no severe commodities/organ failure.

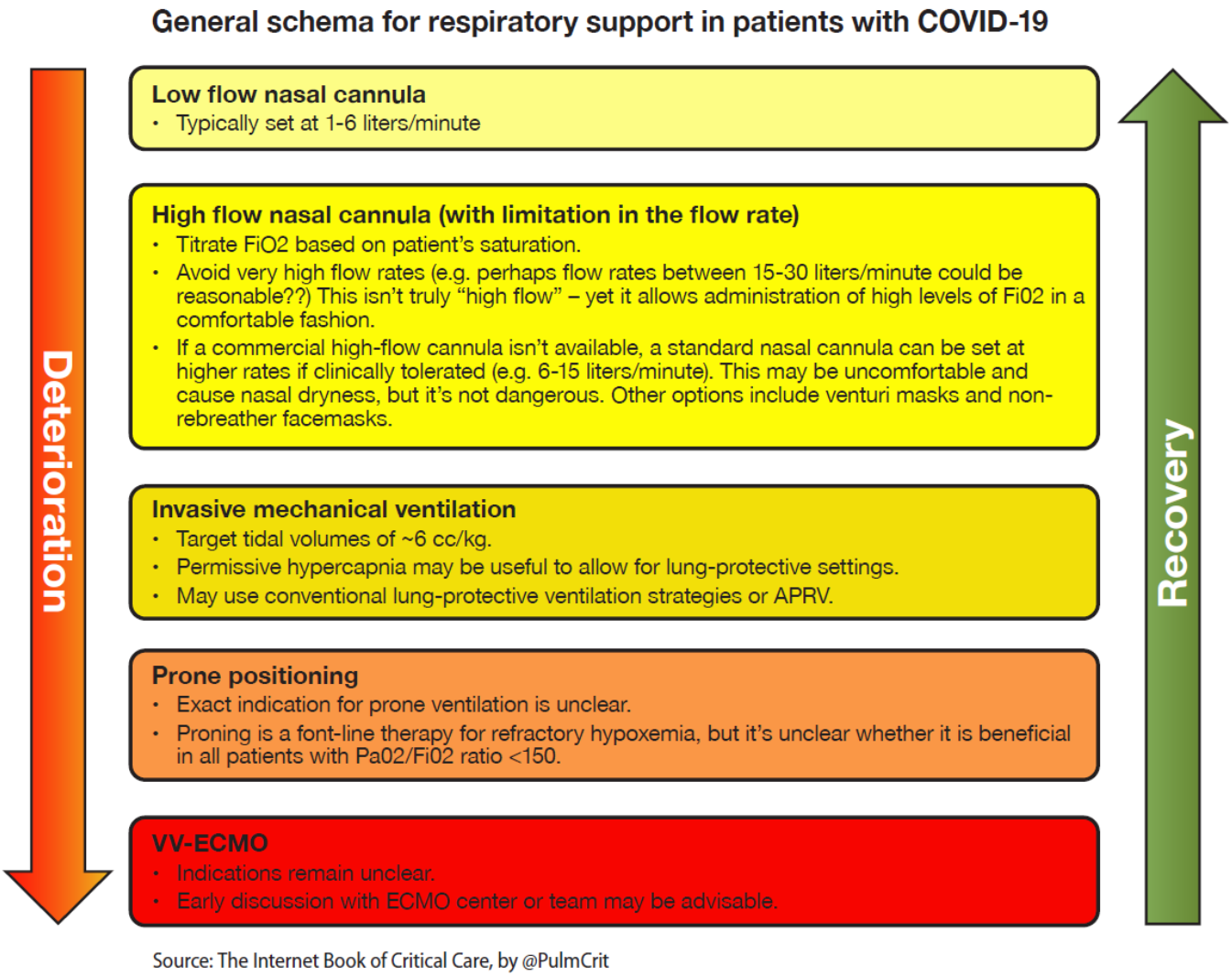
    There is widespread concern that using HFNC could increase the risk of viral transmission. There is however, no solid evidence to support this fear.

    CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

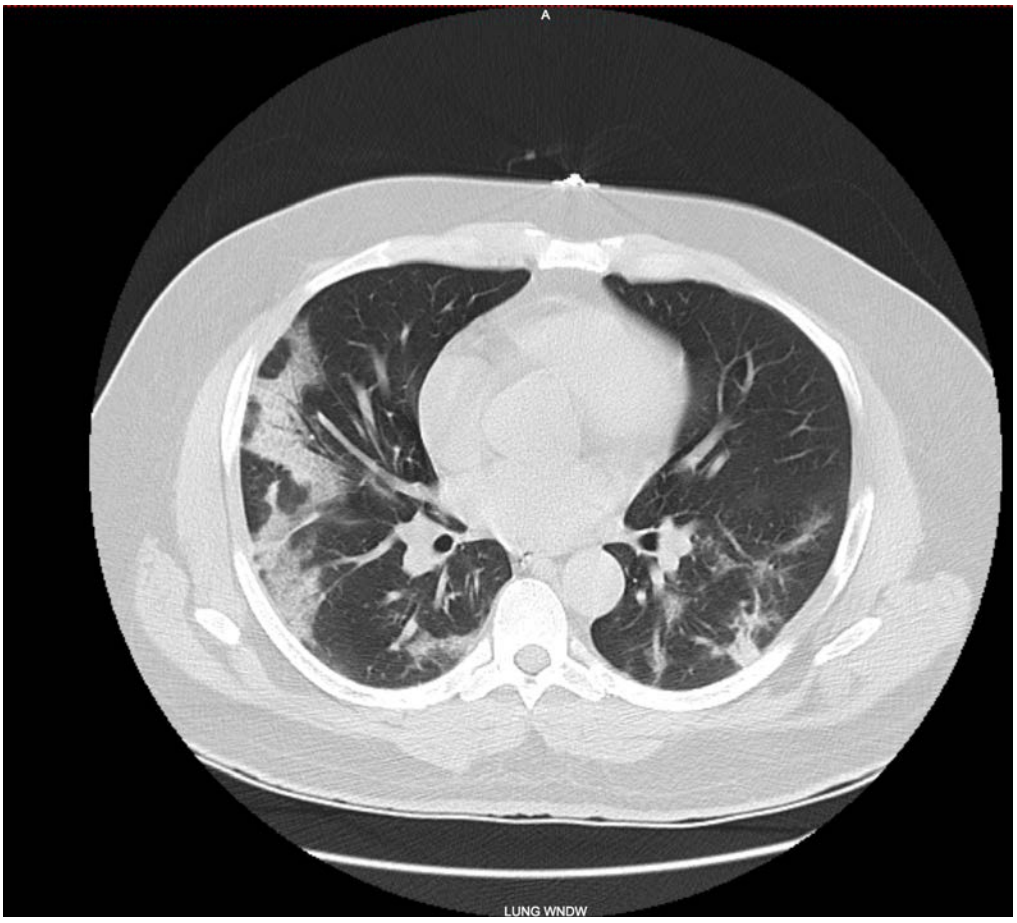
16. Consider plasma exchange for cytokine storm/HLH picture (see steroids below). The use of CVVH filters that remove cytokines should also be considered.
17. **Steroids:**
    This topic is controversial. However, the only study on the use of corticosteroids and COVID (from Wuhan) demonstrates a marked mortality reduction with methylprednisolone (60mg daily)
    - During the early viral replicative stage, probably best to avoid.
    - During the hyperimmune phase (day 6-8 onward) in patients with hypoxia/ARDS. Hydrocortisone 50mg IV q 6 for 4 days is recommended (together with ascorbic acid) based on features of ARDS and high CRP (lung injury is due to cytokine storm) .
    - Patients may evolve into an HLH/cytokine vortex phase, marked by increasing ferrin, IL-6 and worsening oxygenation. These patients may benefit from high dose methylprednisolone. (dose ?? 200-500 mg q 12).

18. Monitoring

- Daily: PCT, CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer, Mg. ke CRP and Ferritin are good biomarkers and track disease severity.
- 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.
- Il-6 at baseline and ? every 3-4 days.
- Monitor QTc interval if using chloroquine/hydrochloroquine and azithromycin and monitor Mg++
- No routine CT scans, follow CXR and chest ultrasound.
- Follow ECHO closely; Pts develop a severe cardiomyopathy.

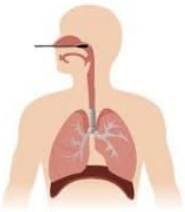


Typical CT scan of “COVID ARDS”



Covid-19 shedding

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

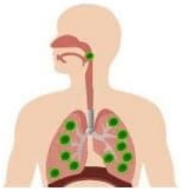


Nasopharyngeal swabs: 31/35 (88.6%)

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, JMV, 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

Found on Internet, source unknown (thank you author)

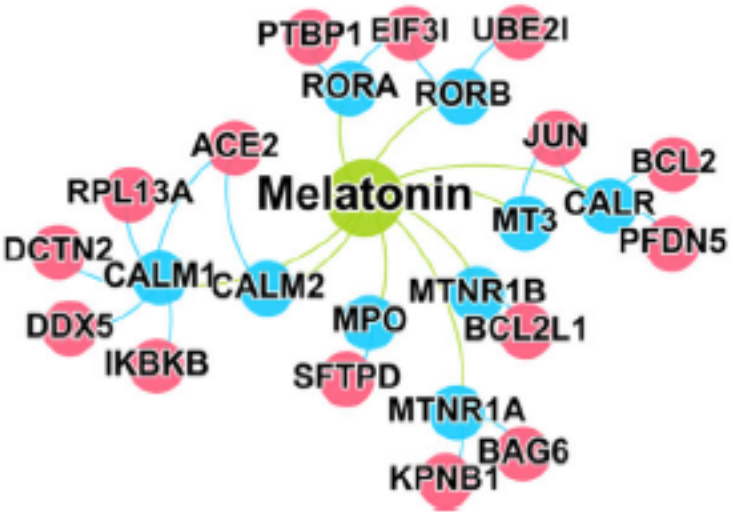
Zhou et al. *Cell Discovery* (2020)6:14
https://doi.org/10.1038/s41421-020-0153-3

Cell Discovery
www.nature.com/celldisc

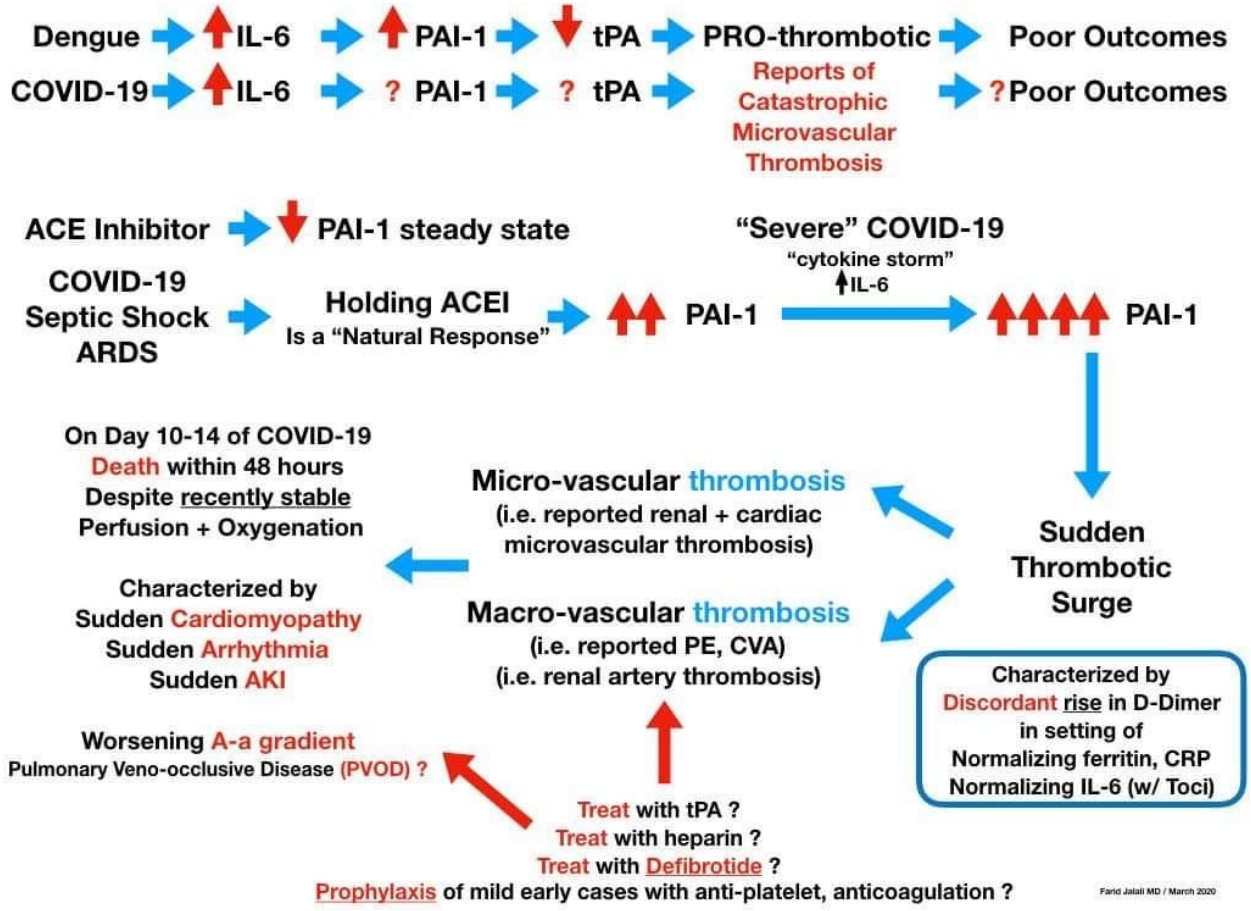
ARTICLE Open Access

Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2

Yadi Zhou[1], Yuan Hou[1], Jiayu Shen[1], Yin Huang[1], William Martin[1] and Feixiong Cheng[1,2,3]



Proposed mechanism of hypercoagulable state.



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