COVID-19 management dilemmas

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Question

46 YOM with history of hypertension, presents with shortness of breath, fevers, dry cough for a week and was found to have positive nasopharyngeal PCR for COVID in the ER. Intubated and moved to ICU on Day 2 of admission due to worsening respiratory failure. Chest X-ray with worsening bilateral ground glass opacities. On admission he had lymphopenia, elevated ALT/AST, troponin. D-Dimer was 1356 ng/mL, procalcitonin was low. He is on Ceftriaxone and Azithromycin for empiric CAP coverage. Lung protective ventilation was initiated, his P/F Ratio was 134 on 100% FiO2 and 16 of PEEP. He is now proned and paralyzed due to ventilator asynchrony. He does not have any other organ failure at this time.

What is the right thing to do?

- Who should be tested or re-tested if the initial test is negative?
- How to support a patient needing oxygen, is high flow and non-invasive “safe”?
- When to move the patient to ICU and intubate?
- What is proper isolation and personal protective equipment?
- Should I be stopping or avoiding certain medications like ACE-I/ARB?
- What is the best strategy for mechanical ventilation, proning, sedation, paralysis?
- What diagnostic and prognostic tests should I obtain?
- Should a pandemic influence our goals of care and code status decisions?
- Can I use any of the ‘miracle drugs’ or off label therapeutic options?

Therapeutic options

- Hydroxychloroquine and Azithromycin
- Remdesivir
- Ritonavir/Lopinavir (Kaletra)
- Anticoagulation
- Tocilizumab
- Corticosteroids
- Antibiotics
- Convalescent plasma
- Zinc/Vitamin C/multivitamins

Hydroxychloroquine

- Mode of action: increases lyposomal pH (interfering virus fusion with cell) and interferes with glycosylation of covid receptors. Relevant adverse effects: Cardiac toxicity, arrythmias, hypoglycemia
- Studies in animals: inhibition (both at entry and post entry stages of SARS-CoV-2), immune modulation
- Availability limited but available under FDA EUA or through clinical trial

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret [a, b, $], Jean-Christophe Lagier [a, c, $], Philippe Parola [a, b], Van Thuan Hoang [a, b, d], Line Meddeb [a], Morgane Mailhe [a], Barbara Doudier [a], Johan Courjon [e, f, g], Valérie Giordanengo [h], Vera Esteves Vieira [a], Hervé Tissot Dupont [a, c], Stéphane Honoré [i, j], Philippe Colson [a, c], Eric Chabrière [a, c], Bernard La Scola [a, c], Jean-Marc Rolain [a, c], Philippe Brouqui [a, c], Didier Raoult [a, c]

- HCQ helped reduce viral load; proportion of people with positive PCR by 75% in the six-day period. When combined with Azithromycin, improved efficacy to 95%.
- Small single center non-randomized study with 26 patients in a single treatment arm of which six dropped out.
- Baseline viral-load in persons receiving HCQ and azithromycin was low
- What is the significance of clearance from nasopharyngeal swab?

Hydroxychloroquine/Azithromycin recommendation

- Insufficient data to determine efficacy
- Enrollment in ongoing clinical trials for treatment and prophylaxis should be considered
- Widespread off label use is causing shortage of drugs in patients who have a true indication
- Has potential serious cardiac side effects in combination with other QT prolonging agents
- Use of Azithromycin if superimposed bacterial infection is suspected

Remdesivir

- Mode of action: Nucleotide analogue that inhibits RNA polymerase
- Relevant adverse effect: Elevated transaminases
- Studies in animals infected with MERS-CoV, Ebola showed benefit
- Studied in humans: Ebola (clinical benefit cannot be excluded as it was not compared to placebo), COVID-19 (ongoing)
- Compassionate use program stopped March 27th (except for pregnant women and children age < 19). Transitioning to "expanded access" program.

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

Jonathan Grein, M.D., Norio Ohmagari, M.D., Ph.D., Daniel Shin, M.D., George Diaz, M.D., Erika Asperges, M.D., Antonella Castagna, M.D., Torsten Feldt, M.D., Gary Green, M.D., Margaret L. Green, M.D., M.P.H., François-Xavier Lescure, M.D., Ph.D., Emanuele Nicastri, M.D., Rentaro Oda, M.D., et al.

- Study findings: Of the 61 patients who received remdesivir, improvement in oxygen-support status was observed in 68%, and overall mortality was 13% over a median follow-up of 18 days.
- Not a randomized control trial, many limitations to the study including small sample size, short follow-up, missing data and patients lost to follow-up

Remdesivir

- Efficacy remains unknown
- Not available currently under compassionate use
- Clinical trials ongoing

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

Bin Cao, M.D., Yeming Wang, M.D., Danning Wen, M.D., Wen Liu, M.S., Jingli Wang, M.D., Guohui Fan, M.S., Lianguo Ruan, M.D., Bin Song, M.D., Yanping Cai, M.D., Ming Wei, M.D., Xingwang Li, M.D., Jiaan Xia, M.D., et al.

- Mode of action: HIV-1 protease inhibitor
- RCT that was well performed and enrolled 199 patients.
- No significant reduction in time to clinical improvement or 28 day mortality.

Table- Interim Guidance on Management of COVID-19

Suggestions for	Vote from CORE process (>70% agreement to make suggestion)
For any COVID-19 patient who receives an intervention suggested in this document, data should be collected in a manner that enables studies that use valid methods for causal inference and control of confounders. The data should be assessed periodically so that patients who received the intervention can be compared those who did not receive the intervention. Management should be modified as-needed based upon the comparisons.	No vote
Hydroxychloroquine (HCQ) or chloroquine (CQ) for patients with confirmed COVID-19 and severe pneumonia if: • Shared decision-making is utilized, and • Data is collected for research comparing HCQ to no HCQ, or CQ to no CQ, and • Illness is severe enough to warrant investigational therapy, and • HCQ or CQ are not in short supply.	73% for HCQ or CQ 16% no suggestion 11% against HCQ or CQ
Prone ventilation for patients with refractory hypoxemia due to progressive COVID-19 pneumonia (i.e., ARDS)	99% for prone ventilation 1% no suggestion 0% against prone ventilation
Consideration of ECMO for patients with refractory hypoxemia due to progressive COVID-19 pneumonia (i.e., ARDS) who have failed prone ventilation	75% for ECMO 23% no suggestion 1% against ECMO
No suggestion for or against	
HCQ or CQ for outpatient COVID-19 patients	18% for HCQ or CQ 36% no suggestion 46% against HCQ or CQ
HCQ or CQ for hospitalized COVID-19 patients without pneumonia	8% for HCQ or CQ 50% no suggestion 42% against HCQ or CQ
Remdesivir for hospitalized COVID-19 patients with pneumonia	68% for remdesivir 26% no suggestion 5% against remdesivir
Lopinavir-ritonavir for hospitalized COVID-19 patients with pneumonia	30% for lopinavir-ritonavir 26% no suggestion 43% against lopinavir-ritonavir
Tocilizumab for hospitalized COVID-19 patients with pneumonia	30% for tocilizumab 56% no suggestion 14% against tocilizumab
Systemic corticosteroids for hospitalized COVID-19 patients with pneumonia	15% for intervention 18% no suggestion 67% against intervention

CORE= Convergence of Opinion on Recommendations and Evidence; ARDS= Acute Respiratory Distress Syndrome; ECMO=

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection

Published , 4/11/2020

- In summary: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine with or without azithromycin, lopinavir/ritonavir, convalescent plasma, tocilizumab in the context of a clinical trial.
- Against steroids used in all patients. Consider in patients with ARDS in the context of a clinical trial

A word about anti-coagulation

- In general patients with sepsis and ARDS are at a higher risk for VTE
- D-Dimer > 1ug/mL in patients with COVID-19 was an independent risk factor of in-hospital death
- Vascular endothelium inflammation and extensive intravascular micro-thrombosis seen on autopsies

Zhou F, et al. Lancet 2020; DOI:10.1016/S0140-6736(20)30566-3 ; Hamming I, et al. J Pathol 2004; 203(2): 631-7.

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Ning Tang, Huan Bai, Xing Chen, Jiale Gong, Dengju Li, Ziyong Sun

First published:27 March 2020 | https://doi.org/10.1111/jth.14817

- Retrospective study
- No difference in mortality at 28 days in all patients on heparin vs not on heparin
- 28-day mortality of heparin users was lower than nonusers In patients with SIC (sepsis-induced coagulopathy) score ≥4 (40.0% vs 64.2%, P=0.029), or D-dimer > 6 fold of upper limit of normal (32.8% vs 52.4%, P=0.017)
- Many limitations to the study
- 22% of 449 patients receiving prophylactic dose of anti-coagulation

Recommendations

- International Society of Thrombosis and Haemostasis
- All COVID-19 patients (including non-critically ill) who require hospital admission should receive prophylactic dose low molecular weight heparin (LMWH), unless they have contra-indications (active bleeding and platelet count < 25 x 10^9/L), to (a) inhibit thrombin generation which may (!) have benefit in reducing mortality, and (b) protect from venous thromboembolism.
- Systemic therapeutic anticoagulation if there is an indication

Primum non nocere

"First do no harm"

and practice evidence-based medicine