UT Health San Antonio Long School of Medicine

EVIDENCE-BASED MEDICINE INFOSHEET: COVID-19 TREATMENT

Updated: 05/05/2020

Review completed by: Shawna Mattathil, Laura Berardo, Austin Gay, Claire Harrison
Peer Review by: Dr. Kristi Traugott and Dr. Elizabeth Hand

Key topic areas / questions identified:

What are current direct-acting agents that could be used to treat COVID-19?

1. Remdesivir
2. Hydroxychloroquine/chloroquine
3. Hydroxychloroquine/Azithromycin
4. Tocilizumab
5. Ivermectin
6. Tenofovir

What do clinicians need to know about supportive care for patients with COVID-19?

1. Immunosuppressants
2. Anticoagulation
3. Ventilator Management
4. ECMO
5. Prone positioning

Vaccine Development

Direct Acting Agents: Remdesivir

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19, does remdesivir, compared with standard supportive care, lead to improved outcomes/decrease duration of illness?

Key Findings:

2 articles were reviewed (Total n=61; Total sample in USA; 1 article non-human study).

- A China lab-based study found via cell research that remdesivir and chloroquine effectively inhibit viral infection *in vitro.*
- An American cohort study cohort study gave a 10-day course of remdesivir, (200 mg IV on day 1, followed by 100 mg daily for the remaining 9 days of treatment) to 61 hospitalized patients with O2saturation <94%. Clinical improvement was observed in 36 of 53 patients (68%). Median follow-up of 18 days: 36 patients (68%) improved in oxygen-support class, 17 of 30 ventilated patients (57%) were extubated. 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among ventilated patients and 5% (1 of 19) among those not ventilated.

Recommendations:

- Remdesivir shows promise for improved clinical outcomes in one compassionate-use cohort study.
- Randomized control trial with placebo necessary for drawing stronger conclusions.

References:

1. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New England Journal of Medicine*. October 2020. doi:10.1056/nejmoa2007016.
2. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0.

Direct Acting Agents: Hydroxychloroquine/Chloroquine

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19, does chloroquine/hydroxychloroquine, compared with standard supportive care, lead to improved outcomes/decrease duration of illness?
For adult patients diagnosed with COVID-19, does a higher dose of chloroquine/hydroxychloroquine, compared with standard lower dose, lead to improved outcomes/decrease duration of illness?

Key Findings:

10 articles were reviewed (Total n=994; Total sample in USA, China, France, Italy, Israel, Brazil).

- A systematic review of 6 articles and 23 clinical trials in China published in the Journal of Critical Care states that there is sufficient pre-clinical rationale and evidence regarding effectiveness of chloroquine for treatment of COVID-19 as well as evidence of safety from long-time use in clinical practice to justify clinical research on the topic. (1)
- Two of the largest and most recent studies thus far (n=181 and 368 in French and American study, respectively) yield the following results:
    - HQ group: 20.2% patients transferred to the ICU or died within 7 days. 2.8% of patients died within 7 days. No-HQ group: 22.1% transferred to the ICU or died within 7 days. 4.6% of patients died within 7 days. (2)
    - Compared to the no HQ group (11.4%), the risk of death from any cause was highest in the HQ group (27.8%), and elevated in the HQ+AZ group (22.1%). The risk of ventilation was similar in the HQ group (13.3 %) and the no HQ group (14.1%), compared to the HQ+AZ group (6.9%). (3)
- Four small clinical trials in China (n=100, 22, 62, 30) suggest that HQ improves outcomes. Primary endpoints used in these studies vary widely; viral load, time to discharge, lung CT findings, duration of cough, etc. These trials have methodologic concerns, including concomitant co-therapies, baseline differences between the groups, and lack of blinding or placebo control. (4-8)
- A Brazilian clinical trial (n=81) to assess safety of HQ dosage showed that the higher dosage group (600 mg BID x 10 days) had 25% of patients with prolonged QTc and higher mortality, as compared to the lower dosage group (450mg x5 days, bid only on the first day) . (9)
- One model suggests that 400 mg BID x 5 days will help reduce viral load while also reducing the risk of prolonged QTc. (10)

Recommendations:

- There is no clear evidence for the benefit of hydroxychloroquine in the treatment of patients hospitalized with COVID-19. If a patient is treated with HQ, they should ideally be enrolled in a clinical trial whenever possible.
- If hydroxychloroquine is used, the dose that is proposed to reduce viral loads and minimize adverse events is 400 mg BID x 5 days.
- Patients treated with hydroxychloroquine should be monitored closely for prolonged QTc. Patients should also be monitored for other less common adverse events: hypoglycemia, neuropsychiatric effects, drug–drug interactions and idiosyncratic hypersensitivity reactions.

References:

1. Cortegiani A, Ingoglia G, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. March 3 2020. J Crit Care doi: 10.1016/j.jcrc.2020.03.005.
2. Mahevas M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. April 14 2020. medRxiv. doi**:**https://doi.org/10.1101/2020.04.10.20060699 Not yet peer reviewed.
3. Magagnoli J, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. April 23 2020. medRxiv doi: https://doi.org/10.1101/2020.04.16.20065920 Not yet peer reviewed.
4. Duan YJ et al. The Trial of Chloroquine in the Treatment of CoronaVirus Disease 2019 (COVID-19) and Its Research Progress in Forensic Toxicology. March 27 2020. Journal of Forensic Medicine. doi: 10.12116/j.issn.1004-5619.2020.02.001
5. Huang, Mingxing et al. Treating COVID-19 with Chloroquine. April 1 2020. J Mol Cell Biol. https://doi.org/10.1093/jmcb/mjaa014
6. Chen ZW et al. Efficacy of hydroxychloroquine in patients with COVID-19: Results of a randomized clinical trial. April 10 2020. medRxiv. doi: https://doi.org/10.1101/2020.03.22.20040758 Not yet peer reviewed.
7. Chen J et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19) March 6 2020. J Zhejiang Univ (Med Sci) doi: 10.3785/j.issn.1008-9292.2020.03.03
8. Tang W et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. April 14 2020. medRxiv. doi: https://doi.org/10.1101/2020.04.10.20060558. Not yet peer reviewed.
9. Borla M, et al. (CloroCovid-19 Study) Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial. April 11 2020. medRxiv doi: https://doi.org/10.1101/2020.04.07.20056424 Not yet peer reviewed.
10. Garcia-Cremades M, et al. Optimizing hydroxychloroquine dosing for patients with COVID-19: An integrative modeling approach for effective drug repurposing. April 14 2020. Clinical Pharmacology and Therapeutics. https://doi.org/10.1002/cpt.1856

Direct Acting Agents: Hydroxychloroquine/Azithromycin

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19, does hydroxychloroquine/azithromycin lead to improved outcomes/decrease duration of illness?

Key Findings:

2 articles were reviewed (Total n=116; Total sample in France).

- A non-randomized open label study published by International Journal of Antimicrobial Agents, studied asymptomatic patients and symptomatic patients with upper or respiratory tract infection symptoms. Cases treated showed a significant reduction of the viral carriage at D6-post inclusion compared to controls and lower average carrying duration than reported of untreated patients in the literature.
- In a second study published by Travel Medicine and Infectious Disease, all but 2 patients improved clinically. A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day7, and 93% at Day8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day5. Patients were able to be rapidly discharged from IDU with a mean length of stay of five days.

Recommendations:
- Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.
- Azithromycin added to hydroxychloroquine accelerated clearance of viral load and decreased duration of disease

References:

1. Gautret, P., Lagier, J.-C., Parola, P., Hoang, V. T., Meddeb, L., Sevestre, J., … Raoult, D. (2020). 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. Travel Medicine and Infectious Disease, 101663. doi: 10.1016/j.tmaid.2020.101663
2. Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Medded, L., Mailhe, M., … Raoult, D. (2020). Hydroxychloroquine and Azithromycin as a treatment of COVID-19: preliminary results of an open-label non-randomized clinical trial. doi: 10.1101/2020.03.16.20037135

Direct Acting Agents: Tocilizumab

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19, does tocilizumab, compared with standard supportive care, lead to improved outcomes/decrease duration of illness?

Key Findings:

7 articles were reviewed (Total n=40; Total sample in China, Italy, France, Switzerland).

- Retrospective study in China found that in most covid-positive patients, acute phase reactant levels were decreased and the patients were getting to a stable condition reflected by a later gradual decrease of IL-6 after TCZ administration. Treated COVID positive patients ranging from moderately to critically ill with 1+ doses of tocilizumab in addition to methylprednisone. 11/15 patients had CRP normalize in 1 week; of 4 critically ill patients treated with single dose 3 died and 1 had CRP remain elevated.
- An open clinical trial in China found 100% fever normalization in 24hr, 15/20 lowered O2 requirements, 16/19 normalization of CRP 5 days post treatment with TCZ. The study was limited by lack of control.
- A collection of French and Swiss articles represented individual patient case studies, primarily in immunocompromised patients already recieving tocilizumab, with promising results.

Recommendations:

- Tocilizumab may reduce inflammation in COVID and elevated IL-6 is an indication
- Multiple doses of tocilizumab should be given to critically-ill patients

References:

1. Cellina M, Orsi M, Bombaci F, Sala M, Marino P, Oliva G. Favorable changes of CT findings in a patient with COVID-19 pneumonia after treatment with tocilizumab. *Diagnostic and Interventional Imaging*. 2020;101(5):323-324. doi:10.1016/j.diii.2020.03.010.
2. Luna GD, Habibi A, Deux JF, et al. Rapid and Severe Covid-19 Pneumonia with Severe Acute Chest Syndrome in a Sickle Cell Patient Successfully Treated with Tocilizumab. *American Journal of Hematology*. 2020. doi:10.1002/ajh.25833.
3. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *Journal of Medical Virology*. 2020. doi:10.1002/jmv.25801.
4. Michot J-M, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report. *Annals of Oncology*. 2020. doi:10.1016/j.annonc.2020.03.300.
5. Mihai C, Dobrota R, Schröder M, et al. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. *Annals of the Rheumatic Diseases*. 2020;79(5):668-669. doi:10.1136/annrheumdis-2020-217442.
6. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proceedings of the National Academy of Sciences*. 2020:202005615. doi:10.1073/pnas.2005615117.
7. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Advances*. 2020;4(7):1307-1310. doi:10.1182/bloodadvances.2020001907.

Direct Acting Agents: Ivermectin

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19, does ivermectin, compared with standard supportive care, lead to improved outcomes/decrease duration of illness?

Key Findings:

1 article was reviewed (no human studies)

- Australian lab-based study found that Ivermectin successfully inhibited viral replication in vitro in Vero/hSLAM cells infected with SARS-CoV-2.

Recommendations:

- Ivermectin has been shown to be an effective treatment for SARS-CoV-2 *in vitro*. While no studies have demonstrated effectiveness for human subjects, *in vivo* trials are merited.

References:

1. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research*. 2020;178:104787. doi:10.1016/j.antiviral.2020.104787.

Direct Acting Agents: Tenofovir

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19, does tenofovir, compared with standard supportive care, lead to improved outcomes/decrease duration of illness?

Key Findings:

1 article reviewed (No human studies)

- Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir bind tightly to RdRp of SARS-CoV-2

Recommendations:

- Tenofovir can tightly bind to the RdRp of the SARS-CoV-2 strain and thus may be used to treat the disease. No toxicity measurements are required for these drugs since they were previously tested prior to their approval by the FDA. Life Sci.

References:

1. Elfiky, Abdo. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. March 31 2020. DOI: 10.1016/j.lfs.2020.117592

Supportive Care: Immunosuppressants

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19 and comorbidities or recent translations requiring immunosuppressants, does the use of immunosuppressants lead to prolong duration of disease?

Key Findings:

3 articles were reviewed (Total n=3; Total sample in United States).

- Long duration and excessive doses of steroids may adversely affect recovery due to the inhibition of antiviral immunity, and may also result in other side effects related to steroids.
- In the case published by American Journal of Transplantation studying 1 a COVID-19 positive patient with a recent kidney transplant, the patient was given 40mg of methylprednisolone daily for 12 days, which may have played an important role in the faster recovery from his pneumonia without the occurrence of severe side effects.
- The number of T cells were significantly decreased in 2 other cases published by American Journal of Transplantation.. T cell reduction is common in severe COVID-19 cases, indicating coronavirus might mainly act on lymphocytes, especially T lymphocytes.
- Immunosuppressed solid organ transplanted patients could be more susceptible to SARS-CoV-2 infection with severe clinical manifestations, the anti-inflammatory effects of immunosuppression could diminish the clinical expression of disease.

Recommendations:

- Discontinuation of immunosuppressants and steroid treatment might help faster recovery from COVID-19 pneumonia.
- The risks and benefits of continuing or discontinuing immunosuppressants should be weighed for each individual case. A lower than standard dose of immunosuppressants could be tried in patients requiring immunosuppressants to facilitate and shorten duration of disease with COVID-19

References:

1. Huang, J., Lin, H., Wu, Y., Fang, Y., Kumar, R., Chen, G., & Lin, S. (2020). COVID-19 in posttransplant patients—report of 2 cases. American Journal of Transplantation. doi: 10.1111/ajt.15896
2. Romanelli, A., & Mascolo, S. (2020). Immunosuppression drug-related and clinical manifestation of Coronavirus disease 2019: A therapeutical hypothesis. American Journal of Transplantation. doi: 10.1111/ajt.15905
3. Zhu, L., Xu, X., Ma, K., Yang, J., Guan, H., Chen, S., … Chen, G. (2020). Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. American Journal of Transplantation. doi: 10.1111/ajt.15869

Supportive Care: Anticoagulation

Key topic areas / questions identified:
For adult patients diagnosed with COVID-19, does early initiation of anticoagulation compared to prolonging initiation improve mortality?

Key Findings:

3 articles were reviewed (Total n=905; Total sample in China).

- D-dimer and FDP levels increased progressively when COVID-19 exacerbated. Patients diagnosed with DIC received low molecular weight heparin (LMWH) treatment, after which their D-dimer and FDP decreased, but there was no significant improvement in clinical symptoms.
- D-dimer, prothrombin time and age were positively, and platelet count was negatively correlated with 28-day mortality in multivariate analysis. No difference on 28-day mortality was found between heparin users and nonusers. But the 28-day mortality of heparin users were lower than nonusers In patients with SIC score ≥4 or D-dimer > 6 fold of upper limit of normal.

Recommendations
- The existence of hypercoagulation status in critical COVID-2019 patients should be monitored closely, and anticoagulation therapy can be considered in selected patients.
- Anticoagulant therapy mainly with LMWH appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.

References:

1. Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of Thrombosis and Haemostasis, 18(5), 1094–1099. doi: 10.1111/jth.14817
2. Yin, S., Huang, M., Li, D., & Tang, N. (2020). Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. Journal of Thrombosis and Thrombolysis. doi: 10.1007/s11239-020-02105-8
3. Zhang, Y, et al. (2020). Clinical and Coagulation Characteristics of 7 Patients with Critical COVID-2019 Pneumonia and Acro-Ischemia. Zhonghua Xue Ye Xue Za Zhi = Zhonghua Xueyexue Zazhi. doi: 10.3760/cma.j.issn.0253-2727.2020.0006.

Supportive Care: Ventilatory Management

Key topic areas / questions identified:

In COVID-19 in danger of respiratory failure, do different ventilator strategies, compared to traditional ARDS protocol, affect mortality and long term health outcomes?

Key Findings:

8 articles were reviewed (Total n=unknown; at least 2,583+; Total sample in China, Italy, review from Germany, USA).

- Threshold for intubation should remain low to prevent increased mortality, but timely intubation is better than early intubation as it prevents re-intubation and risk of disease spread. Adopt ventilator settings for ARDS with some adjustments (PEEP usually higher ~10, low VT ~6), with a focus on preventing ventilator-associated lung injury (Lung Protective Strategy) and reducing transmission (wearing proper PE and decreased re-intubation).
- For pediatric patients, do not delay intubation, use a low tidal volume, and place the child in a prone position 1-2 hours three times daily, early in treatment.
- One study addressing hypercapnia recommends a VT of ~7.7 to prevent or improve hypercapnia.

Recommendations:

- Though mostly anecdotal, there is some evidence on the ventilator settings and differing characteristic of COVID-19 associated ARDS. Ventilator setting recommendations include:
    - Low VT, ≤ 6 mL/kg ideal body weight
    - PEEP >10 cm H2O
    - Oxygen administration at an SpO2 < 90% - 96%.
    - Starting RR of 16 breaths/min.
    - Early prone positioning
- The most experienced team member should perform intubation with as few assistants as possible to reduce exposure. Bag-mask ventilation generates aerosols and should be minimized by performing prolonged pre-oxygenation. Rapid sequence induction with muscle relaxants will reduce coughing.
- In patients who develop hypercapnia, increase VT to ~7.7.
- For timing of intubation:
    - If a patient is on nasal high-flow oxygen therapy, the ROX index [SpO2/(FiO2 x RR)] can be used. If after 12 hours, patients have a ROX index of <3.85, initiate intubation.
    - For NCP patients, if PaO2/FiO2 is <150 mmHg (1mmHg = 0.133 kPa), initiate intubation if receiving more than 2 hours of nasal high-flow therapy or non-invasive ventilation.

Figure 1: UpToDate Table of Ventilator Setting Recommendations for COVID-19 patients

Low tidal volume ventilation in patients with acute respiratory distress syndrome

Initial ventilator settings								
Calculate predicted body weight (PBW)								
Male =	50 + 2.3 [height (inches) - 60] **OR**							
	50 + 0.91 [height (cm) - 152.4]							
Female =	45.5 + 2.3 [height (inches) - 60] **OR**							
	45.5 + 0.91 [height (cm) - 152.4]							
Set mode to volume assist-control								
Set initial tidal volume to 6 mL/kg PBW								
Set initial ventilator rate ≤35 breaths/min to match baseline minute ventilation								
Subsequent tidal volume adjustment								
Plateau pressure goal: Pplat ≤30 cm H_2O								
Check inspiratory plateau pressure with 0.5 second inspiratory pause at least every four hours and after each change in PEEP or tidal volume.								
If Pplat >30 cm H_2O, decrease tidal volume in 1 mL/kg PBW steps to 5 or if necessary to 4 mL/kg PBW.								
If Pplat <25 cm H_2O and tidal volume <6 mL/kg, increase tidal volume by 1 mL/kg PBW until Pplat >25 cm H_2O or tidal volume = 6 mL/kg.								
If breath stacking (autoPEEP) or severe dyspnea occurs, tidal volume may be increased to 7 or 8 mL/kg PBW if Pplat remains ≤30 cm H_2O.								
Arterial oxygenation and PEEP								
Oxygenation goal: PaO_2 55 to 80 mmHg or SpO_2 88 to 95 percent								
Use these FiO_2/PEEP combinations to achieve oxygenation goal:								
FiO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5	5 to 8	8 to 10	10	10 to 14	14	14 to 18	18 to 24
PEEP should be applied starting with the minimum value for a given FiO_2.								

Pplat: plateau pressure; PaO_2: arterial oxygen tension; SpO_2: oxyhemoglobin saturation; PEEP: positive end-expiratory pressure; FIO2: fraction of inspired oxygen.

Adapted from: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301.

References:

1. Bein B, Bachmann M, Huggett S, Wegermann P. SARS-CoV-2/COVID-19: Empfehlungen zu Diagnostik und Therapie. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 2020;55(4):257-265. doi:10.1055/a-1146-8674
2. Giwa AL, Desai A, Duca A. Novel 2019 coronavirus SARS-CoV-2 (COVID-19): An updated overview for emergency clinicians. *Emerg Med Pract*. 2020;22(5):1-28.
3. Liu X, Liu X, Xu Y, et al. Ventilatory Ratio in Hypercapnic Mechanically Ventilated Patients with COVID-19 Associated ARDS. *Am J Respir Crit Care Med*. March 2020. doi:10.1164/rccm.202002-0373LE
4. Marraro GA, Spada C. Consideration of the respiratory support strategy of severe acute respiratory failure caused by SARS-CoV-2 infection in children. *Zhongguo Dang Dai Er Ke Za Zhi*. 2020;22(3):183-194.
5. Meng L, Qiu H, Wan L, et al. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. *Anesthesiology*. March 2020. doi:10.1097/ALN.0000000000003296
6. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med*. April 2020. doi:10.1016/s2213-2600(20)30161-2
7. Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults With COVID-19. *JAMA*. Published online March 26, 2020. doi:10.1001/jama.2020.4914
8. Qiu HB, Li XY, Du B, et al. [The keypoints in treatment of the critical novel coronavirus pneumonia patient]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43(0):E022. doi:10.3760/cma.j.cn112147-20200222-00151

Supportive Care: ECMO

Key topic areas / questions identified:
In COVID-19 patients with respiratory failure and impending death, does ECMO, compared to continued ventilator/supportive care measures, prevent mortality and improve long-term outcomes?

Key Findings:

5 articles were reviewed (Total n=20 (possibly more); Total sample in China, Italy, USA).

- Approximately half of patients receiving ECMO die of organ failure or septic shock.
- A literature review of 87 articles, of which 4 were used in final analysis, found that of 234 patients with COVID-related ARDS, 17 underwent ECMO. Odds of mortality for ECMO vs conventional treatment were not significant.
- Per the majority of articles and WHO, ECMO is still an option. The mortality rate is higher compared to the largest report of MERS patients receiving ECMO.

Recommendations:

- ECMO can be a viable treatment option. WHO recommends use as rescue therapy for hypoxia. Consider ECMO if patient mortality is estimated at 50%; initiate if 80%.
- If properly aerated, start ECMO if one of these conditions/no contraindications are met:
    - (1) PaO2 / FiO 2 <50 mmHg over 3 h
    - (2) PaO2 / FiO 2 <80 mmHg over 6 h
    - (3) FiO2 = 1.0, PaO2 / FiO2 <100 mmHg
    - (4) Arterial blood pH value <7.25 and PCO2 > 60 mmHg for more than 6 h, and respiratory rate >35 breaths/min.
    - (5) Respiratory rate >35 breaths/min, blood pH value <7.2 and plateau pressure >30 cmH2O
    - (6) Severe air leak syndrome
    - (7) Complicated by cardiogenic shock or cardiac arrest
    - Contraindications include multi-organ failure, contraindication to anticoagulation, high mechanical vent for more than 7 days
- Another paper states ECMO should be considered if one following criteria are met:
    - (1) PaO2/FiO2<100mmHg
    - (2) P(A-a)O2>600mmHg
    - (3) pH<7.2 and plateau pressure >30 cmH2O with respiratory rate > 35 breaths per minute
    - (4) <65 years old
    - (5) receiving mechanical ventilation <7days
    - (6) no contraindications

References:

1. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. J Crit Care. 2020;58:27-28. doi:10.1016/j.jcrc.2020.03.011
2. Hong X, Xiong J, Feng Z, Shi Y. Extracorporeal membrane oxygenation (ECMO): does it have a role in the treatment of severe COVID-19? Int J Infect Dis. 2020;94:78-80. doi:10.1016/j.ijid.2020.03.058
3. Li X, Guo Z, Li B, et al. Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019 in Shanghai, China. ASAIO J. March 2020. doi:10.1097/MAT.0000000000001172
4. Support CS of EL. Recommendations on extracorporeal life support for critically ill patients with novel coronavirus pneumonia. Chinese J Tuberc Respir Dis. 2020;43(00):E009-E009. doi:10.3760/CMA.J.ISSN.1001-0939.2020.0009
5. Zeng Y, Cai Z, Xianyu Y, Yang BX, Song T, Yan Q. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: a retrospective case series. Crit Care. 2020;24(1):148. doi:10.1186/s13054-020-2840-8

Supportive Care: Prone Positioning

Key topic areas / questions identified:

Does early initiation of prone positioning during ventilation, compared to supine positioning or later prone positioning, allow for improved outcomes, including less time on the ventilator, recovery of lung capacity, and decreased mortality rates?

Key Findings:

3 articles were reviewed (Total n=2,583; Total sample in China).

- Prone positioning improves hypoxemia, hypercapnia, lung compliance and lung recoil.
- There is little evidence to support prone positioning for treatment of COVID-19 specifically, but the tendency for SARS-CoV-2 to affect the peripheral and dorsal areas of the lungs provides the ideal conditions for a positive oxygenation response to prone positioning.

Recommendations:

- Prone positioning should be applied early, given its association with reduced mortality in other causes of severe ARDS.
- COVID patients should receive prone positioning as soon as possible if not suffering from severe ARDS [oxygenation index less than 150 mmHg (1 mmHg = 0.133 kPa)]. ECMO patients should also be placed in a prone position. Prone positioning should be monitored via electrical impedance imagine

References:

1. Meng L, Qiu H, Wan L, et al. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. *Anesthesiology*. March 2020. doi:10.1097/ALN.0000000000003296
2. Pan C, Zhang W, Du B, Qiu HB, Huang YZ. Prone ventilation for novel coronavirus pneumonia: no time to delay. *Zhonghua nei ke za zhi*. 2020;59:E007. doi:10.3760/cma.j.cn112138-20200304-00184
3. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med.* April 2020. doi:10.1016/s2213-2600(20)30161-2

Vaccines

Key topic areas / questions identified:
What is the current status/progress made towards developing a vaccine to prevent COVID-19?

Key Findings:

5 global studies regarding the early phases of developing a vaccine were reviewed

- Coronavirus seems to evade early detection by the immune system, thus the reason for it having a longer incubation period ~2-11 days, compared to 1-4 for common influenza virus. Transmission is reported to occur in asymptomatic infected individuals; this may be indicative of delayed early response of the innate immune response.
- Vaccine development should focus on previous progress made on SARS and MERS vaccines. Th1 type immune response is a key for successful control of SARS-CoV and MERSCoV and probably true for SARS-CoV-2 as well.
- Studies have begun studying epitopes of SARS-CoV and MERS to identify similarities to SARS-CoV2 to develop a vaccine using previous progress. Multiple vaccines are currently being clinically tried.

Updates:
- WHO provides updates on the clinical trials. Updates on current trials can be found at this link: Draft landscape of COVID 19 candidate vaccines
- Majority of studies are currently in the pre-clinical phase with few in phase 1 and/or 2.

References:

1. Ahmed, Syed Faraz, et al. (2020). Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies. Viruses. doi: 10.3390/v12030254.
2. Baruah, V., & Bose, S. (2020). Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV. Journal of Medical Virology, 92(5), 495–500. doi: 10.1002/jmv.25698
3. Bhattacharya, M., Sharma, A. R., Patra, P., Ghosh, P., Sharma, G., Patra, B. C., … Chakraborty, C. (2020). Development of epitope-based peptide vaccine against novel coronavirus 2019 (SARS-COV-2): Immunoinformatics approach. Journal of Medical Virology, 92(6), 618–631. doi: 10.1002/jmv.25736
4. Prompetchara, E., Ketloy, C., Palaga T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pacific Journal of Allergy and Immunology. doi: 10.12932/ap-200220-0772
5. Shi, Y, et al. (2020). Progress and Challenge of Vaccine Development against 2019 Novel Coronavirus (2019-NCoV). Zhonghua Yu Fang Yi Xue Za Zhi [Chinese Journal of Preventive Medicine.] doi: 10.3760/cma.j.cn112150-20200317-00366.